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Inter-observer variation in pathological review and its impact on clinicopathological risk assessment and patient selection for adjuvant systemic treatment in node-negative breast cancer patients

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Introduction: The aim of this study was to assess the effect of inter-observer variation in pathological examination of node-negative breast carcinomas on clinical risk assessment and the selection of patients for adjuvant systemic treatment.

Methods: In a retrospective multicenter study, the clinical and pathological data of 708 patients of 2 consecutive patient series were analysed: 123 patients of a validation study (Bueno-de-Mesquita, EurJCancerSuppl 2006) and 585 patients of the RASTER study (Bueno-de-Mesquita, Lancet Oncology 2007). Patients (<61 years) had primary unilateral breast cancer (T1−4N0M0); patients with prior malignancies were excluded. Tumour size and histologic grade were assessed locally; central review was performed at the Netherlands Cancer Institute (Amsterdam, the Netherlands). Clinicopathological low or high risk was assessed using national Dutch (CBO) guidelines and the Adjuvant Online program (www.adjuvantonline.com). Patients with a 'low' risk were deemed to have a good prognosis and, therefore, could be spared adjuvant systemic treatment. A low clinical risk based on the Adjuvant Online program was defined as patients with a 10-years survival probability of at least 90%.

Results: The original pathological examination was discordant with the central review for histologic grade in 28% (196/690) of patients (kappa 0.56; missing 18) and for oestrogen receptor in 5% (33/686) patients (kappa 0.85; missing 22). Translation into clinical Dutch CBO risk based on these pathological evaluations was discordant in 15% (102/690) of patients (kappa 0.70; missing 18). Clinical CBO risk based on centrally reviewed data would change high risk into low risk in 9% (61/690) of patients and no adjuvant systemic treatment would have been advised in these patients. Vice versa, 6% (41/690) of these patients would change from clinical CBO low risk to high risk based on the reviewed data and adjuvant systemic treatment would be advised. If Adjuvant Online was used, 8% (55/691) of patients (kappa 0.82; missing 17) would have been given a different clinical risk and adjuvant systemic treatment advice (5% (32/691) high to low risk, and 3% (23/691) low to high risk).

Conclusion: Inter-observer variation in pathological examination of breast carcinomas results in significant differences in clinicopathological risk assessment and adjuvant systemic treatment advice. Dutch CBO guidelines were more sensitive to inter-observer variation than Adjuvant Online.

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Interlaboratory variation in the results of Her2 testing in a population-based series of breast cancer patients

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Introduction: Accurate determination of Her2 receptor status is critical in the selection of breast cancer patients for Her2 targeted therapy. Quality control can be achieved by adhering to good laboratory practice and participating in external quality control programs. The proportion of patients with HER2 overexpression can be used as an additional quality indicator, provided that a suitable benchmark is available to control for differences in patient profiles. In this study, we investigated interlaboratory variation in the prevalence of Her2 positive breast cancers and developed a multivariable model to control for differences in patient-mix.

Patients and Methods: The Rotterdam Cancer Registry covers the southwestern part of the Netherlands, a region with 2.4 million inhabitants, 16 hospitals and 8 Pathology Laboratories. From the registry, we selected patients diagnosed with invasive breast cancer in 2005, in whom Her2 receptor status was determined. Other relevant clinical and pathologic findings were abstracted from the medical files. Determinants of the prevalence of positive HER2 results were analyzed both univariable (chi-square statistics) and multivariable (logistic regression analysis) and significant variables ($p < 0.05$) were used to develop a case-mix model. This model was then applied to analyze results by Pathology Laboratory, controlling for variation in case-mix. Confidence intervals (95% CI) were calculated as exact intervals for binomial proportions.

Results: The study population consisted of 894 patients of whom 168 (19%) were diagnosed with Her2 overexpression. Correlates of Her2 overexpression were non lobular tumour type, younger age at diagnosis, higher grade tumours, negative hormonal receptor status, local and regional metastasis at diagnosis and being diagnosed in the second half of 2005. Standardized prevalence rates varied between laboratories from 6% to 40%, which is equivalent to risk ratios ranging from 0.4 to 1.6, as compared to the mean.

Conclusion: Due to the association between traditional prognostic factors and Her2 overexpression, the actual prevalence is dependent on selection criteria for testing. Because selection criteria may differ between physicians, hospitals and laboratories, multivariable analysis is needed to study variation between Pathology Laboratories. A case-mix model can be used to derive a standardized prevalence. Even after controlling for case-mix, considerable variation between Laboratories was observed. This observation highlights the importance of quality control measures to improve the performance of staining and scoring of tumour material.

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Prediction of prognosis by lymph node ratio of involved axillary lymph nodes to the total number of removed lymph nodes in early stage breast cancer

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Background: Axillary lymph node involvement is a major determinant of stage, prognosis, and adjuvant systemic and radiation therapy in primary breast cancer. The absolute number of positive lymph nodes affects the prognosis and choice of systemic therapy and radiation therapy. However, the total number of LN removed is variable. We investigated the role of lymph node ratio (LNR, the ratio of the number of lymph nodes involved by tumor to the total number of removed lymph nodes) for predicting prognosis in early stage breast cancer.

Materials and Methods: We reviewed the medical records and pathology of patients with early stages (I and II) breast cancer treated at the American University of Beirut Medical Center (AUBMC) between 1990 and 2003.

Results: Out of a total of 1,254 patients, 877 were stages I and II. 52% were below age 50 years and 48% were above 50 years. 73% had modified radical mastectomy (MRM) and 27% had breast conserving surgery (BCS). 182 patients were stage I and 754 patients were stage II. 73.5% of stage II patients had positive axillary lymph nodes (LN). 51% of those patients had 1−3 positive LN, 33% had 4−9 LN and 16% had 10 or more positive LN. Of 877 patients who had lymph nodes examined (includes those who had sentinel lymph node biopsy (SLNB)), the median number of LN removed was 17 (Range 1−46). The average ratio of LN positive to LN removed was 0.6. 83.5% of patients had less than 0.6 LNR positive and 16.5% had more than 0.6 LNR positive. Factors that were associated with negative impact on survival included positive lymph nodes, negative hormone receptor status, and presence of lymphatic invasion. Kaplan–Meier analysis showed that patients with LN ratio over 0.6 versus patients with LN ratio below 0.6 had overall survival of 70% vs 88% at 5 years, 22% versus 77% at 10 years, and 22% versus 77% at 150 months, respectively. We assessed LNR using smaller ratio of 0.2 and this LNR of 0.2 was also predictive of survival. The 10-year survival of patients with LNR $\leqslant 0.2$ was 72% compared to 51% for those with LNR > 0.2.

Conclusions: LNR of number of positive axillary lymph nodes over total number of removed lymph nodes over 0.6, as well as LNR over 0.2, predicts worse survival in early stage breast cancer. LNR may be an important tool in patients with lower numbers of dissected axillary LN.

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Microtubule-associated protein tau is a marker of pathological complete response in Her-2/neu positive neoadjuvant treated breast cancer patients

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Background: Tau protein promotes tubulin polymerization and stabilizes microtubules. Microarray analysis of fresh breast cancer tissues revealed,