Risk assessment tools and adjuvant therapy for breast cancer

Noordhoek, I.

Chapter 1

GENERAL INTRODUCTION

Iris Noordhoek

HISTORY OF ENDOCRINE THERAPY

The treatment of breast cancer has long since consisted of a combination of locoregional management and of systemic cytotoxic and endocrine management. Already in 1896, it was discovered that breast tumors could be sensitive to hormones and metastatic growth reduced by performing an oophorectomy.[1] However, only one third of patients derived clear benefit from this type of treatment.[2] The discovery of the estrogen and progesterone receptor (ER and PR) in 1958 allowed for better selection of patients that would benefit from hormone depletion.[3] When hormones bind to these receptors, a cascade of events is triggered, resulting in cell division and tumor growth.[4] Breast cancer cells that do not express hormone receptors receive growth signals via other pathways, and are not affected by the presence or absence of hormones.

In 1960, oral tamoxifen, a selective estrogen receptor modulator, was introduced as an alternative to surgical ovarian ablation.[5] Tamoxifen has an antagonistic action in breast tissue, preventing estrogen from binding to the receptor and blocking the signaling cascade.[6] Several trials in patients with ER positive breast cancer demonstrated that using tamoxifen decreased the risk of developing breast cancer recurrences. Later, a large meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) established that using tamoxifen for five years significantly decreased breast cancer recurrence and mortality.[7]

During the early 2000's, another type of drug became available to inhibit the growth of hormone receptor positive tumors; the aromatase inhibitor (AI).[8] In postmenopausal women, the only source of estrogen comes from the conversion of androgen to estrogen through the enzyme aromatase.[9] When this conversion is inhibited, there is no estrogen available to bind to the hormone receptors, and the tumor will not receive the signal for cell division. Several trials were conducted to compare different types of endocrine therapy (ET) for postmenopausal patients. Another meta-analyses by the EBCTCG showed that five years of AI monotherapy yields similar results as two to three years of tamoxifen followed by two to three years of an AI. Five years of tamoxifen monotherapy was proven an inferior treatment.[10]

EPIDEMIOLOGY OF BREAST CANCER

Breast cancer is still the most common type of cancer amongst women, though the distribution over different age categories changed significantly.[11,12] The proportion of women that are postmenopausal at diagnosis has increased from 74% in 1989 to 80% in 2019, and patients aged 70 years or over currently represent a third of all breast cancer patients (**figure 1**).[11] Nowadays, the systemic treatment strategy for postmenopausal patients with breast cancer is determined by clinical, histopathological and genetic parameters, and hormone receptors are still the most important of these biomarkers. Approximately 85% of all postmenopausal patients have breast tumors with ER or PR expression, or both.[13,14] Guidelines recommend 5 years of AI treatment for these patients.[15]

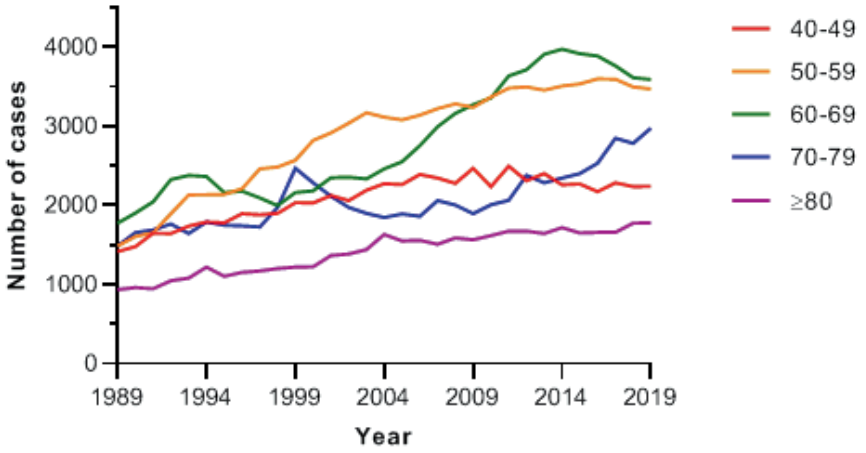

Figure 1: Incidence of invasive breast cancer in the Netherlands from 1989 to 2019 for five age categories. Data was obtained from the Dutch Cancer Registry (NKR).[11]

CHALLENGES IN THE TREATMENT OF BREAST CANCER

Much progress has been made in the past decades, and breast cancer survival has improved significantly. Nevertheless, several concerns in the treatment of hormone receptor positive breast cancer still remain.

Even after optimal locoregional management and adjuvant systemic therapy, breast cancer patients still have a lifetime risk of 20 to 41% of developing a recurrence, depending on tumor size and nodal status at diagnosis.[16] Apparently, endocrine therapy cannot prevent tumor recurrences in all patients with hormone receptor positive tumors and selection of patients that derive long term benefit from ET can still be improved.

Another concern is that hormone receptor positive breast cancer is characterized specifically by late recurrences. Two-thirds of recurrences happen after five years, i.e., after discontinuation of ET, and the risk of developing a recurrence continues to accumulate until 20 years after diagnosis.[16] Recent trials have demonstrated that extending ET beyond five years can reduce the risk of late distant recurrences (DR) and improve disease-free survival (DFS) in patients that have been treated with five years of tamoxifen monotherapy.[17,18] However, the effect of extending ET in patients treated with an AI are inconclusive, and as of yet, a clinically relevant benefit has not been demonstrated.[19-22] Combining these factors with the serious adverse events that accompany prolonged endocrine treatment, it would be irresponsible to treat all patients with extended ET. On the other hand, some patients do benefit from extended ET, and they must be identified to receive their optimal treatment.

Furthermore, the increasing age at which patients are diagnosed presents a problem. As mentioned, 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. 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.[23] On top of that, older patients usually have more comorbidities and frailty than younger patients.[24] 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.[25] Nevertheless, these age-specific factors are often not taken into account when determining the treatment strategy for older patients, which can lead to significant overtreatment of this population.[26,27]

PROGNOSTIC AND PREDICTIVE MODELS

Different types of models exist that can be used to help tailor adjuvant treatment to the individual patient. *Prognostic models* aim to identify patients that have an inherently worse disease prognosis and have a higher risk of developing recurrences. This risk assessment is then used to select patients for specific adjuvant treatment strategies. *Predictive models* are based on the idea that the patients with high risk of breast cancer recurrence are not necessarily the same patients who benefit from more extensive therapy, and aim to identify patients that derive the most benefit from therapy regardless of underlying prognosis.[28]

An obvious example of a predictive marker is the hormone receptor, as patients with ER negative breast cancer derive no benefit from ET at all. Breast tumors are deemed ER or PR positive when 1-10% or more of the cancer cells express these receptors. However, as has been established, some patients with ER positive breast cancer still have little benefit of ET. It is generally claimed that when tumors have a higher number of cells expressing ER or PR, they are more sensitive to and gain more effect from endocrine therapy (ET), though a consensus has not yet been reaches on the definition of high versus low levels of expression.[29] **Chapter 2** of this thesis investigates whether the quantitative assessment of hormone receptors is a better method to select patients for ET than the single cut-off value of 10%.

An example of a prognostic tool that is being used in clinical practice is the CTS5 (clinical treatment score post-5 years). The CTS5 aims to estimate the risk of late DR (i.e., after five years), provided that the patient was recurrence-free in the first five years after diagnosis. The CTS5 calculator generates a percentage that reflects the risk of developing a recurrence between five and ten years after diagnosis, and also categorizes patients as low, intermediate, or high risk. This risk estimation is based on readily available clinical and histopathological parameters.[30] **Chapter 3** of this thesis studies the utility and accuracy of the CTS5 to determine the risk of late DR and whether it can be used to predict benefit from extended ET.

A biomarker panel that was primarily developed as a predictive model is the Breast Cancer Index (BCI). BCI 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.[31] 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.[32] Previous

studies have established that BCI can identify patients that benefit of extended ET after five years of tamoxifen monotherapy. Whether BCI can also identify patients that benefit of extended ET after treatment with an AI, is described in **chapter 4** of this thesis.

Risk estimation in older patients is generally based on the same factors as in younger patients. Therefore, the age-related factors regarding recurrence risk and (adverse) effects of treatment, are often not taken into account when determining the treatment strategy.[26] 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.[33] 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. 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 is examined.

ANOTHER APPROACH TO ADJUVANT THERAPY

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.[34,35] When metastatic cells infiltrate bone tissue, the equilibrium between osteoclasts and osteoblasts is disturbed.[36] 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.[35]

Nitrogen-containing bisphosphonates also affect bone metabolism by inhibiting key enzymes of the intracellular mevalonate pathway. This decreases osteoclast-mediated bone resorption and osteoclast survival, causing an increase in bone density and a decreased release of cytokines and growth factors.[37] It is hypothesized that this makes bone a less attractive environment for metastatic breast cancer cells.[38]

Several trials have investigated the effect of (neo)adjuvant bisphosphonates on (breast) cancer recurrence. 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, but not in the premenopausal subgroup.[39] 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 are described in **chapter 6**.

Chapter 7 discusses and interprets the main results presented in this thesis and provides perspectives for the future.

REFERENCES

1. Beatson GT: On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases. Lancet 2:104-107, 1896
2. Boyd S: On oophorectomy in cancer of the breast. Br Med J 2:1161-1167, 1900
3. Jensen EV, Jacobson HI: Fate of steroid estrogens in target tissues. Biological Activities of Steroids in Relation to Cancer:161-174, 1960
4. Russo J, Russo IH: The role of estrogen in the initiation of breast cancer. J Steroid Biochem Mol Biol 102:89-96, 2006
5. Quirke VM: Tamoxifen from Failed Contraceptive Pill to Best-Selling Breast Cancer Medicine: A Case-Study in Pharmaceutical Innovation. Front Pharmacol 8:620, 2017
6. Lewis JS, Jordan VC: Selective estrogen receptor modulators (SERMs): mechanisms of anticarcinogenesis and drug resistance. Mutat Res 591:247-63, 2005
7. EBCTCG: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687-717, 2005
8. Buzdar A, Howell A: Advances in aromatase inhibition: clinical efficacy and tolerability in the treatment of breast cancer. Clin Cancer Res 7:2620-35, 2001
9. Cui J, Shen Y, Li R: Estrogen synthesis and signaling pathways during aging: from periphery to brain. Trends Mol Med 19:197-209, 2013
10. EBCTCG: Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 386:1341-1352, 2015
11. Dutch Cancer Registry (NKR), IKNL. Obtained through https://www.iknl.nl/nkr-cijfers, accessed on April 4 2021.
12. 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
13. Osborne CK, Schiff R: Estrogen-receptor biology: continuing progress and therapeutic implications. J Clin Oncol 23:1616-22, 2005
14. Rosenberg PS, Barker KA, Anderson WF: Estrogen Receptor Status and the Future Burden of Invasive and In Situ Breast Cancers in the United States. J Natl Cancer Inst 107, 2015
15. Nationaal Borstkanker Overleg Nederland; https://www.oncoline.nl/borstkanker; accessed on April 8, 2021.
16. 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
17. Davies C, Pan H, Godwin J, et al: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381:805-16, 2013
18. Goss PE, Ingle JN, Pritchard KI, et al: Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med 375:209-19, 2016
19. 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
20. Gnant M, Steger G, Greil R, et al: Abstract GS3-01: A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial. Cancer Res 78:GS3-01-GS3-01, 2018
21. Mamounas EP, Bandos H, Lembersky BC, et al: Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 20:88-99, 2019
22. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al: Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol 18:1502-1511, 2017
23. de Boer AZ, van der Hulst HC, de Glas NA, et al: Impact of Older Age and Comorbidity on Locoregional and Distant Breast Cancer Recurrence: A Large Population-Based Study. Oncologist 25:e24-e30, 2020
24. Klepin H, Mohile S, Hurria A: Geriatric assessment in older patients with breast cancer. J Natl Compr Canc Netw 7:226-36, 2009
25. Lee SY, Seo JH: Current Strategies of Endocrine Therapy in Elderly Patients with Breast Cancer. Biomed Res Int 2018:808-820, 2018
26. Cardoso F, Kyriakides S, Ohno S, et al: Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 30:1194-1220, 2019
27. Derks MGM, Bastiaannet E, Kiderlen M, et al: Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: a population-based cohort study from the EURECCA Breast Cancer Group. Br J Cancer 119:121-129, 2018
28. Sechidis K, Papangelou K, Metcalfe PD, et al: Distinguishing prognostic and predictive biomarkers: an information theoretic approach. Bioinformatics 34:3365-3376, 2018

29. Curigliano G, Burstein HJ, Winer EP, et al: De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol 28:1700-1712, 2017
30. 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
31. 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
32. Sgroi DC, Carney E, Zarrella E, et al: Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. J Natl Cancer Inst 105:1036-42, 2013
33. 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
34. 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
35. Coleman RE, Rubens RD: The clinical course of bone metastases from breast cancer. Br J Cancer 55:61-6, 1987
36. Coleman R, Gnant M: New results from the use of bisphosphonates in cancer patients. 3:213-218, 2009
37. Rogers MJ, Crockett JC, Coxon FP, et al: Biochemical and molecular mechanisms of action of bisphosphonates. Bone 49:34-41, 2011
38. van de Ven S, Kroep JR, Hamdy NA, et al: [Antitumour effects of bisphosphonates in breast cancer]. Ned Tijdschr Geneeskd 154:A1951, 2010
39. EBCTCG: Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 386:1353-1361, 2015

1