Risk assessment tools and adjuvant therapy for breast cancer

Noordhoek, I.

Chapter 7

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Iris Noordhoek

RISK ESTIMATION AND PREDICTION FOR (EXTENDED) ENDOCRINE THERAPY

Breast cancer is the most common cancer in women.[1,2] In the past decades, much progress has been made in terms of treatment options, and breast cancer survival has improved significantly. Nevertheless, concerns in the treatment of hormone receptor positive (HR+) breast cancer remain. Even after optimal locoregional management and adjuvant systemic therapy, patients with HR+ breast cancer still have a lifetime risk of 20 to 41% of developing a recurrence.[3] Several prognostic and predictive models have been developed for early breast cancer. To improve tailoring of adjuvant treatment to the individual patient, much effort has been made to identify biomarkers or biomarker profiles capable of predicting the individual risk of recurrence and sensitivity to endocrine treatment. One objective of this thesis was to examine several prognostic and predictive models, to determine which ones are most suitable to use in daily clinical practice.

In **chapter 2** of this thesis, with a review of the literature, we investigated whether the quantitative assessment of hormone receptors is a better method to select patients for endocrine therapy (ET) than the single cut-off value of 10%.[4] We concluded that in patients with an estrogen receptor (ER)-positive tumor (defined as ER ≥10%), a higher ER load as assessed by immunohistochemistry (IHC) is not correlated to better outcome, and no evidence could be found for using quantitative ER load as a prognostic marker. In other words, patients with a higher ER load (e.g. 100%) do not inherently have a better prognosis than patients with a lower ER load (e.g. 20%). Furthermore, no evidence was found for using quantitative ER load as a predictive marker, i.e. patients with a higher ER load do not have more benefit of ET than patients with a lower ER load.

This chapter also concluded that in patients with an HR+ tumor, higher progesterone receptor (PR) load does not seem to be correlated to better outcome. Based on the included studies, quantitative PR load is not a suitable prognostic marker; patients with a higher PR load do not inherently have a better prognosis than patients with a lower PR load, nor is it suitable as a predictive marker. Furthermore, PR load seems to interact with ER load and is therefore not recognized as an independent predictor.

The studies included in the systematic review differed from each other in their way of quantitatively measuring HR load; some studies used a continuous percentage or histoscore, some studies used groups of HR-negative, low HR expression and high HR expression and some divided patients in four or more groups based on Allred score or percentage. This influenced outcomes. Studies were more likely to find a positive association between HR load and outcome if a continuous score was used. However, using a continuous quantitative measure to assess HR expression was questioned by several authors. Inter-observer variability is high, and samples get assigned different HR percentages depending on the pathologist and the lab it was reviewed in. Most importantly, staining breast cancer tissue using IHC does not allow for precise enough measurement of HR load to generate a continuous score and can only quantify into negative, weak positive and strong positive. The problem with this approach is defining “weak” and “strong”. A lack

of generally accepted definition resulted in pathologists and papers choosing their own definition, making it difficult to compare multiple studies.

Based on the results of the review, we propose using both ER and PR expression only as a qualitative measure; defining tumors with less than 10% of cells expressing this receptor as negative, and tumors with ≥10% of cells expressing the receptor as positive. Using a continuous quantitative measure does not seem feasible without centralized, unambiguous and clear pathological measurement. The implications for the daily clinical practice of pathologists are that more detailed information on the HR status beyond "positive" or "negative" should no longer be provided, to prevent oncologists subconsciously or instinctively making different treatment decisions based on this information. Since there is no evidence for different treatment strategies, providing extra information is both unnecessary and undesirable.

In **chapter 3** of this thesis, we studied the utility and accuracy of the clinical treatment score post-5 years (CTS5) to determine the risk of late distant recurrences (DR) and whether it can be used to predict benefit from extended ET. A substantial risk of late DR exists for patients with ER+ breast cancer, even after 5 years of ET, and extended ET may be beneficial.[5] The CTS5 was trained with data from postmenopausal patients who had HR+ breast cancer and were randomly assigned to receive anastrozole alone or tamoxifen alone, and were distant recurrence free after 5 years of follow-up. It was internally validated with data from postmenopausal women with HR+ early-stage breast cancer who were randomized to receive 5 years of letrozole or tamoxifen or sequential therapy (2 years of letrozole followed by 3 years of tamoxifen or opposite sequence), and were distant recurrence free after 5 years of follow-up. The CTS5 aims to estimate the DR rate between 5 and 10 years from diagnosis for postmenopausal patients with ER-positive breast cancer who remain disease free after 5 years of standard ET.

We applied the CTS5 to the TEAM and IDEAL cohorts.[6] The TEAM cohort comprised postmenopausal patients with ER-positive breast cancer randomly assigned to either 5 years of exemestane or 2-3 years of tamoxifen followed by 2-3 years of exemestane, and were disease free at 5 years.[7] The IDEAL cohort consisted of postmenopausal patients with HR+ early breast cancer, who were disease free after 5 years of standard ET and were randomized to either 2.5 or 5 years of extended treatment with letrozole.[8] The CTS5 was developed to discriminate postmenopausal patients with ER+ breast cancer into three risk categories with respect to late DR.[5] In these two large cohorts of trial patients, the risk of late DR as predicted by the CTS5 corresponded to the observed DR rates in low-risk patients, but the CTS5 overestimated the observed risk of DR in patients with a higher predicted risk. Furthermore, the CTS5 could not predict benefit of 5 years over 2.5 years of extended ET using data from the IDEAL cohort.

In conclusion, the CTS5 as applied to patients treated in the TEAM and IDEAL cohorts categorizes patients into low-, intermediate-, and high-risk groups. In low-risk patients, the predicted late DR risks correspond with the observed DR rates, but the CTS5 overestimated the risk of late DRs in high-risk patients from the TEAM and IDEAL cohorts. Using patient

data from the IDEAL cohort, the CTS5 cannot be validated as a predictive tool for extended ET either. Especially in high-risk patients, an unrealistic assessment of the risk to develop a late DR could potentially lead to overtreatment. Therefore, the numerical risk assessment from the CTS5 calculator in its current form should be interpreted with caution when used in daily clinical practice, particularly when used in high-risk patients.

Both the hormone receptor analysis studied in **chapter 2**, and the CTS5 studied in **chapter 3** are models based on clinical factors. They are able to discriminate between low risk and high risk patients, but not capable of further discrimination. Moreover, quantification does not lead to more accurate risk assessment, and both of these models are unable to select patients who are suitable for extended endocrine therapy.

In general, prognostic tools aim to distinguish patients with an inherently worse prognosis from those with a better prognosis, while predictive tools aim to distinguish those patients who will respond well to treatment from those who will not. Often, prognostic tools are not predictive and should not be used as such because patients with a worse prognosis are not necessarily the same patients who benefit from more extensive therapy. This is illustrated with the results from **chapter 2** and **chapter 3**.

More promising as a predictive model may be the assessment of the activity of the ER-pathway to distinguish in which patients the estrogen receptor is not only expressed, but also active and thus a suitable target for ET. In **chapter 4** of this thesis, we examined the BCI [H/I] biomarker panel.[9] BCI [H/I] is a gene expression profile that examines the ratio between two genes, HOXB13 and IL17BR (H/I), that reflects activity of estrogen signaling pathways in breast tumors. When this H/I ratio is high, estrogen signaling is upregulated, and the proliferation of the tumor is likely influenced by the availability of estrogens.

To date, the net benefit of extended endocrine therapy based on tumor biology has incorporated individualized assessment of risk but has lacked individualized assessment of endocrine responsiveness to predict the likelihood to benefit from longer durations of endocrine treatment. Findings from this study confirm the predictive ability of BCI by H/I status to classify patients who demonstrate a high or low degree of endocrine responsiveness with categorical differences in outcome from extended endocrine therapy. Similar relative improvements in outcome based on recurrence-free survival (RFI) by BCI [H/I] category were generally observed in all clinical and pathologic factors examined.

Consistent with previous data, BCI [H/I] expression did not show a strong correlation with canonical endocrine biomarkers, ER and PR. In addition, multiple translational studies in the ATAC, BIG 1-98, and TEAM trials, and our own results from **chapter 2** have reproducibly demonstrated that quantitative ER and PR expression levels in patients with HR breast cancer do not predict benefit from endocrine therapy, suggesting that BCI [H/I] predictive effects are predicated on distinct biological mechanisms that are not directly coupled to ER/PR expression levels.[10-12]

We demonstrated significant prediction of extended endocrine benefit based on BCI [H/I] classification in patients treated with contemporary standards of care for primary adjuvant

endocrine therapy. In conjunction with previous data from MA.17 and Trans-aTTom, BCI predictive performance is established across a comprehensive range of treatment scenarios involving tamoxifen and AIs.[13] Clarifying the magnitude and level of efficacy of extended endocrine therapy with approaches that provide additive and distinct information is important to ensure that overtreatment and undertreatment do not occur. BCI may provide the rationale as a standardized molecular tool that measures preferential response and magnitude of benefit to help individualize patient selection for extending endocrine therapy to 10 years.

In a head-to-head comparison of BCI [H/I] to the CTS5, one analysis revealed that no CTS5-group derived significant benefit from extended ET.[14] The treatment by biomarker interaction was significant for BCI [H/I], but not for CTS5. When re-stratifying CTS5 categories by BCI [H/I] or vice versa, only BCI [H/I]-high patients showed consistent absolute benefit regardless of CTS5 category. In contrast, CTS5-high patients did not show any benefit in the BCI [H/I]-low group. These results demonstrate that CTS5 does not provide predictive information to support extended endocrine therapy decision-making. Only BCI [H/I] was a predictive biomarker of benefit from extended endocrine therapy. These results are consistent with our findings from **chapter 3** and **chapter 4**.

RISK ESTIMATION IN OLDER PATIENTS

A third of all patients with breast cancer are aged 70 years or older at diagnosis, and in this growing population two specific age-related issues arise.[1] As it takes time for a recurrence to develop, and older patients have an increased probability to die of causes unrelated to their breast cancer, the risk of developing a recurrence is inversely correlated to age and the competing risk of other-cause mortality.[15] Also, older patients usually have more comorbidities and frailty than younger patients. Therefore, they may experience more side effects and complications of cancer treatment and are at higher risk of hospitalization and long-term loss of quality of life.[16,17]

Risk estimation in older patients is generally based on the same factors as in younger patients. Therefore, these age-related factors regarding other cause mortality and (adverse) effects of treatment, are often not taken into account when determining the treatment strategy, which can lead to significant overtreatment of this population. Thus, instruments are needed that are validated specifically for the older population. The 70-gene signature test, or MammaPrint, is a genomic risk profile that is already established as an accurate prognostic model in younger breast cancer patients.[18] Previous studies showed that MammaPrint can be used to de-escalate the use of chemotherapy and ET in genomic low and ultralow risk patients, respectively.[19] However, these trials did not include patients aged 70 years or older. In **chapter 5** of this thesis, the validity and accuracy of MammaPrint in older patients was examined.

Our data showed that the 70-gene signature test can be used to accurately estimate DR risk in patients with breast cancer aged ≥70 years.[20] MammaPrint-ultralow risk patients had excellent clinical outcome up to ten years after diagnosis, despite 48% of them not

receiving any systemic therapy. Significantly more MammaPrint-high risk patients developed DR, even though 72% of MP-high risk patients did receive adjuvant ET. Multivariate analyses adjusted for ET usage still showed significantly lower 10-year DR rates for MP-ultralow risk patients.

This is the first study examining a gene-expression profile in the older population. Our data show that genomic ultralow risk patients had excellent long-term outcomes even if clinically high risk. This may be explained by the discontinuation of routine screening at the age of 75. With increasing age, and reduced rates of participation in breast cancer screening, breast cancer is more often diagnosed at higher clinical stages.[21] Larger tumors and more elaborate regional spread may therefore in older women not be signs of aggressive tumor biology, but rather of late diagnoses. Thus, using only clinical parameters to determine recurrence risk for older patients may result in inaccurate risk estimation. Our data show that the 70-gene signature test provides more accurate risk assessment, and it seems reasonable to suggest that all older patients with ultralow risk breast cancer could forgo adjuvant endocrine therapy. This would apply to both patients with a high risk of competing events, and also to those who are relatively fit, since the risk of developing a distant recurrence seems extremely low. Prospective randomized trials should examine whether MammaPrint can indeed be used to decide if these older patients can safely forgo adjuvant ET.

This analysis adds to the growing body of data demonstrating the validity of MammaPrint's ultralow risk threshold. Women with ultralow risk, regardless of clinical stage or grade, had an extremely low risk of recurrence. These data are especially relevant for clinicians working with older patients, who may be frailer and more susceptible to adverse effects of treatment.

ADJUVANT THERAPY WITH BISPHOSPHONATES

Aside from determining which patients have most to gain from (extended) ET, other therapeutic agents might also assist in decreasing the risk of recurrences. Since hormone receptor positive breast cancer cells prefer osseous microenvironments, about 70% of breast cancer metastases are bone recurrences.[22,23] When metastatic cells infiltrate bone tissue, the equilibrium between osteoclasts and osteoblasts is disturbed. The tumor cells stimulate the activity of osteoclasts, which increases bone resorption and the release of growth factors and cytokines. These instigate the proliferation and survival of tumor cells, creating a vicious cycle.

Nitrogen-containing bisphosphonates also affect bone metabolism by inhibiting key enzymes of the intracellular mevalonate pathway.[24] This decreases osteoclast-mediated bone resorption and osteoclast survival, causing an increase in bone density and a decreased release of cytokines and growth factors. It is hypothesized that this makes bone a less attractive environment for metastatic breast cancer cells.

Several trials have investigated the effect of (neo)adjuvant bisphosphonates on (breast) cancer recurrence.[25-27] In 2015, a meta-analysis comparing patients treated with and

without adjuvant bisphosphonates showed a reduction in breast cancer recurrence and mortality in the subgroup of women who were postmenopausal at the onset of treatment or chemically castrated using therapy, but not in the premenopausal subgroup.[28] Thus far, the use of high-dose nitrogen-containing bisphosphonates has not been studied in exclusively postmenopausal patients. The TEAM-IIB trial investigated the effect of daily oral ibandronate on the development of (bone) recurrences in postmenopausal patients with breast cancer, and its results were described in **chapter 6**.[29]

TEAM-IIB, the largest randomized controlled trial in specifically postmenopausal women with HR+ breast cancer, evaluates the benefit of adding an oral nitrogen-containing bisphosphonate, ibandronate, to adjuvant ET, and found no difference in overall disease-free survival (DFS) between the ibandronate arm and the control arm. A significant difference was observed in the first 3 years after diagnosis, which disappeared with longer follow-up. An interaction between time and treatment effect was observed, although a landmark analysis of DFS starting at 3 years after random assignment until end of follow-up showed no significant difference in DFS between the treatment arms. Evaluation of secondary outcomes also showed only a short-term benefit of ibandronate. During the first 5 years after random assignment, patients in the ibandronate arm had few recurrences overall, and also less recurrences in bone, specifically. This is in line with results from preclinical research and the EBCTCG meta-analysis.[28] Despite the favorable short-term effects of ibandronate on disease-free survival and (bone) recurrence rate, ibandronate was not beneficial with longer follow-up. After 8 years of follow-up, the (bone) recurrence rate was similar between the ibandronate arm and the control arm. These results were also consistent with the EBCTCG meta-analysis, and it was especially notable that the point estimates for bone recurrence presented here were almost identical to those of the EBCTCG meta-analysis, namely 7.8% and 8.8% for the ibandronate arm and control arm, respectively, versus 7.8% and 9.0% in the meta-analysis. All landmark analyses starting at 3 years after random assignment showed no statistically significant differences between treatment arms.

Moreover, ibandronate treatment carries considerable side effects. Bisphosphonates are associated with flu-like symptoms, musculoskeletal pain, and hypocalcemia. Incidence of serious AEs, such as osteonecrosis of the jaw (ONJ) and nephrotoxicity, is low. Most trials report an incidence of about 1% for both toxicities. Notably, in TEAM-IIB, the incidence of ONJ was 1.9%, mostly in women using an AI, which raises the question whether the combination with AIs in postmenopausal women may increase this risk. Tamoxifen increases bone mineral density in postmenopausal women by acting as an estrogen agonist in osseous tissue, whereas AIs cause osteoporosis through disrupting the bone remodeling cycle by increasing osteoclast-mediated bone resorption. Bisphosphonates decrease bone remodeling, but also decrease angiogenesis and cause poor wound healing. Therefore, the concurrent administration of AIs and high-dose ibandronate may increase the risk of developing osteonecrosis compared with the combination of ibandronate and tamoxifen. Although patient satisfaction with oral formulations is generally high and oral bisphosphonates are usually well accepted, 18% of TEAM-IIB patients stopped their

ibandronate treatment early because of adverse events, and approximately a third of those had gastro-intestinal complaints.

In conclusion, the data presented here are an important contribution to the field and the results from TEAM-IIB do not support using daily ibandronate as adjuvant treatment in unselected postmenopausal women with HR+ stage I-III breast cancer.

FUTURE PERSPECTIVES

Overall, identifying the breast cancer patients that could benefit most from ET remains important. Roughly, patients can be categorized into four groups.

First of all, there is a group of patients with HR+ breast cancer that have such favorable tumor characteristics, that they will never develop a recurrence, even if they forgo adjuvant treatment altogether. Secondly, some patients will definitely develop a recurrence, even if they are treated with ET. Thirdly, some patients would develop a recurrence, but this can be prevented with the use of ET. And lastly, some patients are elderly or frail, and although they might develop a recurrence, this will not influence their survival nor their quality of life, as they are likely to succumb to "other cause mortality" related to comorbidities before the breast cancer recurs.

Ideally, only the patients from the third group are treated with ET. If oncologists are able to predict to which group of patients people belong, they could better advise them on the use of ET. Considering the frequent and sometimes severe side effects of ET, an improved selection of those who need treatment will lower the treatment burden.

To identify patients belonging to the first group, the 70-gene signature test as described in **chapter 5** can be used. Our data show that genomic ultralow risk patients had excellent long-term outcomes even if clinically high risk. It seems reasonable to suggest that all patients with ultralow risk breast cancer could forgo adjuvant endocrine therapy, since the risk of developing a distant recurrence seems extremely low.

To differentiate between the second and the third group, a potential method to identify those patients is to measure the activity of the ER pathway to distinguish in which patients the estrogen receptor is not only expressed but also active and thus a suitable target for ET. BCI [H/I] as described in **chapter 4** could be a suitable method for this. Other pathway sensitivity analyses could also be advantageous for this goal.[30]

The fourth group could be identified using the PORTRET tool. The PORTRET tool aims to predict recurrence, overall mortality, and other-cause mortality in older patients with breast cancer, including individualized estimations of adjuvant treatment benefits.[31] The tool showed good internal and external validation performance, with improved accuracy in older patients compared with existing breast cancer prediction models, by incorporating comorbidity and geriatric predictors. The accurate prediction of the competing risk of death is a substantial aspect of the PORTRET tool. Although there are existing tools that estimate remaining life expectancy in older adults available such as Lee-index/ePrognosis,

the major advantage of the PORTRET tool is that it combines this outcome with breast cancer-specific outcomes.[32]

This thesis aimed to provide guidance in navigating different risk assessment tools. Once we are able to accurately assign patients to one of the four groups by using risk assessment tools, we can optimize and personalize adjuvant treatment strategies for patients with HR+ breast cancer.

REFERENCES

1. Dutch Cancer Registry (NKR), IKNL. Obtained through https://www.iknl.nl/nkr-cijfers, accessed on April 4 2021.
2. Allemani C, Matsuda T, Di Carlo V, et al: Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 391:1023-1075, 2018
3. Pan H, Gray R, Braybrooke J, et al: 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med 377:1836-1846, 2017
4. Noordhoek I, de Groot AF, Cohen D, et al: Higher ER load is not associated with better outcome in stage 1-3 breast cancer: a descriptive overview of quantitative HR analysis in operable breast cancer. Breast Cancer Res Treat 176:27-36, 2019
5. Dowsett M, Sestak I, Regan MM, et al: Integration of Clinical Variables for the Prediction of Late Distant Recurrence in Patients With Estrogen Receptor-Positive Breast Cancer Treated With 5 Years of Endocrine Therapy: CTS5. J Clin Oncol 36:1941-1948, 2018
6. Noordhoek I, Blok EJ, Meershoek-Klein Kranenbarg E, et al: Overestimation of Late Distant Recurrences in High-Risk Patients With ER-Positive Breast Cancer: Validity and Accuracy of the CTS5 Risk Score in the TEAM and IDEAL Trials. J Clin Oncol 38:3273-3281, 2020
7. Derks MGM, Blok EJ, Seynaeve C, et al: Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 18:1211-1220, 2017
8. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al: Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05). J Natl Cancer Inst 110, 2018
9. Noordhoek I, Treuner K, Putter H, et al: Breast Cancer Index Predicts Extended Endocrine Benefit to Individualize Selection of Patients with HR+ Early-stage Breast Cancer for 10 Years of Endocrine Therapy. Clin Cancer Res 27:311-319, 2021
10. Sgroi DC, Sestak I, Cuzick J, et al: Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. Lancet Oncol 14:1067-1076, 2013
11. van de Water W, Fontein DB, van Nes JG, et al: Influence of semi-quantitative oestrogen receptor expression on adjuvant endocrine therapy efficacy in ductal and lobular breast cancer - a TEAM study analysis. Eur J Cancer 49:297-304, 2013
12. Viale G, Regan MM, Maiorano E, et al: Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98. J Clin Oncol 25:3846-52, 2007
13. Bartlett JMS, Sgroi DC, Treuner K, et al: Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol 30:1776-1783, 2019
14. Sgroi D, Zhang Y, Schnabel CA: Comparative performance of Breast Cancer Index (BCIN+) and CTS5 in hormone receptor-positive (HR+) lymph node-positive (N+) breast cancer patients with one to three positive nodes (N1). J Clin Oncol 37:555, 2019
15. van de Water W, Bastiaannet E, Hille ET, et al: Age-specific nonpersistence of endocrine therapy in postmenopausal patients diagnosed with hormone receptor-positive breast cancer: a TEAM study analysis. Oncologist 17:55-63, 2012
16. Klepin H, Mohile S, Hurria A: Geriatric assessment in older patients with breast cancer. J Natl Compr Canc Netw 7:226-36, 2009
17. Lee SY, Seo JH: Current Strategies of Endocrine Therapy in Elderly Patients with Breast Cancer. Biomed Res Int 2018:808-820, 2018
18. Cardoso F, van't Veer LJ, Bogaerts J, et al: 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 375:717-29, 2016
19. Lopes Cardozo JMN, Drukker CA, Rutgers EJT, et al: Outcome of Patients With an Ultralow-Risk 70-Gene Signature in the MINDACT Trial. J Clin Oncol 40:1335-1345, 2022
20. Noordhoek I, Bastiaannet E, de Glas NA, et al: Validation of the 70-gene signature test (MammaPrint) to identify patients with breast cancer aged ≥ 70 years with ultralow risk of distant recurrence: A population-based cohort study. J Geriatr Oncol 13:1172-1177, 2022
21. Cappellani A, Di Vita M, Zanghì A, et al: Prognostic factors in elderly patients with breast cancer. BMC Surg 13 Suppl 2:S2, 2013
22. Brockton NT, Gill SJ, Laborge SL, et al: The Breast Cancer to Bone (B2B) Metastases Research Program: a multi-disciplinary investigation of bone metastases from breast cancer. BMC Cancer 15:512, 2015
23. Coleman RE, Rubens RD: The clinical course of bone metastases from breast cancer. Br J Cancer 55:61-6, 1987
24. van Acker HH, Anguille S, Willemen Y, et al: Bisphosphonates for cancer treatment: Mechanisms of action and lessons from clinical trials. Pharmacol Ther 158:24-40, 2016

25. Coleman RE, Collinson M, Gregory W, et al: Benefits and risks of adjuvant treatment with zoledronic acid in stage II/III breast cancer. 10 years follow-up of the AZURE randomized clinical trial (BIG 01/04). J Bone Oncol 13:123-135, 2018
26. Gnant M, Mlineritsch B, Stoeger H, et al: Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. Ann Oncol 26:313-20, 2015
27. Paterson AH, Anderson SJ, Lembersky BC, et al: Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial. Lancet Oncol 13:734-42, 2012
28. EBCTCG: Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 386:1353-1361, 2015
29. Vliek SB, Noordhoek I, Meershoek-Klein Kranenbarg E, et al: Daily Oral Ibandronate With Adjuvant Endocrine Therapy in Postmenopausal Women With Estrogen Receptor-Positive Breast Cancer (BOOG 2006-04): Randomized Phase III TEAM-IIB Trial. J Clin Oncol 40:2934-2945, 2022
30. Inda MA, Blok EJ, Kuppen PJK, et al: Estrogen Receptor Pathway Activity Score to Predict Clinical Response or Resistance to Neoadjuvant Endocrine Therapy in Primary Breast Cancer. Mol Cancer Ther 19:680-689, 2020
31. van der Plas-Krijgsman WG, Giardiello D, Putter H, et al: Development and validation of the PORTRET tool to predict recurrence, overall survival, and other-cause mortality in older patients with breast cancer in the Netherlands: a population-based study. Lancet Healthy Longev 2:e704-e711, 2021
32. Lee SJ, Lindquist K, Segal MR, et al: Development and validation of a prognostic index for 4-year mortality in older adults. Jama 295:801-8, 2006