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Molecular Breast Cancer Subtypes: Relationship With Angiogenesis Genes Polymorphism, Efficacy of Neoadjuvant Chemotherapy and Survival

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Background: Breast cancer heterogeneity suggests that specific molecular subtypes will have distinct biological characteristics and clinical behavior. The purpose of this study was to analyze the polymorphisms of angiogenesis genes and their impact on the response to treatment and outcome of breast cancer patients according to molecular cancer subtypes.
Material and Methods: Our subjects comprised 272 breast cancer patients who received 2−4 cycles of neoadjuvant chemotherapy in the Tomsk Cancer Research Institute. The patients were classified into two subtypes: triple negative (TN) and non-TN. The VEGF-2578C/A (rs699947), FGFR2A/G (rs1219648) and TGFB1–509C>T (rs1800469) TGFB1−29T>C (rs1982073) genotypes were determined by polymerase chain reaction and restriction fragment length polymorphism method.
Results: A marginal trend towards significant association of TGFB1–29(CT/TT) genotypes with positive lymph nodes status was found among non-TN patients compared to TN cases (P = 0.057). In addition, we observed that this non-TN group with TGFB1−29 (CT/TT) genotypes tended to have shorter overall survival after neoadjuvant chemotherapy than TN patients (P = 0.08). A similar pattern was found between non-TN and TN patients carrying VEGF-2578 (CC) genotype (P = 0.08). However, the survival curves of wildtype VEGF genotype patients were very similar between the non-TN and TN groups (P = 0.18). Overall survival of women with the TGFB1–509 (CT/TT) genotypes was significantly worse than for TGFB1–509 (CC) carriers independent of patients molecular subtype (P = 0.009). Only TN women carrying FGFR2 (AA) genotype showed an association with better response to neoadjuvant chemotherapy in comparison non-TN (P = 0.02). In the logistic regression analysis, the FGFR2A/G genotype and molecular subtypes were the independent factors that predicted the probability of pathological regression (P = 0.013).
Conclusion: Our study indicates that the analysis of angiogenesis-related gene polymorphisms may help to identify patient subgroups at high risk for the progression of breast cancer. FGFR2A/G may be considered as a prognostic factor for efficacy to neoadjuvant chemotherapy in TN patients.

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Immunohistochemical Profiling of Signalling Pathways in Cancer of Unknown Primary (CUP)

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Background: The molecular biology of Cancer of Unknown Primary (CUP) has not been studied, resulting in a lack of candidate biomolecules for therapeutic targeting.
Methods: 15 mm tissue cores from 100 CUP tumours were loaded in tissue microarrays in duplicate and studied for immunohistochemical (IHC) expression of transmembrane receptors and associated ligands (Notch1, 2, 3, Jagged1, cMET), signal transducers and regulators (PTEN, phosphoAKT1, 2, 3 at Thr308, phospho-p44/42 MAPK at Thr202/Tyr204), cell cycle controllers (Cyclin D1, p21), effectors of protein synthesis (phospho-S6Rp at Ser235/236). The percentage of staining tumour cells was recorded and IHC cut-off values were based on distributional analyses and the medical literature. Complete clinicopathologic and management data were electronically recorded for analysis. Cox regression and Breslow testing were applied for prognostic analysis.
Results: The study population consisted of 100 patients with CUP (47 males, 53 females), of a median age of 65 and fit performance status (PS 0−1 in 75%). Histological diagnosis was adenocarcinoma in 60%, squamous ca in 22% and undifferentiated carcinoma in 17% of cases, with high grade seen in 50% of CUP. The clinicopathologic subgroups were visceral 30%, axillary nodal 8%, peritoneal carcinomatosis 22%, nodal disease 40%. Therapy consisted of palliative chemotherapy (platinum-based combination regimens in 55%). The median progression-free survival and overall survival (OS) were 7 and 12 months respectively. Biomolecules with frequent expression or activation (median % of staining tumour cells across all cases) were Notch3 (95%), p44/42 MAPK (52%), PTEN (60%), pS6Rp (72%), pAKT1/2/3 (97%). At univariate analysis, high IHC tumoural expression of p44/42 MAPK Thr202/Tyr204, pAKT Thr308, pS6Rp Ser235/236 and low cMET were associated with adverse outcome (Table 1). In fact, the adverse prognostic impact was enhanced in tumours with concurrent high IHC expression of both p44/42 MAPK Thr202/Tyr204 and pAKT Thr308. In multivariate analysis, high p21 and high cMET IHC tumoural expression were associated with reduced risk of death (RR of death 0.34, p = 0.005 for p21, RR 0.48, p = 0.025 for cMET), while high expression of pAKT Thr308 (RR 2.39, p = 0.01) and high expression of pS6Rp Ser235/236 (RR 2.76, p = 0.008) were linked to increased risk.
Conclusions: The major intracellular AKT and MAPK axes are frequently activated in CUP and carry adverse prognostic significance. Further findings incriminate the AKT axis, activating pS6Rp and inhibiting the tumour suppressor p21, as biologically important and worth exploration for therapeutic targeting.

Table 1. Biomolecules with significant prognostic utility in CUP

Biomolecule	IHC cut-off	Median OS (months)	95% CI	Breslow P
cMET	⩾20% <20%	15 9	9.1–20.9 4.5–13.5	0.05
phospho p44/42 MAPK Thr202/Tyr20	⩾40% <40%	9 17	3.7–14.3 10−24	0.016
phospho AKT1,2,3 Thr308	⩾85% <85%	11 15	7.3–14.7 8.7–21.2	0.047
Both p44/42 MAPK and pAKT positive	yes no	8 17	5.2–10.7 13.1–20.8	0.001
phospho S6Rp Ser235/236	⩾60% <60%	9 17	6−12 8−26	0.03

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Breast Cancer Molecular Subtypes in Omani Patients: Correlation With Age, Histology, Stage Distribution and Outcome − an Anaylsis of 542 Cases

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Background: Breast cancer is the commonest malignancy and a major health issue globally. There is initial evidence and high possibility of molecular differences across the ethnic and geographic groups. This may be responsible for variation in presentation, responses to treatment, and outcome.
Patients and Methods: Breast cancer data from 2006–2010 at National Oncology Center − The Royal Hospital Oman was retrospectively retrieved from electronic patient record system. It was analyzed with respect to ER, PR, and Her-2 status and tumours were classified on molecular basis. Molecular subtypes with correlated with age, histology, and treatment out come. The results were compared with published international and regional data.

Parameter	Study			
	Southern Switzerland (Ticino)	The Polish Breast Cancer Study	The Carolina Breast Cancer Study	National Oncology Center Royal Hospital, Oman
No. of patients/IHC markers done	1214 (91%)	804 (34%)	496 (43%)	452 (100%)
Time period	2003–2007	2000–2003	1993–1996	2006–2010
Age	All ages	20−74 years	20−74 years	All ages
Race	Caucasian	Caucasian	African and Non-African Americans	Omani
Luminal A	73.2%	69%	54.8%	34.7%
Luminal B	13.8%	6.0%	16.6%	15.9%
Her2 +ve	5.6%	12.0%	7.1%	24.1%
BCL (TNBC)	7.4%	8.0%	21.5%	25.3%

Results: A total of 542 cases were available for evaluation (7 male and 535 female: 452 Omani and 83 Non-Omani). Right, Left, and bilateral tumours were 42.6%, 51.4% and 6%. IDC were 79.6%. G1 were 7.7%, while other grades were equally distributed. Luminal A, Luminal B, Basal like (TNBC), and Her-2 positive were 35.9%, 15.8%, 25.5% and 22.8% respectively.