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EXPRESSION OF p53 IN HUMAN BREAST CANCER

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Introduction: p53 is one of the most intriguing potential factors implicated in the metastatic process. It directly controls the transcription of genes responsible for cell adhesion, motility, invasion and anoikis. The wild-type p53 tumor suppressor protein acts in G1 cell cycle and in response to DNA damage promotes repairing or cell death. Immunohistochemically this protein is not expressed in normal breast, due to its short time of action. Loss of its function was associated with poor outcome in breast cancer.

The aim of present research was to highlight p53 expression in invasive breast carcinoma of no special type (NST) and evaluate its role in stratifying patients from molecular classification position. As a result most of p53 positive cases were related to Luminal B subtype.

Materials and Methods: Tumors from 84 patients, paraffin embedded as traditionally were immunohistochemically stained for estrogen receptor (clone Er/6F11), progesterone receptor (clone Pr16), human epidermal growth factor receptor-2 (HER2/polyclonal), basal cytokeratin CK5 (clone XM26), nuclear proteins Ki67 (clone K2) and p53 (p53/DO-7). In all cases a Madden modified radical mastectomy was used. The hematoxylin solution, Harris modified (HHS32, SigmaAldrich) was used for counterstaining.

The hormone receptors were scored as the percentage of nuclear positively stained cells from at least 1000 cells assessed. Was followed the guidelines of ER and PR assessment purposed by Allred *et al.*^[1] Cases scored +1 to +3 were considered positive. The threshold of positivity was 10%. The HER2 status was interpreted according American Society of Clinical Oncology recommendations and cases evaluated as +2 and +3 were considered positive^[2]. Tumors were evaluated also by FISH as international rules recommend (PathVysion HER-2 DNA Probe Kit II, Abbot). Ki67, as well hormone receptors were counted by the semi-quantitative method performed by Suciu *et al.*^[3]. A 14% threshold was used for Ki67 positivity.

The CK5 expression was interpreted in accordance with Azoulay *et al.* recommendations, as follow: 0 – no tumor cells stained; +1 – fewer than 10% of tumor cells stained; +2 – 10-50% positive tumor cells; +3 – >50% of tumor cells stained [4]. Cases evaluated as +1 to +3 were considered positive.

The p53 was assessed in Yamashita *et al.* manner: **0** – no specific staining; **+1** – less of 10% tumor cells are p53 positive; **+2** – 10-30% of cells express p53; **3** – more than 30% exhibit a specific nuclear pattern^[5].

Molecular subtypes were clustered as Goldhirsch *et al.* recommended^[6].

Results. Tumors were clustered by histological grade as: G1 in 6%/5 cases, G2 found in 45 cases (53.6%) and G3 in 40.5%/34 cases.

The p53 positive expression was clustered by tumors' grade of differentiation as: 1 case/ 1.2% with G1, 29 cases/34.5% with G2, 21 cases/25% with G3. The p53 expression was determined positive in majority of NST tumors – 51 cases/60.7%. Tumors were considered ER⁺ in 68 cases/81%, PR⁺ in 58 cases/69%, HER2⁺ in 18 cases/21.4% and CK5⁺ in 11 cases/13.1%.

ER⁺ tumors in 40 cases/47.6% were considered p53 positive too. PR⁺ cells in 33 cases/39.3% coexpressed p53, HER2⁺ tumors exhibited p53 in 15 cases/17.9% and CK5-p53 coexpression was described in 7 cases/8.3%.

Ki67 was considered positive (≥ 14) in 50 cases/59.52% of tumors. The negative p53 expression was supported in 12 cases/14.3% by a high proliferation rate and in 21 cases/25% by a Ki67 level less than 14. The positive p53 cases were a highly proliferating in 45.2% (38 cases) and low proliferating in 15.5% (13 cases).

The most often developed subtype by tumors was Luminal B (8 cases/9.5% of Luminal B/HER2 and 37 cases/44% of Luminal B/Ki67), followed by Luminal A (26 cases/31%) and hormone-negative group (HER2⁺ with 8 cases/9.5% and triple-negative subtype in 5 cases/6%). The positive p53 marker had the highest expression in Luminal B/Ki67 group (27 cases/32.1%), followed in diminution by Luminal A (9 cases/10.7%), Luminal B/HER2 (7 cases/8.3%), HER2 (5 cases/6%) and triple-negative (3 cases/3.6%).

The p53 regulates cell proliferation and is considered the “guardian” of genome stability. By several transcription-regulating functions, including the induction of G1 cell cycle arrest by activation of p21 and by down-regulation of BCL2 it induces the apoptosis in response to irreparable DNA damage. Due to its short life the p53 protein is not detected immunohistochemically in normal tissues.

The TP53 gene, which is encoding p53 protein, is considered as the most frequently (more than 50%) mutated gene in human cancers. In case of breast cancers about one-third of cases have mutations in the TP53 gene, which are associated with high histological grade and clinical aggressiveness. In the present study have been described a higher (51 cases/60.7%) expression of p53 by NST carcinomas.

Most of TP53 alterations found in breast carcinomas are point mutations leading to the synthesis of a stable, mal-functional, and non-degradable protein that accumulates in tumor cells. The result of these mutations is detected by immunohistochemical assays as a nuclear accumulation of the protein.

By Yamashita *et al.* the expression of p53 is associated with a poor prognosis in breast cancer^[5]. The authors determined a significant correlation of p53 with HER2 and Ki67 level, in detriment of overall survival. Our study confirms the positive association of p53 expression with the proliferation activity of tumors, Ki67 measured.

Silwal-Pandit *et al.* demonstrated that TP53 mutations have a different clinical relevance in molecular subtypes of breast cancer and suggest diverse roles for TP53 in the biology of breast cancer development^[7]. TP53 mutations were associated with increased mortality of patients with Luminal B, HER2-enriched and Normal-like tumors, but not in case of patients with Luminal A and Basal-like tumors. Plus, the presence of p53 was found to be an independent marker of poor prognosis in estrogen receptor-positive cases. Unfortunately, in the present study the majority of p53 positive expressions were related to Luminal B tumors.

Breast carcinomas of no special type prefer to express p53 protein. p53 positive tumors are highly proliferative one and like to coexpress ER, PR receptors. Most of p53 positive carcinomas have a Luminal B signature.

References:

1. Allred D.C., Harvey J.M., Berardo M., Clark G.M. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod. Pathol.* 1998; 11:155-168.
2. Wolff A.C., Hammond M.E., Hicks D.G. et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. *J. Clin. Oncol.* 2013; 31(31):3997-4013.

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3. Suciú C, Muresan AM, Cornea R. et al. Semiautomated evaluation of Ki67 index in invasive ductal carcinoma of the breast. *Oncol Lett.* 2014; 7:107-114.
 4. Azoulay S., Laé M., Fréneaux P., Merle S. et al. KIT is highly expressed in adenoid cystic carcinoma of the breast, a basal-like carcinoma associated with a favorable outcome. *Mod. Pathol.* 2005; 18(12):1623-31.
 5. Yamashita H., Nishio M., Toyama T. et al. Coexistence of HER2 over-expression and p53 protein accumulation is a strong prognostic molecular marker in breast cancer. *Breast Cancer Res.* 2004; 6:R24-30.
 6. Goldhirsch A., Winer E.P., Coates A.S., Gelber R.D. et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer. *Ann Oncol.* 2013;24(9):2206-23.
 7. Silwal-Pandit L., Vollan H.K., Chin S.F., Rueda O.M., McKinney S., Osako T. et al. TP53 mutation spectrum in breast cancer is subtype specific and has distinct prognostic relevance. *Clin Cancer Res.* 2014;20(13):3569-80.
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