Biological markers and response to adjuvant radiotherapy in breast cancer

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ABSTRACT

The purposes of this PhD dissertation were to update a subgroup of patients from the DBCG82 B&C studies to present standards with hormonal receptors (estrogen receptor (ER) and progesterone receptor (PgR)) and HER2 receptor and furthermore to examine the importance of different experimental biological markers not used routinely.

Tissue microarrays (TMA's) were constructed for 1000 out of the 3083 high-risk breast cancer patients randomized to receive either post-mastectomy radiotherapy and systemic therapy or systemic therapy alone in the period 1982-1989. Immunohistochemical stainings for ER, PgR, HER2, carbonic anhydrase IX (CA-IX), BCL2 and p53 were made.

Patients with hormonal receptor negative, HER2 positive and/or BCL2 negative tumors had a significantly poorer survival. Patients with these poor biological prognostic criteria did not experience a significant survival improvement after post-mastectomy radiotherapy, despite a significant reduction in locoregional recurrence probability. A significant survival improvement after post-mastectomy radiotherapy was restricted to patients with good biological prognostic criteria, such as hormonal receptor positive, HER2 negative, and/or BCL2 positive tumors. Furthermore, despite significant survival improvements after post-mastectomy radiotherapy for patients with poor prognostic clinicopathological criteria such as many positive lymph nodes, large tumor size, and high malignancy grade, the survival improvement disappeared when the subgroups were confined to patients with even more aggressive disease characterized by two or three poor prognostic clinicopathological criteria.

The results above could be explained if the spectrum hypothesis by Samuel Hellman explains the natural history of the breast cancer disease most correctly. The spectrum hypothesis suggests that breast cancer is a heterogeneous disease covering a large spectrum of diseases from tumors destined to remain localized, to tumors with the potential to metastasize but without distant micrometastases at time of diagnosis and to tumors always presenting with at least aggressive distant micrometastases not responding to the systemic therapy applied. Patients in this last subgroup will due to the aggressiveness and extent of the disease, despite significant reductions in locoregional recurrence probability after locally applied radiotherapy, not be subjected to a survival improvement after radiotherapy.