Annals of Oncology Advance Access published May 27, 2015

original article

Annals of Oncology 00: 1–7, 2015
doi:10.1093/annonc/mdv215

Identifying clinically relevant prognostic subgroups of postmenopausal women with node-positive hormone receptor-positive early-stage breast cancer treated with endocrine therapy: a combined analysis of ABCSG-8 and ATAC using the PAM50 risk of recurrence score and intrinsic subtype

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Received 19 November 2014; revised 10 April 2015; accepted 24 April 2015

Background: In the adjuvant treatment of hormone receptor-positive (HR+) breast cancer, variables like tumour size, grade and nodal status have great impact on therapy decisions. As most node-positive patients with HR+ breast cancer currently receive adjuvant chemotherapy improved methods for characterization of individuals' metastasis risk are needed to reduce overtreatment.

Patients and methods: Tissue specimens from node-positive patients of the ABCSG-8 and ATAC trials who received adjuvant tamoxifen and/or anastrozole were included in this study. Analysing RNA from paraffin blocks using the PAM50 test, the primary objective was to evaluate the prognostic information of the risk of recurrence (ROR) score added to combined clinical standard variables in patients with one positive node (1N+) and in patients with two or three positive nodes (2–3N+), using log-likelihood ratio tests.

Results: At a median follow-up of 9.6 years, distant metastases occurred in 97 (18%) of 543 node-positive patients. In a multivariate analysis, the PAM50-derived ROR score provided reliable prognostic information in addition to and beyond established clinical factors for 1N+ ($P < 0.0001$) and 2–3N+ patients ($P = 0.0002$). Ten-year distant recurrence risk was significantly increased in the high-risk compared with the low-risk group derived from ROR score for 1N+ [25.5%, 95% confidence interval (CI) 17.5% to 36.1%versus 6.6%, 95% CI 3.3% to 12.8%] and compared with the combined low/intermediate risk group for 2–3N+ patients (33.7%, 95% CI 25.5% to 43.8% versus 12.5%, 95% CI 6.6% to 22.8%). Additionally, the luminal A intrinsic subtype (IS) exhibited significantly lower risk of distant recurrence compared with the luminal B subtype in 1N+ and 2–3N+ patients.

Conclusion: PAM50 ROR score and IS can identify node-positive patient subgroups with limited risk of metastasis after endocrine therapy, for whom adjuvant chemotherapy can be spared. The PAM50 test is a valuable tool in determining treatment of node-positive early-stage breast cancer patients.

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original article

Key words: early-stage breast cancer (EBC), node-positive patients, multigenomic testing, prognostic subtypes, risk of recurrence (ROR), intrinsic subtype (IS)

introduction

In the adjuvant treatment of hormone receptor-positive (HR+) breast cancer, we face the dilemma of undertreatment versus overtreatment [1]. The relapse risk of individual patients treated with adjuvant endocrine therapy varies greatly in HR+ early-stage breast cancer (EBC) [2, 3]. Outcomes among oestrogen receptor (ER)-positive, HER2-negative patients and HER2-positive patients have significantly improved due to the clinical benefit of adjuvant endocrine [4] and trastuzumab [5] treatments in biomarker-defined subgroups. In treatment situations of low overall recurrence risk, absolute chemotherapy benefits will be small to the point where many physicians and patients consider it reasonable to avoid adjuvant chemotherapy with all its side-effects.

Therefore, assessing an individual patient's risk of metastasis as accurately as possible is an important goal in EBC, and directly impacts on therapy decisions. Risk assessment currently is still mainly based on clinicopathological variables such as tumour size, grade and nodal status, of which nodal status is considered to be most important [6]. As a consequence, most node-positive patients with HR+ breast cancer receive adjuvant chemotherapy.

Several multi-parameter tests such as Mammaprint®, OncotypeDX® and Endopredict® have been developed in recent years to evaluate the prognosis of patients; however, these evaluations were mostly done in node-negative cohorts. With the exception of 367 patients of the N+ intergroup trial S8814 analysed using OncotypeDX® [7], there is no firm evidence that any of the existing molecular tests is clinically useful, as the number of node-positive patients included in the respective pivotal trials was usually small [8–10].

As a 'second'-generation multi-gene expression assay, the PAM50 test (50 discriminator genes + 8 controls) was developed to identify the four intrinsic breast cancer subtypes (luminal A/B, HER2-enriched, basal-like), reflecting the underlying biology associated with ER and HER2 pathways and including proliferation genes and markers of the basal phenotype [11]. Level I evidence criteria according to Simon et al. [12] were fulfilled by the PAM50 assay showing, through prospectively defined analyses, that the test provides more accurate prognostic information than routine clinicopathological factors in ABCSG-8 [13, 14] and transATAC [15].

The objective of this work was to determine whether clinically relevant prognostic subgroups, among postmenopausal women with node-positive HR+ EBC treated with endocrine therapy, could be identified by using the PAM50 risk of recurrence (ROR) score and intrinsic subtype (IS). In order to accomplish this goal, we combined cohorts of two well-known large randomized aromatase inhibitor trials with long-term outcome to result in a sufficiently large sample size of node-positive patients.

This study was planned to determine whether ROR score provides additional prognostic information for risk of metastasis over and above standard clinical variables alone in either of the subsets of patients with one positive node (1N+) or with two to three positive (2–3N+) nodes. We hypothesized that a molecular-based characterization of residual risk of metastasis after endocrine therapy using the ROR score and/or IS may identify node-positive patient subgroups with limited risk of metastasis better than clinicopathological risk assessment by the Clinical Treatment Score (CTS).

methods

The underlying clinical trials and procedures as well as the analytical validation of the molecular assay have been described previously [13–15], and are summarized in supplementary Methods, available at *Annals of Oncology* online. Eventually, 543 samples of patients with one to three positive (1–3N+) nodes were available for this analysis (Figure 1).

study end points

The primary end point was distant recurrence-free survival (DRFS), defined as the interval from randomization until distant recurrence or death due to breast cancer in either of the subsets of patient samples with 1N+ and with 2–3N+ nodes. Contralateral breast cancer and death due to causes other than breast cancer were treated as censoring events. Death due to breast cancer where a recurrence was not recorded was considered an event at the date of death.

statistical analysis

All analyses were fully pre-specified and defined in a written statistical analysis plan. Log-likelihood ratio testing was applied to evaluate additional prognostic information ($\Delta LR\chi^2$) of the ROR score, ROR-based risk groups and ISs (luminal A and luminal B) compared with CTS alone at a significance level of $\alpha = 0.025$ for nodal subgroups (for details see supplementary Methods, available at *Annals of Oncology* online). For comparison purposes, analyses based on 1N+ and 2–3N+ subgroups were repeated for nodal negative subgroup (N0) and patients with 1–3N+ nodes.

results

Patient characteristics of node-negative patients and patients with 1–3N+ nodes in both the ABCSG-8 and the transATAC cohort are listed in supplementary Table S1, available at *Annals of Oncology* online. Median follow-up for the entire population was 10 years [interquartile range (IQR) 8.3–11.0], for the node-positive subgroup 9.6 years (IQR 7.1–10.9). A total of 234 DRFS events (distant recurrence or death from breast cancer) were recorded in 2197 patients. Among the 1654 node-negative patients, 146 (8.8%) DRFS events occurred; among the 543 patients with 1–3N+ nodes, 97 (17.9%) DRFS events were documented (1N+: 47; 2–3N+: 50).

In the group of patients with one positive node, absolute 10-year risk of distant recurrence was 6.6% [95% confidence interval (CI) 3.3% to 12.8%] in the ROR-based low-risk group versus 15.5% (95% CI 9.5% to 25.0%) in the intermediate risk group versus 25.5% (95% CI 17.5% to 36.1%) in the high-risk group $P = 0{\cdot}0002$ and 8.4% (95% CI 5.3% to 13.3%) in the luminal A subgroup versus 25.3% (95% CI 17.4% to 36.0%) in the luminal

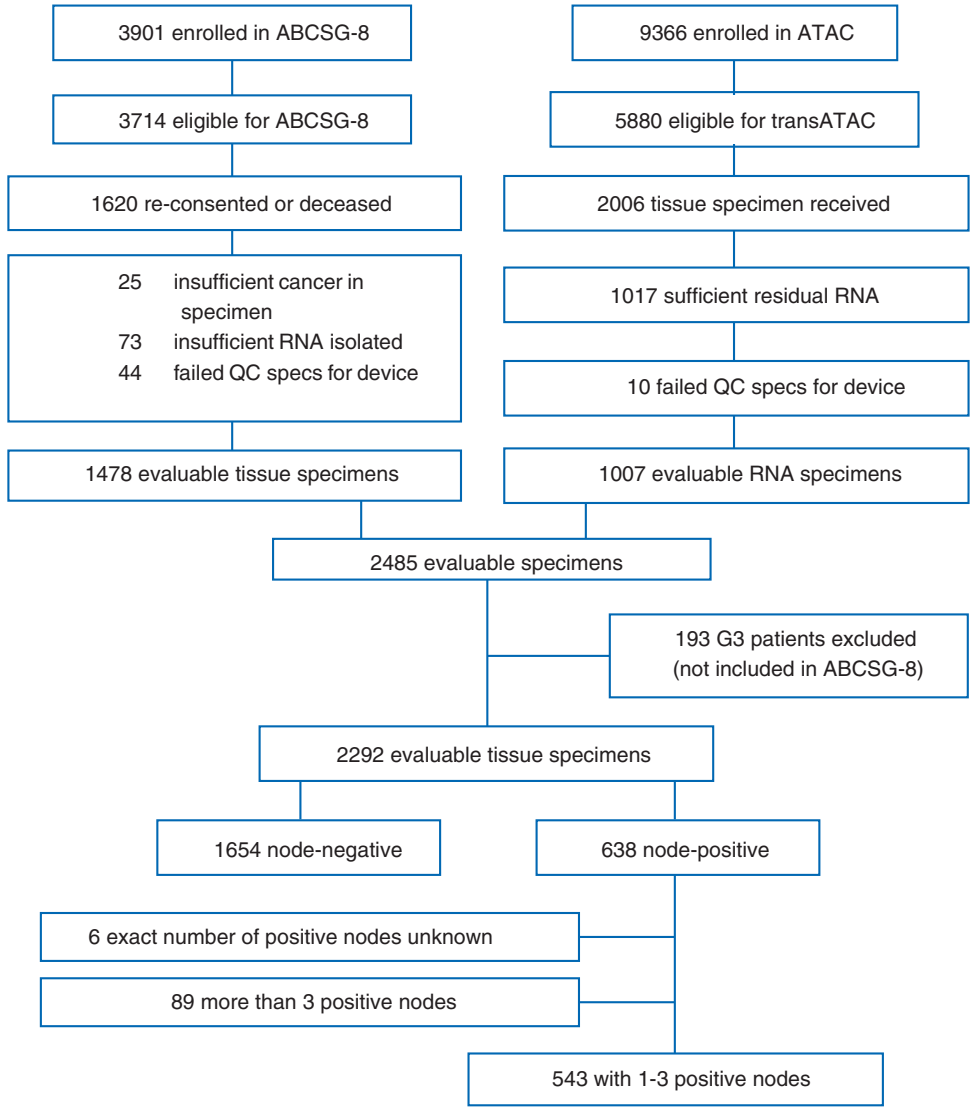

Figure 1. Risk of distant recurrence after 10 years estimated by the ROR score for nodal negative patients (solid lines) and patients with one to three positive nodes (dashed lines). The thin lines represent the 95% CI bands.

B ($P < 0.0001$; Table 1). In all nodal subgroups, 10-year ROR significantly differed between low- and high-risk groups as well as between luminal subtypes.

The relationship between 10-year risk of distant recurrence and the ROR score differs markedly between node-negative patients and patients with 1–3N+ nodes (supplementary Figure S1, available at *Annals of Oncology* online). CTS alone already showed significant prognostic effect in both the 1N+ (HR = 1.008, 95% CI 1.004–1.013, $P = 0.0006$) and 2–3N+ patients (HR = 1.011, 95% CI 1.006–1.016, $P < 0.0001$), but the inclusion of the ROR score resulted in a further highly statistically significant addition of prognostic information in 1N+ patients (Table 2). A similar discriminating effect was also seen in the subgroups of N0 and in all 1–3N+ patients (Table 2).

Patients in each nodal subgroup were assigned to three risk groups defined by previously published cut-off values [13]

Table 1. Ten-year risk of distant recurrence (%) for patients with one, two to three or no positive nodes within ROR-based risk groups and within intrinsic subgroups

Risk group	1N+ Risk (95% CI)	2–3N+ Risk (95% CI)	Node negative Risk (95% CI)
ROR-based groups			
Low	6.6 (3.3–12.8)	12.5[a] (6.6–22.8)[a]	4.9 (3.7–6.4)
Intermediate	15.5 (9.5–25.0)		15.0 (11.6–19.2)
High	25.5 (17.5–36.1)	33.7 (25.5–43.8)	20.3 (14.7–27.7)
Intrinsic subgroups			
Luminal A	8.4 (5.3–13.3)	16.5 (10.7–24.8)	5.4 (4.2–6.9)
Luminal B	25.3 (17.4–36.0)	38.8 (27.2–53.2)	17.0 (13.4–21.4)

[a]Due to small numbers of patients and events in the low-risk group, low and intermediate risk groups were combined.

Table 2. Additional prognostic information of ROR score, of ROR-based risk groups and of the intrinsic subtypes (IS) luminal A versus luminal B compared with CTS alone as difference in log-likelihood ($\Delta LR\chi^2$) in patients with one or two to three positive nodes and in all patients with no or one to three positive nodes

Group	Number of		$\Delta LR\chi^2$	*P* value
	Patients	Events		
CTS+ROR versus CTS				
1N+	331	47	17.53	<0.0001
2–3N+	212	50	14.16	0.0002
Node neg	1654	146	45.18	<0.0001
1–3N+	543	97	32.45	<0.0001
CTS+risk groups versus CTS				
1N+	331	47	11.32	0.0035
2–3N+	212	50	13.15	0.0014
Node neg	1654	146	38.19	<0.0001
1–3N+	543	97	21.05	<0.0001
CTS+IS versus CTS				
1N+	320	42	12.16	0.0005
2–3N+	201	45	8.58	0.0034
Node neg	1604	132	26.10	<0.0001
1–3N+	521	87	20.48	<0.0001

associated with a 10-year ROR (supplementary Table S2, available at *Annals of Oncology* online). Even though no clearly significant difference between the intermediate and the low-risk group was observed, the probability of distant recurrence was significantly increased in the high-risk compared with the low-risk group among 1N+ patients (intermediate versus low risk: HR = 2.11, 95% CI 0.92–4.846, $P = 0.078$; high versus low risk: HR = 3.56, 95% CI 1.62–7.80, $P = 0.0016$) (Figure 2A). The ROR-based risk groups provided prognostic values in addition to CTS (log-likelihood test: $\Delta LR\chi^2 = 11.32$, $P = 0.0035$; Table 2). Among 2–3N+ patients, risk group added significant information as well (log-likelihood test: $\Delta LR\chi^2 = 13.15$, $P = 0.0014$). In the analysis of 2–3N+, due to the small numbers of patients and events in the low-risk group, low and intermediate risk groups were combined and compared together to the high-risk group (Figure 2B). Again, ROR-based risk groups added significant information (log-likelihood test: $\Delta LR\chi^2 = 10.93$, $P = 0.0001$) and risk of distant metastasis was significantly lower in the low/intermediate group (high versus low/intermediate risk: HR = 3.023, 95% CI 1.462–6.249, $P = 0.0028$). The additional prognostic value of the ROR score and that of the ROR-based risk groups are not restricted to node positive but are also present in node-negative patients (Table 2): In node negatives, the gain of information is even more pronounced for the ROR score (log-likelihood test: $\Delta LR\chi^2 = 45.18$, $P < 0.0001$) and the ROR-based risk groups (log-likelihood test: $\Delta LR\chi^2 = 38.19$, $P < 0.0001$).

Two thirds of patients with one, two or three positive nodes were assigned to the luminal A category and slightly less than one third to luminal B by PAM50 based on the nearest centroid (supplementary Table S1, available at *Annals of Oncology* online). Twenty patients were classified into HER2-enriched and only two patients into basal-like subtypes.

DRFS was significantly higher in luminal A compared with luminal B patients in the 1N+ subgroup (univariate Cox: HR = 3.360, 95% CI 1.829–6.172, $P < 0.0001$) and the 2–3N+ subgroup (univariate Cox: HR = 2.444, 95% CI 1.361–4.386, $P < 0.0028$). Classification according to luminal subtypes added significant prognostic information to CTS in both nodal groups (1N+: multivariate Cox; CTS: HR = 1.007, 95% CI 1.002–1.013, $P < 0.0066$; luminal A/B: HR = 2.986, 95% CI 1.621–5.503, $P < 0.0005$; log-likelihood test: $\Delta LR\chi^2 = 12.16$, $P < 0.0005$; 2–3N+: multivariate Cox; CTS: HR = 1.012, 95% CI 1.006–1.018, $P = 0.0001$; luminal A/B: HR = 2.426, 95% CI 1.350–4.359, $P < 0.0030$; log-likelihood test: $\Delta LR\chi^2 = 8.58$, $P < 0.0034$) (Table 2). Already within three years after randomization, estimates of ROR were significantly higher for luminal B compared with luminal A patients with one positive node (Figure 3A). Also, a difference between these two subtypes was detected in the 2–3N+ patients, reaching statistical significance around 10 years after randomization (Figure 3B).

discussion

Our results from this combined analysis of two pivotal clinical trials clearly demonstrate that PAM50-derived ROR, risk groups, and ISs usefully differentiate risk of metastasis among node-positive breast cancer patients. Based on the large number of patients we were able to assess and the long follow-up period of more than 10 years in this series, these results are of clinical relevance, because they provide firm evidence for clinical decision-making in node-positive ER+/HER2− EBC.

While node-positive breast cancer patients are traditionally considered to be at high risk for recurrence—and treated accordingly—based on the metastatic involvement of their axillary nodes, we here demonstrate using a modern molecular tool that a significant proportion of HR+ EBC patients with one positive node has very limited long-term risk of metastasis. Even for some patients with two or three positive nodes, the risk of metastasis was limited when defined by ROR score and the presumed necessity of adjuvant chemotherapy can be seriously questioned in these cases.

Particular strengths of this study in node-positive patients, which is to the best of our knowledge the largest report on the subject, are the homogeneity of patients involved, the reliability of the data as derived from the prospective database of pivotal randomized trials, and the long median follow-up of more than 10 years.

The PAM50 assay has achieved level I evidence for clinical validity of its ability to predict the probability of distant recurrence by demonstrating added prognostic information over and above standard clinical variables in the two individual endocrine-treated cohorts described here [13, 14]; however the information on node-positive patients was numerically limited in the two individual cohorts. In transATAC [15], PAM50 was shown to provide more accurate prognostic information than the Oncotype Recurrence Score [2].

Compared with other molecular tests used in breast cancer, the PAM50 test includes 50 genes, and unlike Oncotype® or Endopredict®, provides subtype information as well as risk score (This statement is true for the Ex-US market—the commercial version of ProSigna® in the US does not provide IS information). Particular strengths of the PAM50 test also include its demonstrated reproducibility, the inclusion of tumour size in its risk score, and the option of decentralized testing. As others, it is

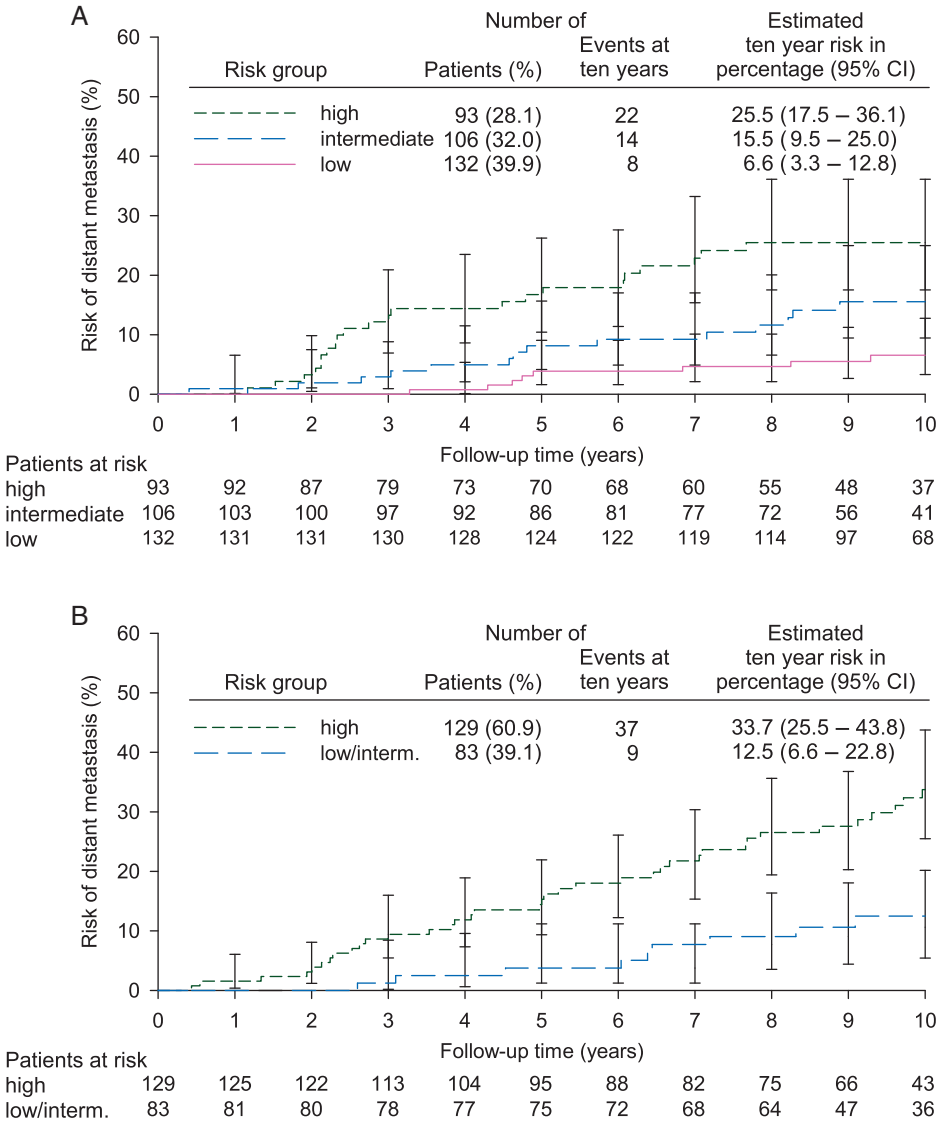

Figure 2. Risk of distant metastases per ROR-based risk group through 10 years with (A) 1N+ patients and (B) 2–3N+ patients with low and intermediate risk group combined.

routinely carried out on FFPE tissue. In comparison to immunohistochemistry, RNA-based methods measure more genes and have the advantage of higher analytical objectivity, reproducibility, and quantification. Other molecular prognosticators that have been described include HOXB13/IL17BR, *TP53* gene mutations, chemokine receptor CXCR4, as well as the microtubule-related parameters τ protein and tubulin III. While OncotypeDX® is well established in node-negative disease [16], there is less evidence that it adds prognostic information beyond established clinicopathological parameters in node-positive disease, with the exception of S8814 (which yields similar results to our study) and a smaller series in a decision-impact study.

The individualised risk assessment of node-positive breast cancer still is severely limited, and largely based on classical clinicopathological parameters such as grade, proliferation rate (e.g. assessed by Ki67), and quantitative receptor content. Maybe because in many health care environments all node-positive patients are treated with chemotherapy anyway, efforts to more accurately identify low-risk patients have been less stringent than in node-negative disease. Several reports claim that lymph node ratio may be more important than absolute number of affected lymph nodes [17], but in the post-ACOSOG-Z0011 era, neither information may be regularly available in the future.

Of note, for 71% of patients with one positive node the IS was defined as luminal A, carrying a 10-year risk of metastasis of 8.4%. For 40% of the patients with one positive node the ROR score was categorized as low risk and the 10-year metastasis risk of these patients was 6.6%. These results clearly demonstrate that the notion that nodal involvement defines high risk of metastasis in all patients is simply not true. While we observed a limited median metastasis risk for the N2–3+ subgroup, the 95% CI of 23% suggests caution for applying our results to that particular subgroup.

Node-positive patients in this cohort identified as molecularly high-risk show a 10-year risk of metastasis of 33.4%. Since these patients did not receive adjuvant chemotherapy, it is probably

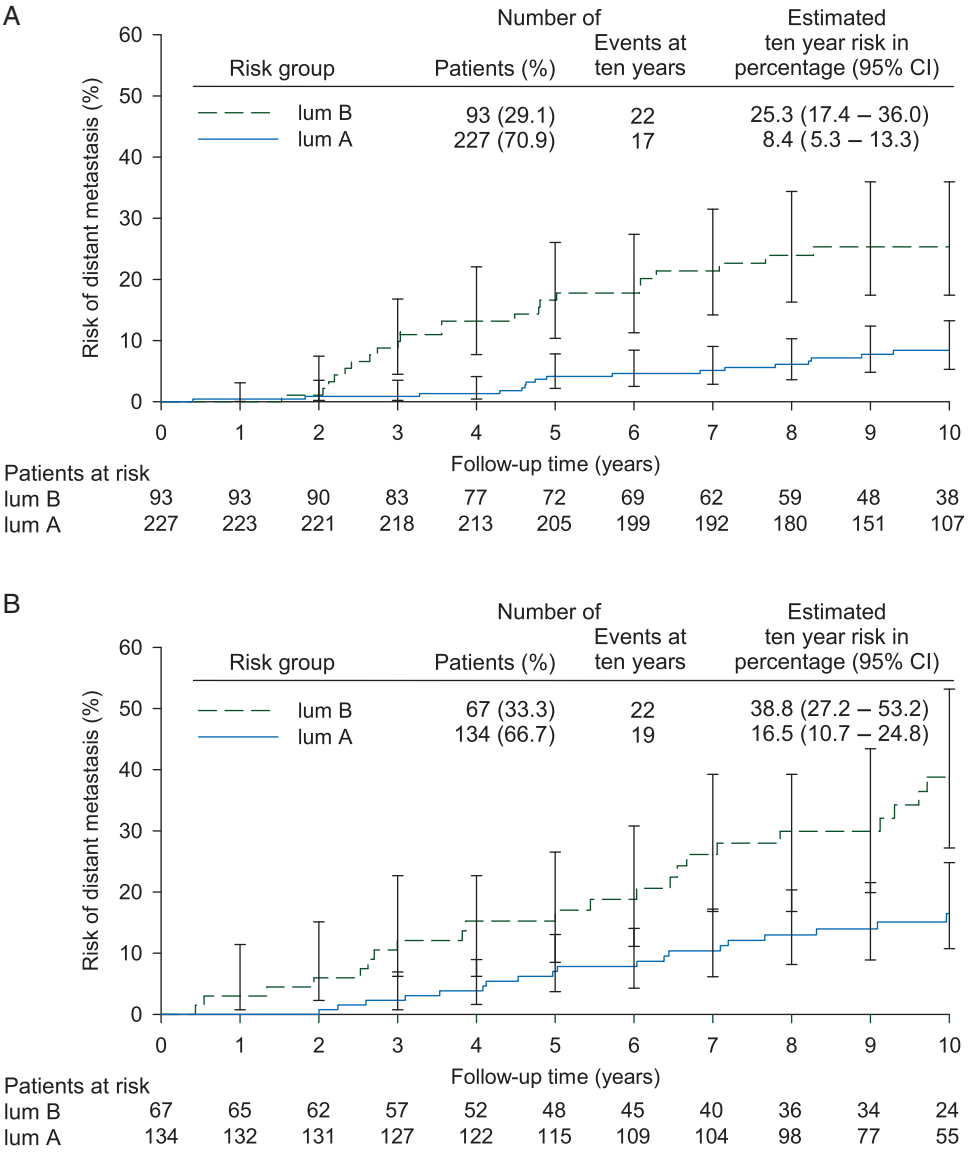

Figure 3. Risk of distant metastases per intrinsic subtypes through 10 years with (A) 1N+ patients and (B) 2–3N+ patients.

fair to say in retrospect that these patients should have received adjuvant cytotoxic treatment. Also in PAM50 'low-risk' N2–3+ patients with their nominal risk of 12.5%, a potential relative reduction of metastasis risk by 25%–30% by chemotherapy would have resulted in an absolute 3%–4% benefit, which may be considered worthwhile by many.

However, while we tend to agree with that sentiment, molecular determination of high risk has to be considered prognostic rather than predictive, and such conclusions cannot be firmly drawn before results of prospective assessment of the actual predictive value of these tests, such as TailoRx (NCT00310180) and MINDACT (NCT00433589) become available.

On the other hand, the contrary statement can be made firmly: if a (non-chemotherapy treated) node-positive patient cohort is identified as having a 10-year metastasis risk of 6.6% (which is considerable less than 1% per year), it is almost impossible that adjuvant chemotherapy would significantly improve that outcome in a clinically justifiable manner. These patients—despite being node positive—do not have a favourable benefit-burden balance with respect to adjuvant cytotoxic therapy, which if applied would constitute significant overtreatment. Also, such overtreatment poses a significant economic burden for the health care system. From the patient perspective, health care spending may be better invested in the funding of molecular testing than on unnecessary, potential harmful overtreatment.

In summary, PAM50-derived ROR, ROR risk groups and ISs provide reliable prognostic information for metastasis risk in addition to and beyond established clinicopathological factors in node-positive HR+ breast cancer. These PAM50-derived molecular assessments accurately discriminate patients into low and high risk in this large combined dataset. Node-positive patients with molecular low-risk PAM50 should be spared the side-effects of adjuvant chemotherapy. In any case, large proportions of patients may be advised of their low ROR despite

the previous perception of a dire diagnosis of breast cancer with nodal metastasis.

Acknowledgements

We thank all patients and their families who contributed to ABCSG-8, ATAC and other clinical trials; Additional acknowledgements can be found in supplementary Materials, available at *Annals of Oncology* online.

funding

The original clinical trials were partly supported by AstraZeneca. Additional follow-up, re-consent procedures, and database maintenance was supported by NanoString Technologies (no grant number).

disclosure

MG reports personal fees and travel support from NanoString during the conduct of the study as well as grants and personal fees from Novartis, grants and personal fees from AstraZeneca, grants from Sanofi-Aventis, grants and personal fees from Roche, grants and personal fees from GlaxoSmithKline, grants from Pfizer, grants from Smith Medical, personal fees from Accelsiors, outside the submitted work, and honoraria and travel support from Amgen, Novartis, GlaxoSmithKline, Astra Zeneca and Roche outside the submitted work. As a co-inventor of the PAM50 test that has been licensed to NanoString. TN reports grants from NanoString Technologies during the conduct of the study. NanoString provided equipment and funding to complete the study, although the work of this study was done completely independently as it was a fully pre-specified registry study. TN reports other payments from Bioclassifier LLC of which TN is a founder, outside the submitted work. In addition, TN has a patent Gene expression profiles to predict breast cancer outcomes with royalties paid to NanoString. SF reports he was a stockholder and employee of NanoString Technologies, Inc., during the conduct of the study, and outside the submitted work. In addition, SF has patents on applications of PAM50 signature pending, patents on NanoString nCounter technology issued, and patents on NanoString nCounter technology pending. CF reports grants from NanoString, during the conduct of the study. MB reports indirect payments from NanoString during the conduct of the study. CS reports personal fees from NanoString Technologies, during the conduct of the study and personal fees from NanoString Technologies, outside the submitted work. JC reports grants and personal fees from AstraZeneca, personal fees from NanoString, during the conduct of the study and grants from AstraZeneca, outside the submitted work. JWC was an employee of and stock holder in NanoString Technologies. MF reports personal fees from NanoString Technologies, personal fees from Sividon Diagnostics, outside the submitted work. PD reports unpaid advisory and lecture fees from Sividon, unpaid advisory and research support from Agendia and unpaid advisory for Genomic Health. MD reports grants from Breakthrough Breast Cancer and from AstraZeneca during the conduct of the study. MD reports grants from NanoString outside the submitted work. All other authors declare that they have no competing interests.

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