386 Poster

Special histologic subtypes of estrogen receptor positive breast cancer by quantitative RT-PCR

F. Baehner[1,2], D. Watson[3], J. Anderson[1], C. Millward[1], I. Chen[5], G. Palmer[4], S. Shak[4]. *[1]Genomic Health, Pathology, Redwood City CA, USA; [2]University of California, Deparment of Pathology and Laboratory Medicine, San Francisco, USA; [3]Genomic Health, Department of Biostatistics, Redwood City CA, USA; [4]Genomic Health, Medical affairs, Redwood City CA, USA; [5]Genomic Health, Lab operations, Redwood City CA, USA*

Background: Invasive estrogen receptor positive (ER+) breast carcinoma is morphologically characterized by many histologic subtypes. Some special histologic subtypes have been reported to be prognostically significant (Rosen, 2009). We report here the histologic subtypes of estrogen receptor positive breast carcinoma and their associated patterns of observed gene expression as measured by the 21 quantitative gene Oncotype DX® assay.

Material and Methods: 100,000 tumor specimens successfully examined in the Genomic Health laboratory from July 2005 through May 2009 were included in these analyses. Academic surgical pathologists reviewed all specimens for invasive carcinoma and categorized them by histologic subtype using World Health Organization criteria (IARC 2003). Quantitative expression of 16 individual cancer related genes was measured on a scale from 0 to 15 (relative to reference genes), where a one unit increment is associated with a approximate 2-fold change in expression. Recurrence Score (RS) was calculated using the published equation (Paik et al, NEJM 2004). Descriptive statistics for the RS and the individual genes [estrogen receptor (ER), progesterone receptor (PR), HER2, invasion gene expression (IGE) and proliferation gene group (PGG): ki-67, cyclin b1, survivin, STK15, MYBL2] among the different subtypes were obtained.

Results: The vast majority of the cancers (94.3%) were ductal, lobular, or mixed. Using ductal carcinoma as the comparator, papillary carcinoma had the highest ER (10.9) and PR (9.2) with low IGE and lowest RS. Medullary-like tumors (4.6 per 1000 cases) had the lowest ER, negative PR, higher PGG and highest RS which may make them more responsive to chemotherapy. The RS, on average, was lower for the classic lobular, mixed ductal/lobular, solid/alveolar lobular, tubular, cribriform, mucinous, and papillary subtypes. The special histologic subtypes (tubular, cribriform, mucinous) were characterized by higher PR, lower IGE, lower PGG and higher ER (except for tubular carcinoma that may reflect bias in submission for RS testing).

Conclusion: Histologic subtypes are characterized by differential gene expression profiles. The special subtypes of invasive breast cancer tend to have higher ER, PR and lower proliferation and invasion gene expression; however, outlier cases are not infrequent within each of the special subtypes of invasive breast cancer in this large observational cohort of estrogen receptor positive tumors.

387 Poster

Frequency of low ER-positive tumors by RT-PCR in patients with low recurrence scores in Europe and Middle East

F. Baehner[1,2], C. Yoshizawa[3], G. Palmer[4]. *[1]Genomic Health, Pathology, Redwood City CA, USA; [2]University of California, Deparment of Pathology and Laboratory Medicine, San Francisco, USA; [3]Genomic Health, Department of Biostatistics, Redwood City CA, USA; [4]Genomic Health, Medical affairs, Redwood City CA, USA*

Background: The Recurrence Score (RS), derived from the quantitative RT-PCR analysis of 21 individual genes, has been shown to quantify the likelihood of distant recurrence and of chemotherapy benefit in hormone-treated patients with estrogen receptor (ER)-positive breast cancer. We examined the frequency of low Recurrence Scores (<18) in the lowest quartile of ER-positive expressing samples submitted for Onco*type* DX® testing in Europe and Middle East (EME).

Material and Methods: Since January 2008, a quantitative ER value has been provided with all RS results. Tumor specimens submitted by EME physicians that were successfully examined in the Genomic Health laboratory from February 2008 through October 2009 were eligible. Quantitative expression of 16 individual cancer related genes was measured by the pre-specified 21 gene Recurrence Score assay on a scale from 2 to 15 (relative to reference genes), where a one unit increment is associated with an approximate 2-fold change in expression. ER status by RT-PCR (with ER positivity prespecified as $\geqslant$6.5) has been shown to be highly concordant with ER by Central IHC (93% in Badve et al, JCO, 2009; 96% in Habel, ASCO Breast 2007). For the ER pos tumors by RT-PCR, the RS by risk group was analyzed by quantitative ER by quartiles.

Results: 2,645 tumors were eligible for analysis. 29 cases were excluded from the analysis because they were ER-neg by RT-PCR, leaving 2,616 evaluable tumors. The distribution of quantitative ER by quartiles for the low (<18), intermediate (18−30), and high ($\geqslant$31) RS groups is shown in the Table. Of the 652 samples in the lowest ER-pos quartile, ER values ranged from 6.5−9.1 and 31.9% of these low ER-pos expressing tumors had RS < 18.

Er					RS group		
Quartile	Min	Max	Average	Number	Low	Intermediate	High
1	6.5	9.1	8.5	652	31.9%	54.3%	13.8%
2	9.2	9.9	9.6	653	55.4%	35.4%	9.2%
3	10	10.7	10.3	684	65.1%	26.6%	8.3%
4	10.8	12.5	11.4	627	69.4%	21.5%	9.1%

Conclusion: Many low ER-pos expressing tumors have low Recurrence Scores. However, patients with a RS < 18 have been shown to have a good prognosis and minimal, if any, chemotherapy benefit. (Paik et al., JCO, 2006; Albain et al., SABCS 2007). The Recurrence Score incorporates other important biological pathways beyond ER that provide additional clinically meaningful information.

388 Poster

Ductal carcinoma in situ of the breast: interobserver reproducibility of three classification schemes

F. Schuh[1], J.V. Biazús[1], E. Resetkova[2], C.Z. Benfica[3], M.I.A. Edelweiss[4]. *[1]Hospital de Clínicas de Porto Alegre (HCPA), Breast Unit, Porto Alegre, Brazil; [2]The University of Texas, MD Anderson Cancer Center, Houston, USA; [3]Universidade Federal de Ciências da Saúde de Porto Alegre, Faculdade de Medicina, Porto Alegre, Brazil; [4]Hospital de Clínicas de Porto Alegre (HCPA), Pathology Unit, Porto Alegre, Brazil*

Background: Several systems have been proposed for the classification of ductal carcinoma in situ of the breast (DCIS). The objective of the study is to determine the degree of diagnostic agreement among pathologists between three DCIS classification systems.

Material and Methods: 43 cases with a diagnosis of DCIS were reviewed by two pathologists and selected for interobserver analysis. Thirteen pathologists, one of them a specialist in breast pathology, received the same set of digitized images of microscopy of the DCIS cases in JPG format, and answered a questionnaire containing the criteria to compose the three classification systems studied − Holland, modified Lagios and Van Nuys. For this purpose a computer program was created, which organizes the information collected from each pathologist, supplying the histological grading of the cases for the three classification systems. The results were analyzed using percentagewise agreement and the Kappa test.

Results: Diagnostic agreement for the three DCIS of the breast classification systems presented K values that varied from 0.27 to 0.37. Among the three classifications studied the best agreement was for Van Nuys, showing a Kappa index of 0.37. Analysis of subgroups of pathologists showed that there was greater diagnostic reproducibility for the group of specialists compared to the group of pathology residents for the Van Nuys and modified Lagios systems ($p = 0.005$ and 0.023, respectively). The accuracy similarly accompanied the results of the interobserver agreements, with Kappa indices varying from 0.13 to 0.64 for the Holland classification, 0.23 to 0.61 for the modified Lagios classification, and 0.23 to 0.74 for the Van Nuys classification.

Conclusion: Comparing the three classification systems, better agreement was obtained for the histological grade with the Van Nuys scheme. Pathologists specialized in breast pathology showed greater reproducibility for all the criteria evaluated. Diagnostic accuracy was superior for the classification of Van Nuys compared to modified Lagios and Holland.

389 Poster

Reasons for over- and underestimation of lymphatic vessel invasion in breast cancer

I. Ivanov[1], S. Popovska[1], T. Betova[1], G. Baitchev[2]. *[1]MU-Pleven, Department of General and Clinical Pathology, Pleven, Bulgaria; [2]Military Medical Academy, Clinic of Thoracic Surgery, Sofia, Bulgaria*

Background: Lymph vessel invasion (LVI) can be decisive for treatment and prognosis of breast cancer patients but often it is over- or underestimated in the routine practice.

Aim of our study was to establish the reasons leading to over- or underestimation of LVI in breast cancer, which occur in the routine practice and to create a reliable and applicable protocol for its appropriate evaluation.