Luminal Breast Cancer (LBC) – (Neo) Adjuvant Chemotherapy

Multidisciplinary management, standards of care, therapeutic targets and future perspectives

Dr. Janice Tsang
MBBS, MRCP(UK), FRCP(Lond.), FRCP (Edin.), FHKCP, FHKAM(Medicine)
Specialist in Medical Oncology & Hon. Clinical Assistant Professor
Li Ka Shing Faculty of Medicine, The University of Hong Kong
Founding Convenor, Hong Kong Breast Oncology Group (HKBOG)

21st November, 2017

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DISCLOSURES

Consultant or Advisory Role:

AstraZeneca, Aptus, Astellas, Eisai, GlaxoSmithKline, Foundation Medicine, Novartis & Pfizer
(Neo)adjuvant chemotherapy for Luminal Breast Cancer
Breast cancer was initially thought as a strictly local disease…

Based on William Stewart Halsted (1852-1922)’s theory: Breast cancer is a strictly local disease, only curable by radical surgery…

Early breast cancer used to be managed exclusively by surgeons…
Breast cancer was then thought as a *systemic* disease...

The work of **Bernard Fisher**, breast surgeon & chairman of the National Surgical Adjuvant Breast & Bowel Project (NSABP) in the 1960s has led to the development of breast cancer being a systemic disease...

Leading to a paradigm shift in breast cancer management with the introduction of adjuvant therapy...
Personalized treatment of breast cancer started in the 1960s...

Professor Elwood V. Jensen, first identified the Estrogen receptor (ER) in 1958...

Introduction of TAMOXIFEN as a first “targeted agent” in the 1970s...
Breast cancer subtypes

- ER+ 65-75%
- HER2+ 15-20%
- TN 15%
Classical prognostic & predictive factors

- Age
- Tumour size
- Grade
- Histological subtypes
- ER/PR and HER2 status
- Presence of lymphovascular invasion
- High proliferative index (Ki-67)
- Tumor margins
Changing Portraits of Breast Cancer
Intrinsic Subtypes
Perou et al., Nature, 2000
Sorlie et al., PNAS, 2003
Cheang et al., CCR 2008
Cheang et al., JNCI 2009
Parker et al., JCO, 2009
Nielsen et al., CCR 2010
Cheang et al., CCR 2012
Dowsett et al., JCO 2013
Hoadley et al., Cell, 2014
Carey et al., JCO 2015

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THE chemosensitivity OF A BREAST TUMOUR DEPENDS ON many factors

In favor of adjuvant chemotherapy
- ER negative
- Ductal histology
- Grade 3
- High proliferation
- High uPA and PAI1
- Basal and HER2 positive
- High MammaPrint® or Oncotype DX® or GGI

Against adjuvant chemotherapy
- ER positive
- Lobular histology
- Grade 1
- Low proliferation
- Low uPA and PAI1
- Luminal A
- Low MammaPrint® or Oncotype DX® or GGI

Bedard & Cardoso. Nature Reviews Clinical Oncology 2011 8(272-279)
Added value of adjuvant chemotherapy?

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials

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### The EBCTCG Overview - Subgroup Analyses

#### Table 1: Anthracycline Deaths

<table>
<thead>
<tr>
<th>Deaths/women</th>
<th>Anthracycline deaths</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allocated anthracycline</strong></td>
<td><strong>Allocated CEF</strong></td>
<td><strong>Log rank D-E</strong></td>
</tr>
<tr>
<td>31/0402 (82% 28%)</td>
<td>69/0347 (22%)</td>
<td>0.60</td>
</tr>
<tr>
<td>27/0304 (84%)</td>
<td>71/0310 (22%)</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>209/2542 (22%)</strong></td>
<td><strong>509/698 (22%)</strong></td>
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</table>

#### Table 2: Non-anthracycline Deaths

<table>
<thead>
<tr>
<th>Deaths/women</th>
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#### Table 3: Subgroup Analyses

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### EBCTCG Lancet, 2012

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The EBCTCG Overview - Subgroup Analyses

Subgroup analysis of breast cancer mortality in ER positive patients by HER2, age and tumour grade.
Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials

**Figure 6:** Subgroup analyses of breast cancer mortality (mortality with recurrence, by log-rank subtraction) for any anthracycline-based regimen versus no chemotherapy
The EBCTCG Overview: Bottom-line Message

- Anthracycline/taxane-based regimens reduce breast cancer mortality by, on average, about one-third.
- Proportional benefits in the ER positive population do not seem to be affected by age, HER2 status or tumour grade.

Interpretation

10-year gains from a one-third breast cancer mortality reduction depend on absolute risks without chemotherapy (which, for oestrogen-receptor-positive disease, are the risks remaining with appropriate endocrine therapy). Low absolute risk implies low absolute benefit, but information was lacking about tumour gene expression markers or quantitative immunohistochemistry that might help to predict risk, chemosensitivity, or both.

Funding

Cancer Research UK; British Heart Foundation; UK Medical Research Council.

EBCTCG Lancet, 2012
Who responds to anthracycline better?

3452 patients: CMF vs anthracyclins

Di Leo, Lancet Oncol 2011

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(Neo)adjuvant chemotherapy for Luminal A-like vs Luminal B-like
An exploratory analysis to test sensitivity to different chemotherapy regimens by luminal subtype


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An exploratory analysis to test sensitivity to different chemotherapy regimens by luminal subtype


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When cytotoxic chemotherapy is indicated for luminal disease:

- the specific choice of regimen depends on the position within the spectrum of degree of endocrine responsiveness and risk of relapse.
- On average, for ‘luminal B-like’ tumors, the Oxford overview supports the inclusion of both an anthracycline and a taxane.
- while in ‘luminal A-like’ tumors, there is little evidence of an advantage compared with older regimens such as AC and CMF.
- If given, chemotherapy for ‘luminal B-like’ disease should not extend beyond four courses of the same treatment, especially, for patients with a lower burden of disease.
- The addition of taxanes should be considered for patients with more extensive disease burden.
- A slim majority considered that there was a high-risk group for which dose-dense therapy with G-CSF support should be preferred.
Adjuvant Chemotherapy

The St. Gallen vote on adjuvant chemotherapy focused on patients who might have a prognostic benefit from postoperative chemotherapy and should therefore receive chemotherapy postoperatively.

When considering patients without lymph node involvement (pN0), their prognosis as well as the decision for or against adjuvant chemotherapy should be based on immunohistochemical assessment of the tumor biology, which can be supplemented by multigene expression testing in cases of lacking Relative indications for adjuvant chemotherapy are poorly differentiated G3 tumors, lymph node involvement (pN+), high Ki-67 proliferation index, very young patient age (<35 years) and low hormone receptor (HR) expression (<10%). The German experts agree with the St. Gallen panelists and add that, based on these criteria, it is important to consider the risk-benefit ratio.

The majority of St. Gallen panelists also considered extensive lymphovascular tumor invasion a relative indication for adjuvant chemotherapy. The German experts refer to the current AGO guidelines and state that lymphovascular tumor invasion is not an indication for chemotherapy. From the German point of view, chemotherapy is not necessarily indicated if there are no additional risk factors.

Luminal B-like breast cancer without HER2 overexpression

For patients with luminal B-like breast cancer, a common question in clinical practice is whether adjuvant chemotherapy is indicated in addition to endocrine therapy. Adjuvant chemotherapy is indicated if there is an increased risk of recurrence. The German experts agree with the majority of St. Gallen panelists that adjuvant chemotherapy should be recommended to patients with early luminal B-like breast cancer and prognostically unfavorable tumor biology confirmed by immunohistochemistry, irrespective of lymph node status. The German experts point out that in patients with no lymph node involvement tumor size should also be taken into account for treatment decision. If the primary tumor is very small (≤1 cm pT1a pN0) and there are no additional negative criteria,
Luminal B-like breast cancer without HER2 overexpression

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The St. Gallen panelists and the German experts confirm again that multi-gene expression analysis can be an effective method in patients with luminal B-like breast cancer to determine whether the patient has an increased 10-year risk of metastasis and chemotherapy is therefore indicated. The majority of St. Gallen panelists voted that adjuvant chemotherapy is not necessary if RS is low as long as there is no lymph node involvement or less than three nodes are involved. The German experts agree with this opinion and refer to the prospective data collected in the TAILORx trial which had a follow-up of five years. The findings of this study have been confirmed by recent data from the West German Study Group (WGS) Phase III Plan B trial, which also had a follow-up of just under five years.

The findings referred specifically to low-risk patients with an RS of less than 11 and no lymph node involvement or fewer than three involved lymph nodes and a follow-up of five years. If the RS score is intermediate, the St. Gallen panelists and the German specialists agree that avoiding adjuvant chemotherapy should only be considered in individual cases. For the final assessment (adjuvant chemotherapy indicated yes/no) it is necessary to wait until data on patients with intermediate scores are available from the TAILORx trial.

Initial prospective data on patients with 1–3 involved lymph nodes with a follow-up of just under five years are now also available for the MP score. Based on preliminary data, adjuvant chemotherapy is not required for patients with 1–3 involved lymph nodes if the risk profile is low according to MP score. No prospective data are available yet for ROR and EP. However, according to retrospective data from prospective studies with EP, the cumulative risk of metastasis for low-risk, node-positive patients (just under 20% of patients) who receive only endocrine therapy is about 3%. This means that chemotherapy is not necessary in this patient population. The German specialists additionally point out that results of the votes of the St. Gallen panelists were not always consistent with previous votes on multi-gene expression signatures.

The St. Gallen panelists and the German experts agree that adjuvant chemotherapy should be anthracycline-based and taxane-based for patients with luminal B-like (HER2-negative) breast cancer.

Triple-negative breast cancer

For patients with early invasive ductal triple-negative breast cancer (TNBC: ER−, PR−, HER2−), the established...
Current Status...

- No strong evidence in favour of anthracycline or taxane-based regimens in Luminal A-like breast cancer – lack of robust data.
- Anthracycline/taxane-based regimens seem to be the most appropriate treatment choice in Luminal B-like tumour.
Precision Medicine for (Neo)adjuvant chemotherapy Luminal EBC
Predictive Marker vs Prognostic Marker

- **Predictive Marker** ↔ Treatment Response (Treatment Sensitivity)
- **Prognostic Marker** ↔ Risk of Recurrence or Risk of Relapse

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Plan for future studies – Idea Trials (awaited)

Eligible patients

- ER+, LUM A or LUM B
- pre/post
- candidate to chemotherapy according to the treating doctor

“soft” chemo → optimal HT
(CMF, AC, TC, weekly paclitaxel)

“intensive” chemo → optimal HT
(A → T for ± 6 months)

Separate analysis for LUM A and LUM B cohorts
Even within ER+ subtype – a heterogeneous population
Not just luminal BC disease...
Current Limitations or Challenges…

- There is no specific biomarkers to predict which patient is of high risk disease besides the histopathological status.
- There is no predictive biomarkers for specific chemotherapy regimen.
- Prognostic value of molecular subtypes.

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### Individualized Test Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Selection</strong></td>
<td>HER2 (Anti-HER-2 targeted agents) ER+ (Tamoxifen/Aromatase Inhibitors)</td>
</tr>
<tr>
<td><strong>Drug Dosage</strong></td>
<td>• Not yet available</td>
</tr>
<tr>
<td><strong>Drug Efficacy</strong></td>
<td>• Not yet available</td>
</tr>
<tr>
<td><strong>Disease Status</strong></td>
<td>• Not yet available</td>
</tr>
<tr>
<td><strong>Recurrence Risk</strong></td>
<td>• Oncotype DX / MammaPrint/Prosigna (PAM50)/Endopredict</td>
</tr>
<tr>
<td></td>
<td>• Multivariate analysis</td>
</tr>
<tr>
<td></td>
<td>• uPA/PAI-1 (node negative)</td>
</tr>
<tr>
<td><strong>Predisposition</strong></td>
<td>• BRCA-1/2</td>
</tr>
</tbody>
</table>

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Prognostic Multigene Assays

- Aimed at dividing patients into those with good prognosis and those with a poor prognosis.

- To minimize overtreatment of patients at low risk of recurrence.
A considerable proportion of EBC not receiving adjuvant systemic chemotherapy actually do not relapse...

Bonadonna G et al, BMJ 2005

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High Recurrence Score® result correlates with greater benefit from chemotherapy (NSABP B-20)


PATIENTS WITH HIGH RS: 28% absolute benefit from tamoxifen + chemotherapy

4.4% absolute benefit from tamoxifen + chemotherapy

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Recurrence Score/Oncotype DX®

- A RT-PCR-based gene signature that measures the expression of 21 genes (16 cancer-related genes and 5 reference genes)
- *It uses the Recurrence score (RS) to predict the risk of distant relapse within 10 years*
- Developed in **ER+, under tamoxifen** treatment
- Extensive retrospective validation; ongoing prospective validation

![Graph showing risk of distant recurrence with and without recurrence score](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis without recurrence score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at surgery</td>
<td>0.004</td>
<td>0.57 (0.39–0.83)</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td>0.06</td>
<td>1.44 (0.99–2.11)</td>
</tr>
<tr>
<td>Analysis with recurrence score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at surgery</td>
<td>0.08</td>
<td>0.71 (0.48–1.05)</td>
</tr>
<tr>
<td>Clinical tumor size</td>
<td>0.23</td>
<td>1.26 (0.86–1.86)</td>
</tr>
<tr>
<td>Recurrence score</td>
<td>&lt;0.001</td>
<td>3.21 (2.23–4.61)</td>
</tr>
</tbody>
</table>

*Paik, NEJM 2004*
Oncotype DX® in Node Negative BC
Paik, JCO 2006

- **NSABP B-20**: ER+, N0, CT (CMF regimen); 651 pts (227 TAM / 424 TAM+CT)

- **High RS (≥ 31)**: benefited from CT (RR 0.26 (95% CI, 0.13 - 0.53), relative risk reduction in 10 yrs **27.6%** (SE 8.0%))

- **Low RS (< 18)** no significant benefit from CT (RR 1.31 (95% CI, 0.46 – 3.78), relative risk reduction in 10 yrs **-1.1%** (SE 2.2%))

![Graph showing the relative risk and benefit of chemotherapy for different RS categories.](image)
Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes

Joel S. Parker, Michael Mullins, Maggie C. U. Cheang, Samuel Leung, David Voduc, Tammi Vickery, Sherri Davies, Christiane Fauron, Xiaping He, Zhiyuan Hu, John F. Quackenbush, Inge J. Stijleman, Juan Palazzo, J.S. Marron, Andrew B. Nobel, Elaine Mardis, Torsten O. Nielsen, Matthew J. Ellis, Charles M. Perou, and Philip S. Bernard

50 gene predictor (qRT-PCR)
Training set N=189 BC
Validation set N=761 BC

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Combined Analysis: Clinical Validation in Over 2,400 Patients

- Prospectively defined analysis of two registration-quality databases with ≥10-yr median follow-up in postmenopausal women with ER+ ESBC treated with endocrine therapy alone
  - Primary objective: Validate published observations that the ROR score provides additional prognostic information above standard clinical variables for DRFS at 10 yrs
    - Primary Analysis: All patients
    - Secondary Analysis: Node -/+ , HER2-negative patients
  - Secondary objective: Validate observations that Luminal A and Luminal B patients have statistically significantly different DRFS at 10 years

<table>
<thead>
<tr>
<th>TransATAC</th>
<th>ABCSG-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>• N = 1,007</td>
<td>• N = 1,478</td>
</tr>
<tr>
<td>• Patients: Postmenopausal women with ER/PR+ early-stage breast cancer treated with endocrine therapy alone</td>
<td>• Patients: Postmenopausal women with ER/PR+ early-stage breast cancer treated with endocrine therapy alone</td>
</tr>
<tr>
<td>• Design: Prospective, retrospective</td>
<td>• Design: Prospective, retrospective</td>
</tr>
<tr>
<td>• Output: Prognosis</td>
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ROR Defined Risk Groups have statistically significant different outcomes at 10 years – Node Negative Patients

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Patients (%)</th>
<th>Number of Events through 10 years</th>
<th>Estimated percentage of risk at 10 years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>166 (10.0)</td>
<td>31</td>
<td>20.3 (14.7 - 27.7)</td>
</tr>
<tr>
<td>intermediate</td>
<td>388 (23.5)</td>
<td>52</td>
<td>15.0 (11.6 - 19.2)</td>
</tr>
<tr>
<td>low</td>
<td>1100 (66.5)</td>
<td>50</td>
<td>4.9 (3.7 - 6.4)</td>
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</tbody>
</table>
ROR Defined Risk Groups have different outcomes at 10 years - 1 to 3 positive nodes

<table>
<thead>
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<th>Patients (%)</th>
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<th>Estimated percentage of risk at 10 years (95% CI)</th>
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<tbody>
<tr>
<td>high</td>
<td>233 (41.1)</td>
<td>58</td>
<td>29.9 (23.9 - 37.1)</td>
</tr>
<tr>
<td>intermediate</td>
<td>188 (34.6)</td>
<td>22</td>
<td>13.8 ( 9.2 - 20.3)</td>
</tr>
<tr>
<td>low</td>
<td>132 (24.3)</td>
<td>10</td>
<td>7.9 ( 4.3 - 14.1)</td>
</tr>
</tbody>
</table>

Patients at risk:
- high: 223
- intermediate: 188
- low: 132

Follow-up time (years):
- high: 218, 208, 191, 175, 164, 157, 141, 128, 108, 80
- intermediate: 185, 183, 178, 173, 164, 155, 149, 144, 121, 87
- low: 131, 131, 130, 128, 124, 121, 118, 110, 87, 60
• 6,600 pts < 70
  – FEB 2007-AUG 2011
  – 11,291 registered pts
  – 6,673 enrolled (59.1%)
MINDACT TRIAL DESIGN

Registration & Screening Surgery

N= 6694

Clinical-Pathological (C) risk
(Adjuvant! Online)

Genomic (G) risk
(70-gene signature)

C-high/ G-high

Discordant cases
C-high/G-low or C-low/G-high

1st randomization to treatment
use Clinical vs. Genomic risk

Chemotherapy

2nd randomization
Anthracycline -based vs. Capecitabine-Docetaxel

HR+

Endocrine therapy

3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

C-low/G-low

No Chemotherapy

HR+
MINDACT population at 5y median follow-up
DMFS IN ALL 4 RISK GROUPS

Distant Metastasis Free Survival

% at 5 year

- cL/gL: 97.6 (96.9, 98.1)
- cL/gH: 94.8 (92.4, 96.4)
- cH/gL: 95.1 (93.8, 96.2)
- cH/gH: 90.6 (89.0, 92.0)

F. Cardoso, NEJM 2016
The MINDACT population: CT assignment according to a “Clinical” vs a “Genomic” strategy

Whole population N = 6,693

- N=2745 clinical Low/genomic Low
- N=592 clinical Low/genomic High
- N=1550 clinical High/genomic Low
- N=1806 clinical High/genomic High

«Clinical» strategy
CT to 1550 + 1806 = 3,356 pts
= 50 %

«Genomic» strategy
CT to 592 + 1806 = 2,398 pts
= 36 %

14% reduction

F. Cardoso, NEJM 2016
GENOMIC TESTS IN ALL OR ONLY SELECTED BREAST CANCER CASES?

TRIPLE NEGATIVE (ER-, PR-, HER-2 neg)
CT indispensible

LUMINAL
ER+ HER-2 neg
“Clear” indication from classical factors
All LOW risk: high levels ER, PR, grade 1, node negative, low proliferation
All HIGH risk: low levels ER, PR, grade 3, node positive, high proliferation

HER-2 POSITIVE
CT + anti-HER indispensible

“No Clear” indication from classical factors; some high & some low risk

CRUCIAL IMPORTANCE OF HIGH QUALITY PATHOLOGY
HT alone
CT → HT

GENOMIC TEST

Courtesy of Professor Fatima Cardoso, ESMO 2017

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Neoadjuvant chemotherapy for Luminal Breast Cancer
Efficacy of Neoadjuvant Chemotherapy ↔ Adjuvant Chemotherapy

Wolmark, JNCI Mongr 2001, Maurl JNCI 2005
Objectives of Neoadjuvant Chemotherapy

- For technically inoperable primary breast tumour to become technically operable
- For tumour only deemed for mastectomy to become also eligible for BCT
- Down-size thus down-staging the disease
- Control occult metastases
- To assess treatment response with serial monitoring
- To achieve better outcome esp high chance of complete pathological response, e.g. HER2 positive and triple negative disease.
Those with G3 tumour, ER and PgR negative and TNC do better…
I-SPY: Neoadjuvant Chemotherapy for Breast Cancer and Biomarker Analysis

I-SPY: study to identify biomarkers of response to neoadjuvant CT

<table>
<thead>
<tr>
<th></th>
<th>ER (P &lt; .0001)</th>
<th>PgR (P &lt; .0001)</th>
<th>HER2 (P = .02)</th>
<th>KI67 Index (P &lt; .0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ (n = 115)</td>
<td>- (n = 88)</td>
<td>+ (n = 95)</td>
<td>- (n = 107)</td>
</tr>
<tr>
<td>pCR +</td>
<td>16%</td>
<td>44%</td>
<td>12%</td>
<td>43%</td>
</tr>
<tr>
<td>Low</td>
<td>Low (n = 50)</td>
<td>Int (n = 62)</td>
<td>High (n = 70)</td>
<td></td>
</tr>
</tbody>
</table>

- Tumor basal (ER⁻/PgR⁻/HER2⁻), luminal B (ER⁺/PgR⁺/HER2⁺), and HER2 (ER⁻/PgR⁻/HER2⁺) associated with higher pCR rates
- Luminal A (ER⁺/PgR⁺/HER2⁻) showed low pCR (9%)
- ER⁻/HER2⁺ tumors showed higher pCR (88%) compared to ER⁺/HER2⁺ tumors (25%)

The implication of pCR in Luminal Breast Cancer…

Cortazar, Lancet 2014
Association between pCR and EFS by BC subtype

Is pCR really important in luminal BC?

6,377 patients treated with neoadjuvant anthracycline-taxane based chemotherapy

patients achieving pCR

luminal A tumors

luminal B HER2(+) tumors

von Minckwitz, JCO 2012
Holistic Multidisciplinary Team (MDT) Approach

Breast Cancer Patients

Clinical Oncologists
Supporting Staff
Surgeons
Pathologists
Nurse Specialists
Clinical Psychologists
Medical Social Workers
Physiotherapists
Occupational Therapists
Dietitians

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