Benefit of the 70-gene profile for widely used guidelines: an answer to increased selection for adjuvant chemotherapy in breast cancer

Michael Knauer MD DSc1, V Retèl MD, PhD,2 LJ van ‘t Veer PhD1, and SC Linn MD, PhD3
1: Netherlands Cancer Institute, 2: Academic Medical Center and 3: Agenda BV, Amsterdam, Netherlands

Abstract

The New Dutch Guidelines

Introduction:
Risk assessment for breast cancer patients differs substantially among treatment guidelines. The National Comprehensive Cancer Network (NCCN), St. Gallen, AdjuvantOnline, and Dutch 2008 guidelines are less restrictive in comparison to the 2004 Dutch guidelines and Nottingham Prognostic Index, when selecting patients for adjuvant systemic treatment. The Dutch Institute for Healthcare Improvement (CBO) has introduced slight changes in the concept 2008 guidelines. Adjuvant systemic treatment is only advised when the absolute 10-year survival benefit is 5% or more. The new recommendations for adjuvant systemic treatment are based on survival tables used in the Adjuvant! software. The changes affect only node-negative patients aged >35 years: since 2004 patients with G2/G3 tumors >1cm or every tumor >2cm are advised to undergo adjuvant systemic therapy, while in 2004 this was the case for tumors G2/G3, G2/G3 or every tumor >3cm.

Patients and Methods:
Risk was assessed for 427 lymph node negative patients in the prospective RASTER-study (Bueno-de-Mesquita et al, 2007), that was performed between 2004 and 2006 in 16 community-based hospitals in the Netherlands as well as for the 151 lymph node negative patients in the NEJM-series (van de Vijver et al, 2002). Clinical risk was calculated using the 2004 and 2008 Dutch guidelines as well as the present St.Gallen guidelines and the Nottingham Prognostic Index. Genetic risk was assigned according to the result of the Amsterdam 70-gene signature (MammaPrint®). Survival analyses were done according to the Kaplan-Meier method. Discordance was measured by Cohen’s kappa coefficient and significance for discordance interpreted by the Landsis-Koch method (5).

Results:
Instead of 57% in 2004, in 2008 only 24% of patients were assigned to clinical low risk in the RASTER-study population, and 141 patients (33%) changed from low to high risk (p<0.001) with a κ=0.385, suggesting only fair agreement between the guidelines. The discordance of finding discordances between clinical assessment and 70-gene signature increased from 30% in 2004 to 41% in 2008 (p<0.001). Details for NPI and St.Gallen guidelines are shown in table 1. Similar results were obtained for the 151 patients of the NEJM-series: The proportion of patients assigned to clinical low risk was halved from 43% to 19% in the 2008 guidelines. With κ=0.48, suggesting moderate agreement, 36 patients changed from low risk to high risk in 2008. The discordance between the 70-gene signature and the 2004 and 2008 CBO guidelines changed from 30% to 35% in 2008 respectively, with κ falling from 0.386 to 0.196, suggesting now only slight agreement. At 10 years FU, differences between the high and low risk categories according to the 2004, 2008, St.Gallen guidelines and the 70-gene profile, were best predicted by the latter: distant disease-free survival (DDFS) log-rank p=0.002, p=0.11, p=0.12 and p=0.001 respectively.

Discussion:
As adjuvant systemic treatments become more effective, guidelines become less restrictive, resulting in more patients being selected for adjuvant therapy. Since newer treatment guidelines do not better predict survival, the magnitude of the 70-gene profile’s benefit, which is defined as proportion of patients in whom overtreatment and undertreatment can be avoided, depends on present guidelines for risk assessment and shows a remarkable increase.

Introducción: Transmisión de las guías médicas: un estudio comparativo en pacientes con cáncer de mama.

En este trabajo se analizan las guías de tratamiento para pacientes con cáncer de mama en conjunto con el perfil genético de 70 genes. Se comparan las guías con el objetivo de evaluar la concordancia entre ellas y su efectividad en la selección de pacientes para tratamiento adyuvante.

Nótes:
1. Remite al software Adjuvant! para la determinación de riesgo en pacientes con cáncer de mama.
2. Remite al índice de pronóstico de Nottingham para el análisis de riesgo en pacientes con cáncer de mama.
3. Remite a la guía de la Organización Médica Internacional (OMS) para la selección de pacientes para tratamiento adyuvante.
4. Remite a la guía de la Sociedad Neerlandesa de Oncología (NCON) para la selección de pacientes para tratamiento adyuvante.
5. Remite al índice de pronóstico de las guías de la Organización Médica Internacional (OMS) para la selección de pacientes para tratamiento adyuvante.

Conclusion: The magnitude of the 70-gene profile benefit, which is defined as proportion of patients in whom overtreatment and undertreatment can be avoided, depends on present guidelines for risk assessment and shows a remarkable increase.