of less than <0.05 was considered as indicative of statistically significant difference.

Results: Pretreatment CA15.3 levels ranged from 3.3 to 237.6 U/ml. Elevated CA15.3 levels (>28 U/ml) were found in 21 (8.5%) patients. Statistical analysis revealed that preoperative serum CA15.3 levels were directly related to tumor size (p = 0.015) and lymph node involvement (p = 0.009), while no significant relationship between CA15.3 measurements and age, histological type, grade, HER2/neu positivity, ER and PR status was observed. In the univariate analysis, high CA15.3 levels were significantly associated with a lower probability of disease free survival (DFS) in the overall group of patients (p = 0.0001). On the contrary, multivariate regression method showed that CA15.3 was not an independent risk factor for a shorter DFS, with a hazard ratio of 0.177 (95% CI 0.074–0.422; p = 0.001).

Conclusions: In this study of 247 cases of pT1−2 infiltrating breast carcinomas, high preoperative CA15.3 levels correlate with large size tumors and the presence of lymph node metastases and suggest that this antigen could be possibly used as a complementary prognostic marker.

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TNBC Has Disproportionately Poor Prognosis Among AJCC Stages

J. Lee[1], B.H. Son[2], S.H. Ahn[2]. *[1]Inje University Haeundae Paik Hospital, Surgery, Busan, Korea; [2]Ulsan University Asan Medical Center, Surgery, Seoul, Korea*

Background: Subtypes defined by clinicopathological criteria are similar to but not identical to intrinsic subtypes and represent a convenient approximation. Not only previous known prognostic factors, such as lymph node status, tumor size, and patient's age but also molecular subtypes might be some correlations with breast cancer's prognosis, especially similar stages.

Methods: 1305 women diagnosed and/or treated with invasive breast cancer during 1989–2004 at Asan Medical Center were studied. Primary endpoint (locoreginal, and distant metastasis) and secondary endpoint (OS) were evaluated using chi-square tests and Cox proportional hazards models. Breast cancer samples were categorized into molecular subtypes based on immunohistochemical profiles. Samples that were ER- or PR-positive and Her-2/neu-negative were classified as luminal A, samples that were ER- or PR-positive and Her-2/neu-positive were classified as luminal B, samples that were ER- and PR-negative and Her-2/neu positive were classified as Her-2/neu-enriched, and samples that were ER-, PR- and Her-2/neu-negative were classified as triple-negative.

Parameter	TNBC	Her-2/neu	Luminal A	Luminal B	*p*-value
Number	256(19.6)	220(16.9)	564 (43.2)	265 (20.3)	
Tumor size (mm)	27.0 (±19.7)	32.6 (±23.4)	27.2 (±17.2)	24.9 (±12.4)	<0.001
Age(years)					<0.001
<35	40(15.6)	19(8.6)	36(6.4)	26(9.8)	
35−49	143(55.9)	110(50.0)	361(64.0)	151(57.0)	
>50	73(28.5)	91(41.4)	167(29.6)	88(33.2)	
Stage					<0.002
I	84(32.8)	72(32.7)	178(31.6)	83(31.3)	
II	155 (60.5)	111 (50.5)	343 (60.8)	148 (55.8)	
III	13 (5.1)	32 (14.5)	40 (7.1)	32 (12.1)	
IV	4 (1.6)	5 (2.3)	3 (0.5)	2 (0.8)	
p53					<0.006
−	135 (52.9)	90 (40.9)	492 (87.4)	199 (76.0)	
+	120 (47.1)	130 (59.1)	71(12.6)	63(24.0)	
Type					0.01
IDC	254 (99.2)	219 (99.5)	545 (96.6)	260 (98.1)	
ILC	2 (0.8)	0	19 (3.4)	5 (1.9)	
Others	0	1 (0.5)	0	0	
Chemotherapy					<0.001
no	25 (9.8)	31 (14.1)	203 (36.4)	93 (35.4)	
yes	229 (90.2)	189 (85.9)	354 (63.4)	170 (64.6)	
unknown					
OP					<0.001
BCO	79 (30.9)	31 (14.1)	148 (26.2)	45 (17.0)	
MRM	177 (69.1)	189 (85.9)	416 (73.8)	220 (83.0)	
LN					<0.021
(−)	158 (62.5)	120 (55.6)	286 (51.7)	131 (50.8)	
(+)	95 (37.5)	96 (44.4)	267 (48.3)	127 (49.2)	

Results: Triple negative breast cancer was 256 patients (19.6%), luminal A; 564 (43.2%), Her-2/neu positive breast cancer 220 (16.9%), and luminal B 265 (20.3%) (Table 1). Median follow up was 60months, triple negative breast cancer carried worse prognosis than other typed breast cancer before 3 years but it was so disproportionately represented among each stages after 3 years, and luminal A breast cancers were better survival than other typed breast cancer every stages Triple negative breast cancer carries a poor prognosis so is disproportionately represented among all stages. On multivariate survival analyses, AJCC stage, lymph node status, and breast cancer subtypes were independent prognostic factors.

Conclusion: Breast cancer subtypes have heterogenous effects on disease free survuval in a silimar stage, but disproportionately among all stages. Her-2/neu positive and triple negative breast cancer are seem to be independent prognostic factors in a limited sized analysis.

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Immunohistochemical P53 Over-expression and Hormonal Therapy Benefit in Invasive Breast Cancer

J.W. Lee[1], W. Han[2], J. Cho[3], G. Gong[4], K.H. Jung[5], S.H. Ahn[1], H.J. Kim[6]. *[1]ASAN Medical Center, Surgery, Seoul, South Korea; [2]Seoul National University Hospital, Surgery, Seoul, South Korea; [3]Dongsan Hospital, Surgery, Daegu, South Korea; [4]ASAN Medical Center, Pathology, Seoul, South Korea; [5]ASAN Medical Center, Medical Oncology, Seoul, South Korea; [6]ASAN Medical Center, Medical Statistics, Seoul, South Korea*

Purpose: To confirm prognostic and predictive values of immunohistochemical p53 accumulation, we analyzed the prognostic role of p53, particularly in invasive breast cancer patients according to the intrinsic subtypes by hormone receptor and HER2 status.

Materials and Methods: Data about p53 immunohistochemistry results along with estrogen receptor (ER), progesterone receptor (PgR), and HER2 of 60 hospitals' own patients were retrospectively retrieved from web-based database of Korean Breast Cancer Society (KBCS). A total of 15,598 patients diagnosed between 1997 and 2004 were enrolled in this analysis. The chi square test was used to determine the differences in variables between pairs of groups. Overall survival (OS) and breast cancer specific survival (BCSS) were estimated by the Kaplan-Meier method. Log-rank tests were used for the comparison of survival curves. Multivariate analyses were performed using stratified Cox's proportional hazard regression model. A model with interaction terms of p53 by both hormonal therapy and chemotherapy was evaluated to determine the treatment benefit from both modalities.

Results: Immunohistochemical p53 over-expression was statistically associated with advanced pathological stage; higher tumor grade; hormone receptor (HR) negativity; and HER2 positivity. The median follow-up for this cohort of patients was 53 months. The 5-year OS was 88.0% for positive p53 patients, and 91.3% for negative p53 patients ($P < 0.0001$). The 5-year BCSS was 88.5% for positive p53 patients, and 91.8% for negative p53 patients ($P < 0.0001$). In a multivariate analysis, p53 over-expression was a weak but independent prognostic factor (Hazard ratio (HR) = 1.17; 95% CI, 1.01–1.34 for OS and HR = 1.39; 95% CI, 1.12–1.73 for BCSS). Its poor prognostic value was prominently valid in the luminal A (HR+ and HER2−) subtype for OS and BCSS with a hazard ratio of 1.44 (95% CI, 1.08–1.93) and of 1.47 (95% CI, 1.09–1.99) respectively, compared to those in the other subtypes. The hazard ratios of p53 over-expression for OS/BCSS were 1.27 (95% CI, 0.98–1.66)/1.26 (95% CI, 0.96–1.65), 1.25 (95% CI, 0.96–1.60)/1.21 (95% CI, 0.94–1.57), and 0.94 (95% CI, 0.73–1.20)/0.92 (95% CI, 0.71–1.18) in luminal B (HR+ and HER2−), HER2 over-expressing, and basal-like subtype, respectively. The model with interaction terms revealed that hormonal therapy has a significant interaction with p53 status (p = 0.002 and 0.007 for OS and BCSS, respectively), resulting in insignificant prognostic value of p53 status (p = 0.268 and 0.296 for OS and BCSS, respectively). The interaction between chemotherapy and p53 status was not found in this model.

Conclusions: Immunohistochemical p53 over-expression has an independent prognostic value, especially in luminal A invasive breast cancer, most likely caused by differential treatment benefits from hormonal therapy according to the immunohistochemical p53 status.

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Clinical Dilemmas in Bilateral Breast Cancer

S. Tang[1], M. Hartman[2], E. Yun[3], M. Sandberg[3], K.S. Chia[3], K. Czene[4], H.M. Verkooijen[5]. *[1]National University Hospital, Department of Surgery, Singapore, Singapore; [2]Yong Loo Lin School of Medicine National University of Singapore, Department of Surgery, Singapore, Singapore; [3]Yong Loo Lin School of Medicine National University of Singapore, Center for Molecular Epidemiology Department of Epidemiology and Public Health, Singapore, Singapore; [4]Karolinska Institute, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden; [5]Geneva University, Geneva Cancer Registry, Geneva, Switzerland*

Background: Women with breast cancer are at an increased risk of bilateral breast cancer(BBC), a disease with a relatively poor prognosis. This review aims to highlight clinical difficulties in treating women with

bilateral disease and how it can be used as a unique model to study breast cancer etiology and prognosis.

Methods: By reviewing etiological and outcome studies (n = 35) on bilateral cancer, we identify clinically unique features, fields of research interest and opportunities aimed at improving our understanding of breast cancer etiology, as well as prognosis of the bilateral breast cancer.

Results: Bilateral breast cancer(BBC) occurs in 2−11% of breast cancer patients. Multiple studies evaluating aetiological factors have identified a positive family history, lobular carcinoma, oestrogen receptor negativity, human epidermal growth factor receptor 2 (HER2) positivity and obesity (Body Mass Index of >25 kg/cm^2) as risk factors for metachronous BBC. Age has a contrasting effect on BBC, with increased synchronous tumours but decreased metachronous tumours with increasing age.

There is a strong hormone receptor concordance in BBC, with it being most pronounced in those with synchronous tumours. The identification of microsatellite instability in metachronous BBC suggests a possible relation to the adjuvant treatment of the initial primary breast cancer. Patients treated with adjuvant endocrine therapy after the first primary breast cancer appeared to have a protective effect against metachronous BBC, whilst those who received chemotherapy after the first breast cancer had a worse prognosis after the subsequent breast cancer.

Studies have shown a worse prognosis in those with BBC, particularly in those with synchronous tumours and a shorter time interval (<3 years) between the first and second primary breast cancers. However, the overall survival of metachronous BBC approximates that of unilateral breast cancers when the second primary breast cancer is diagnosed 10 or more years after the first breast cancer.

Conclusion: An ever increasing number of women are at risk of a bilateral cancer, a disease with high risk and relatively poor prognosis, yet our understanding of bilateral disease remains limited with virtually no data from clinical trials. Bilateral cancer offers a biological model to enhance our understanding of breast cancer etiology and outcome.

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Ki67 Proliferation Index in Invasive Lobular Carcinoma of the Breast − Clinicopathologic Correlation and Prognostic Significance

H. Wong[1], S. Lau[2], P. Cheung[3], R. Leung[1], J. Chiu[1], T.T. Wong[3], R. Liang[4], R.J. Epstein[5], T. Yau[1]. *[1]Queen Mary Hospital, Department of Medicine, Hong Kong, Hong Kong; [2]Hong Kong Sanatorium & Hospital, Medical Physics & Research Department, Hong Kong, Hong Kong; [3]Hong Kong Sanatorium & Hospital, Breast Care Centre, Hong Kong, Hong Kong; [4]Hong Kong Sanatorium & Hospital, Comprehensive Oncology Centre, Hong Kong, Hong Kong; [5]St. Vincent's Hospital, Department of Oncology, Sydney, Australia*

Background: Invasive lobular carcinoma (ILC) of the breast has distinct clinical and biological characteristics, including lower Ki67, when compared with invasive ductal carcinoma (IDC). Ki67 is an established independent negative prognosticator for disease-free survival and overall survival in IDC, although its role in ILC remains undefined due to lack of dedicated studies.

Material and Methods: We analyzed a consecutive cohort of ILC patients undergoing upfront surgery in a tertiary referral center in Hong Kong between August 2001 and August 2011; patients with pathology other than ILC, metastatic disease or neoadjuvant treatment were excluded. Tumor Ki67 levels were correlated with various clinicopathological parameters and recurrence outcomes. Univariate and multivariate regression analyses were also performed.

Results: A total of 144 patients were included in the analysis. All were female; median age was 50 (range 34−82). Higher Ki67 was significantly associated with higher tumor grade (Spearman correlation coefficient r = 0.2, p = 0.028), tumor size (r = 0.181, p = 0.047), lymphovascular infiltration (r = 0.218, p = 0.031) and lymph node involvement (r = 0.242, p = 0.005). However, there was no significant correlation between Ki67 level and ER, PR or HER2 status. Moreover, Ki67 failed to emerge as an independent predictor of recurrence on univariate and multivariate regression analyses.

Conclusion: In ILC, although high Ki67 correlated with poor-risk pathological features, it did not independently affect recurrence.

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Different Immunohistochemistry-based Subtypes of Early Invasive Breast Cancers in a Monoinstitutional Series: Correlation with Other Known Prognostic Factors, Different Clinical Behavior and Prognosis

A. Ferro[1], A. Caldara[1], R. Triolo[1], C. Eccher[2], M. Barbareschi[3], L.V. Cuorvo[3], F. Berloffa[4], M.C. Di Pasquale[1], E. Galligioni[1]. *[1]Santa Chiara Hospital, Medical Oncology, Trento, Italy; [2]E-Health, FBK, Trento, Italy; [3]Histopathology, S Chiara, Trento, Italy; [4]E-Health, FBK Fundation, Trento, Italy*

Background: Invasive breast cancer (IBC) is an heterogeneous disease. Gene expression profiling of invasive breast cancer (IBC) has identified several biologically distinct subtypes of IBCs. As proposed by Cheang et al, immunohistochemical (IHC) markers can be used as a surrogate for the molecular classification of breast cancers. Subtypes defined by IHC panel are similar to but not fully identical to intrinsic subtypes and represent a convenient approximation.

Purpose: The aim of our study was to evaluate different clinical behavior, relationship with other clinical-pathological features and survival outcomes for patients (pts) with different subtypes of IBC as classified using four ICH markers (ER, PR, HER2 and Ki67).

Methods: We evaluated data from 3403 cases of IBC treated from 1995 to 2008 classified as: luminal A (positive ER and PR, negative HER2 and Ki67 <14%), luminal B (positive ER and/or PR, negative HER2 and Ki67⩾14%), luminal C (positive ER and/or PR, positive HER2, any Ki67), HER2+ (negative ER and PR, positive HER2, any ki67), triple negative-TN (negative ER and PR, negative HER2, any ki67). Log-rank test and Cox regression model were performed to evaluate the impact of ICH subtypes on overall survival (OS), Event Free Survival (EFS) and their correlation with other known prognostic factors.

Results: We identified 917 (26.9%) luminal A, 1731 (50.9%) luminal B, 279 luminal C (8.2%), 183 (5.4%) HER2+ and 293 (8.6%) triple negative. Median age was 61 years. Luminal A was more frequently (p < 0.001) associated with older age, smaller size, negative axilla involvement, low grading. Observed events (relapses, contralateral and second tumors) were: 54 (6%) in luminal A, 215 (16%) in luminal B, 40 (14%) in luminal C, 42 (23%) in HER2+ and 59 (20%) in triple negative. Disease free interval (DFI) was shorter in luminal C, HER2 and TN (median DFI: 30, 26 and 19 months) than in Luminal A and B (median DFI: 51 and 41 month). Luminal A and B presented more bony and less visceral recurrences than luminal C, HER2 and triple negative tumors. At median follow up of 51 months EFS and OS (p < 0.001) were 94.1 and 95.3% in luminal A, 87.5 and 89% in luminal B, 85.5 and 89.2% in luminal C, 76.8 and 80.9% in HER2+, 79.7% and 81.9% in triple negative. Different subtypes EFS according to nodal status, grading, tumor size and age, were reported in table 1.

Table 1. Subtypes EFS by N, G, size and age

	Luminal A (%)	Luminal B (%)	Luminal C (%)	HER2+ (%)	Triple negative (%)	p
N0	95.5	91.5	92.8	86.2	88.7	0.007
N+	91.3	81.8	75.2	66.3	66.1	<0.001
G1	96.2	89.6	83.3	100.0	81.8	0.09
G2	92.6	89.5	87.4	81.5	83.7	0.195
G3	92.2	83.1	86.3	74.8	79.1	0.02
T1	95.6	91.5	90.7	81.6	86.8	<0.001
T2	88.9	83.4	79.3	72.5	75.9	0.013
T3−4	91.3	73.2	76.5	72.7	55.2	0.015
Age <40	90.5	75.9	75.9	57.9	83.3	0.013
Age 40−55	93.8	88.4	83.5	79.6	76.3	<0.001
Age >55	94.3	87.8	88.8	78.8	81.3	<0.001

Considering only luminal subtypes, Luminal B and C vs Luminal A IBCs were significantly associated with poor EFS in both N0 (p = 0.046) and N+ (p < 0.001), in T1 (p = 0.013) and T2 (p = 0.03), in patients older 40 years (p = 0.002).

Conclusions: IHC-based classification of IBC subtypes is useful for clinical management and it is superior to the WHO classification to define different prognostic groups.