A difficult balancing act : Informing breast cancer patients about adjuvant systemic therapy

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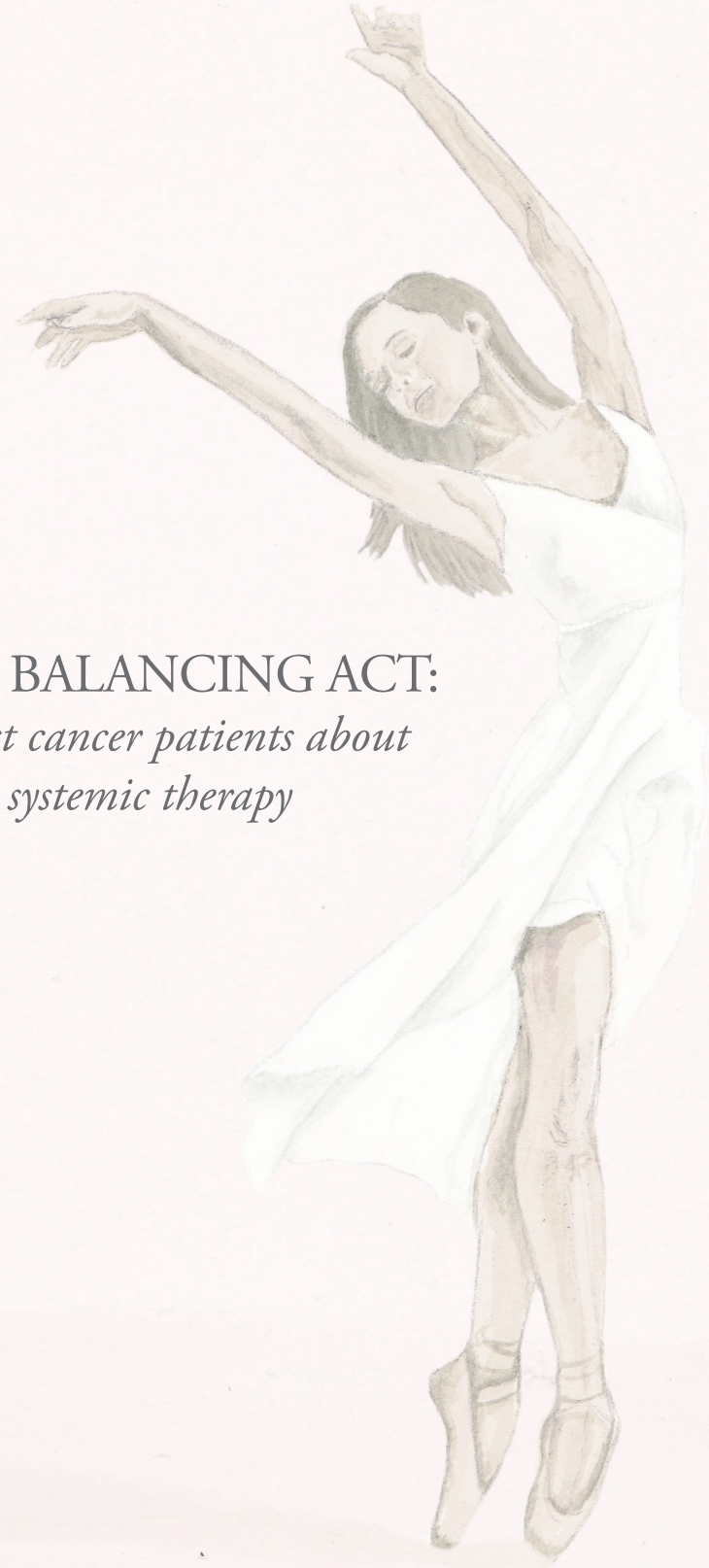

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In loving memory of Lucio Engelhardt and Herbert Provence

Caminante, son tus huellas,
el camino y nada más.
Caminante, no hay camino,
se hace camino al andar.
Al andar se hace el camino,
y al volver la vista atrás.
se ve la senda que nunca
se ha de volver a pisar.
Caminante no hay camino
sino estelas en la mar.

(Antonio Machado – Excerpt from Proverbios y cantares XXIX in Campos de Castilla, 1912)

Content

Part I

General introduction

Chapter 1

Introduction

Ellen Engelhardt

Epidemiology and treatment of early–stage breast cancer

Breast cancer is the third most frequently diagnosed type of cancer in the Netherlands (1), and the most common type of cancer diagnosed in women (1). In 2015, a total of 14.449 women were diagnosed with invasive breast cancer in the Netherlands (1). Due to advances in treatment and earlier detection of tumors, survival has improved over the past decades (1). Overall five-year survival rates are about 90% and 10-year survival is on average about 70% (1). Unfortunately, in the Netherlands on a yearly basis still more than 3.000 women die due to breast cancer (1).

The primary treatment for breast cancer is radical excision of the tumor (via a mastectomy or breast conserving surgery). Surgery is commonly supplemented with adjuvant treatments, i.e., radiotherapy and systemic therapy (2). The focus of this thesis is on the systemic therapy modalities for early-stage breast cancer, namely chemotherapy alone or in combination with biological response modifiers (e.g., trastuzumab) and/or endocrine therapy. These treatment modalities are intended to decrease the probability of the cancer recurring and consequently improving patients' long-term survival (3-5). However, they are also associated with side-effects that can significantly impact patients' quality of life (3,4,6,7).

Prediction tools and communication of risks

Adjuvant treatment modalities essentially target a risk and not demonstrable disease. This means that a proportion of patients who undergo treatment do so unnecessarily as they either had already been cured by the resection of the primary tumor or would have developed a disease recurrence and/or distant metastases in spite of adjuvant treatment. Notwithstanding the advancements in medical science, it is not (yet) possible to predict a priori whether an individual patient will be amongst the patients that profit from adjuvant systemic therapy. Eligibility for systemic therapy is currently based on consensus amongst medical experts about how much survival gain is minimally needed for the benefits of treatment to outweigh the loss in quality of life due to its side-effects. The uncertainty about whether or not treatment is necessary is one of the factors that can make decision-making about adjuvant systemic therapy complex for oncologists. Current (inter-) national clinical breast cancer treatment guidelines deem 3-5% absolute 10-year survival gain sufficient to discuss adjuvant systemic therapy with patients (2,8,9). This means that minimally about one in every 20-30 patients treated should benefit from the treatment. For some subgroups of patients, e.g., those with Her2-positive disease, benefits smaller than 3% are also deemed acceptable in clinical guidelines (2,8,9).

Clinical decision-making about adjuvant systemic therapy relies, among others, on statistical evidence to assess the risk of disease recurrence and death. Many tools, such as nomograms and prediction models, have been developed to primarily inform

clinicians' decision-making process. Such tools use clinical characteristics (e.g., tumor size and the presence of nodal metastases) or biomolecular markers to estimate relapse and/or mortality risk with/without the potential treatment benefit. Well-known prediction tools are for example Adjuvant! (10), PREDICT (11), MammaPrint (12), and Oncotype Dx (13). The use of Adjuvant! (2,8,9), and Oncotype Dx (8) to support decision-making is endorsed by clinical guidelines. These tools seem to meet a need in clinical practice, as the be it limited evidence available on the use of for example Adjuvant!, suggests that it is commonly used by clinicians (14,15). However, evidence is lacking on clinicians' reasons for using such tools and how and when they use them.

Although most prediction tools were primarily developed to aid clinicians' decision-making, they can be used during consultations with patients. A frequently uttered argument against the use of prediction tools to inform patients about their prognosis is that people generally struggle to understand probabilistic information. The literature underscores this (16). It is feared that patients might not grasp the fact that the estimates provided by prediction tools are just that – estimates. Patients might cling too much to the numbers and not realize that it is not possible to predict the outcome a priori, and that there is a margin around the survival estimates. Risk communication experts argue from an ethical perspective that if oncologists communicate survival estimates from prediction tools to patients, then they should also explicitly discuss the uncertainty associated with these estimates (17). It is unclear whether or not oncologists explicitly discuss these uncertainties during patient consultations. Also, it is unclear whether patients are aware of the uncertainty associated with the survival estimates.

Decision-making about adjuvant systemic therapy

The expected survival gain due to treatment can be modest for patients with early-stage breast cancer, especially those with stage I disease, and treatment is associated with side-effects. Foregoing treatment is therefore, also a medically viable option. These treatment decisions are preference-sensitive, there is usually no 'right' choice regarding systemic therapy, and decision-making needs to be guided by patients' values and their informed preferences. Oncologists are tasked with helping their patients to form a judgement on whether treatment is worthwhile or not. Firstly, oncologists must make their patients aware that a treatment decision needs to be made and that patients' input is essential. Secondly, to facilitate patient participation in the decision-making process, oncologists need to inform them about all the relevant pros and cons of the viable treatment options – including the option to forego treatment. It is crucial that information provision is comprehensive and balanced. Finally, once patients are made aware of the pros and cons of treatment, oncologists should ascertain how their patient weighs the pros and cons. This discussion should be the basis for decision-making, irrespective of who makes the final treatment decision.

The steps described above are the cornerstones of shared decision making (SDM), which is advocated as an ideal approach to clinical decision-making. Although, these steps might seem straightforward and clinicians indicate they practice SDM, available evidence suggests that the implementation of SDM in clinical practice is limited (18). For example, Kunneman et al. (19) evaluated the implementation of the first step of SDM in oncology consultations where preference-sensitive treatment decisions needed to be made. In only 3 out of 100 consultations oncologists explicitly stated that a treatment decision needed to be made (19). The focus of this thesis will be on the second step of SDM. Thus, information provision and the potential barriers to balanced information provision in the context of adjuvant systemic therapy for breast cancer.

Thorough and balanced information provision is crucial to help patients weigh the pros and cons and develop informed treatment preferences. However, providing patients with balanced and comprehensive information is difficult. Presenting all available information is not always possible or desirable. Adjuvant systemic therapies for breast cancer, for example, are associated with numerous potential side-effects. It is thus unfeasible, ineffective and arguably unnecessary to discuss all these side-effects with patients. Oncologists need to find a way to inform their patients without overwhelming them with too much information, thus choices must be made with regards to which information is provided and how it will be presented. Current clinical breast cancer guidelines do not offer guidance on what information should minimally be discussed (2,8,9). Therefore, oncologists must make a judgement call about what information is essential for patients to know in order to decide about treatment. This lack of guidance on what minimally needs to be communicated can cause unwanted variability in information provision between (and also within) oncologists. Indeed, this has been shown in the literature (20). Oncologists' valuation of what information is relevant for patients to know in the context of decision-making, need not match the patient's needs and preferences (21). For example, side-effects deemed irrelevant by oncologists, might be perceived as an unacceptable burden on their quality of life by patients. In order to determine whether it is relevant to communicate a specific side-effect, it is important to have some insight into the patients' personal situation and their preferences. The literature suggests that clinicians rarely explore patients' personal situation and the veracity of their assumptions with regard to what is relevant for the patient to know (18,22).

Further, the use of tools such as Adjuvant!, can help oncologists and patients get a better grasp on the magnitude of the potential treatment benefits. However, Adjuvant! (like other tools) does not provide information about side-effects. Thus, the use of prediction tools could shift the focus of the consultation towards the survival probabilities to the detriment of information provision about side-effects. This imbalance in information provision could prevent adequate valuation of the trade-off involved between the benefits and harms of treatment. There currently is no evidence on whether and

how the use of prediction tools influences information provision.
The choices oncologists make with regard to which information they convey or omit and how they frame the information presented to patients, could (unconsciously) be influenced by their preferences/beliefs about which treatment option is in their patients' best interest. It is perhaps unrealistic to expect that clinicians are conscious of their preferences and preconceptions and are able to put these aside during consultations, and provide patients with information not colored by their (clinical) experiences and beliefs. Even if oncologists consciously tailor their information to steer patients towards the treatment option they favor, they most likely act in what they believe is in their patient's best interest. Hence, is framing a cause for concern? Especially, in clinical situations where there is no obvious best option from a medical perspective (i.e., a preference-sensitive treatment decision), the choices clinicians make, can have important unwanted consequences. From the oncologist's selection and way of presenting the information, patients might for example, get the impression that the option their oncologist seems to favor is the best option, and might therefore feel compelled to consent to a treatment plan that does not fit with their own goals and preferences. Systematic evaluation is lacking of whether implicit value judgements are used in information provision about adjuvant systemic therapy. There are indications from other settings that such behaviors are used in clinical practice (23,24).

Aim of this thesis

Patient participation in the treatment decision-making process is widely advocated and essential in the context of preference-sensitive treatment decisions. A key requirement to achieve this goal is thorough and balanced information provision about the benefits and harms of the viable treatment options. There are many factors that can negatively influence information provision in clinical practice. Unfortunately, insights in information provision during real-time patient consultations involving preference-sensitive decisions is limited. The objective of the work presented in this thesis is to assess information provision about adjuvant systemic therapy during consultations between early-stage breast cancer patients and medical oncologists in general. In this era of personalized medicine, prediction tools (e.g., Adjuvant!) are becoming an integral part of information provision during patient consultations. However, evidence is lacking about a) how prevalent the use of such tools is during patient consultations, and b) whether and how the use of such tools influences information provision. Therefore, this thesis in addition to assessing the availability and the quality of prediction tools for the early-stage breast cancer setting, also zooms in on the use of such tools during patient consultations and their impact on the content of consultations.

Outline of this thesis

This thesis consists of three parts. In Part I, two studies are presented that investigate the availability and accuracy of risk prediction models for decision-making about adjuvant

systemic therapy for early-stage breast cancer. An essential prerequisite for the use of such tools, is that their estimates have to be accurate. In Chapter 2 we provide a systematic overview of published risk prediction models for adjuvant systemic therapy selection in early-stage breast cancer. This review provides insight in the strengths and weaknesses of the identified models. Most prediction tools were developed to inform clinicians' decisions, yet they are also used to inform patients. Therefore, in this chapter we also assessed the required literacy level to comprehend the content of the output provided by these tools. In Chapter 3 we assessed the prognostic accuracy of Adjuvant! and PREDICT's 10-year all-cause mortality estimates in breast cancer patients aged <50 years at diagnosis. These are two well-known freely available prognostic tools used in clinical practice. We now focus on young patients as previous validation studies had too few young patients (e.g., (25)), and/or the follow-up time was too brief (e.g., (26)) to draw conclusions about the accuracy of these tools in this younger patient population. Available studies do suggest that Adjuvant! underestimates mortality in young patients (e.g., (27)).

The second part consists of two studies in which we assessed oncologists' attitudes towards and self-reported use of tools to communicate the benefits of adjuvant systemic therapy for early-stage breast cancer. In Chapter 4 we assess oncologist's perception of the minimal benefit that makes treatment worthwhile given the side-effects. Clinical guidelines indicate that 3-5% is the minimum benefit that makes treatment worth considering given its side-effects (2,8,9). We assessed whether oncologists' minimally required benefit to tip the scale in favor of treatment is in line with the guidelines. These insights are relevant as oncologists' preferences and beliefs can influence their information provision and treatment recommendations. Further, little is known about oncologists' perceptions of and reasons for using prediction tools, and views on communicating the uncertainty associated with prognostic estimates from such tools. Therefore, we investigated this in the study reported in Chapter 5.

The third part consists of three studies assessing information provision about the benefits and harms of adjuvant systemic therapy for early-stage breast cancer during real-time patient consultations. In Chapter 6 we assessed the frequency and the influence of the use of Adjuvant! on information provision about the benefits and harms of adjuvant systemic therapy, and whether the use of this tool is associated with the likelihood of reaching a decision during the consultation. In Chapter 7 we zoom in on a controversial element of risk communication, namely the communication of the uncertainty associated with the prognostic estimates provided by prediction tools. There currently are no generally accepted guidelines on whether and how to communicate uncertainty, and evidence on whether uncertainty is communicated in clinical practice is also lacking. In the study reported in this chapter, we assessed whether and which type of uncertainty was communicated during patient consultations in which Adjuvant!

was used. We also assessed how patients perceived the uncertainty associated with the prognostic estimates communicated during the consultation. Finally, in Chapter 8 we explored whether the presentation of information about adjuvant systemic therapy during the consultation contained implicitly persuasive elements. Such behaviors could inadvertently steer patients facing preference-sensitive decisions towards a particular choice that might not be in line with the patients' values and goals.

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Part II

Availability and accuracy of risk prediction models for decision-making about adjuvant systemic therapy for early-stage breast cancer

Chapter 2

Predicting and communicating the risk of recurrence and death in women with early-stage breast cancer: *a systematic review of risk prediction models*

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Abstract

Background

It is a challenge for oncologists to distinguish breast cancer patients who can forego adjuvant systemic treatment without negatively affecting survival from those who cannot. Risk prediction models (RPM) have been developed for this purpose. Oncologists seem to have embraced RPM (particularly Adjuvant!) in clinical practice, and often use them to communicate prognosis to patients. We performed a systematic review of published RPM, and provide an overview of the prognosticators incorporated and reported clinical validity. Subsequently, we selected the RPM that are currently used in the clinic for a more in-depth assessment of clinical validity. Finally, we assessed lay comprehensibility of the reports generated by RPM.

Methods

PUBMED, EMBASE and Web of Science were searched. Two reviewers independently selected relevant papers and extracted data. Agreement on paper selection and data extraction was achieved in consensus meetings.

Results

We identified RPM based on: clinical prognosticators (N=6) and bio-molecular features (N=14). Generally predictions from RPM appear to be accurate, except for patients ≤50 years or ≥75 years at diagnosis, and Asian populations. RPM reports contain much medical jargon or technical details, which are seldom explained in lay terms.

Conclusions

The accuracy of RPM's prognostic estimates is suboptimal in some patient subgroups. This urgently needs to be addressed. In their current format RPM reports are not conducive to patient comprehension. Communicating survival probabilities using RPM might seem straightforward, but it is fraught with difficulties. If not done properly, it can backfire and confuse patients. Evidence to guide best communication practice is needed.

Introduction

Breast cancer is a heterogeneous disease with great diversity in morphology and clinical behavior (1). A major challenge for oncologists is determining which patients might benefit from adjuvant systemic therapy. Prognosis estimates, the basis for selecting patients who might benefit from systemic therapy, are usually based on traditional clinicopathological factors, such as nodal status and hormone receptor status. Increased awareness, screening, and improvements in breast cancer diagnosis have led to early detection of smaller tumors without lymph node involvement. Using the traditional clinical prognosticators, one would assume that these tumors have a low recurrence risk, and more patients might be spared systemic therapy without adversely affecting survival. Yet, small tumors have also been shown to have metastatic potential, and the lack of sufficiently discriminating predictors has led to the broadening of the indication for systemic therapy (1-4). Nowadays, virtually all breast cancer patients meet eligibility criteria for adjuvant systemic therapy (5, 6). It has been argued that up to 60% of these patients, treated according to current guidelines, only experience loss of quality of life due to toxicity with little or no survival benefit (5).

In light of patients' loss of quality of life and financial costs to society, reducing over-treatment is an important goal to patients, oncologists, and policy-makers alike. As a result, many risk prediction models (RPM) have been developed to help oncologists select patients who might derive benefit from systemic therapy. RPM are primarily designed to provide oncologists with standardized, reproducible, and evidence-based tools to aid clinical decision-making. The earliest models were solely based on (a subset of) the traditional clinicopathological factors, e.g. Nottingham Prognostic Index (NPI) (7) and Adjuvant! (8). In the last decade RPM based on genetic profiles or other bio-molecular features were introduced, such as Oncotype Dx (9) and MammaPrint (10). RPM generally provide pretreatment prognostic information to quantify the benefit that patients can obtain from various available adjuvant systemic therapies and/or classify patients according to their risk of death and/or cancer recurrence. RPM can be valuable and reliable aids in decision-making for oncologists, but they face two major challenges. First, RPM differ in what information they use to predict prognosis and adjuvant treatment benefit. Therefore the choice of RPM can affect the probabilities given for an individual patient. Second, communicating probabilities from these models to patients is difficult.

Small surveys in the US (11) and UK (12) found that the majority of oncologists (>95%) used Adjuvant!. Two thirds frequently discuss the RPM estimates with patients (12). Studies have reported that less than half of breast cancer patients provided with prognostic estimates from Adjuvant! were able to accurately indicate their prognosis after the consultation (13, 14).

RPM often provide a report or a graphical representation of the probability estimates that could facilitate the presentation of this type of information to patients. A small UK survey found that 20% of oncologists frequently provide patients with a printout of the Adjuvant! report (12). However, since the target audience of RPM are oncologists rather than patients, it remains unknown to what extent patients understand the RPM reports and whether they benefit from these graphical presentations.

The number of RPM has increased steadily. As we expect their use to become even more common, insight into their clinical validity is becoming increasingly relevant. The aim of this review is threefold. Firstly, we provide a systematic overview of all published RPM that aim to aid adjuvant systemic therapy selection in early-stage breast cancer. For the identified RPM we describe a) the prognosticators incorporated, b) reported prognostic strengths and weaknesses, and c) presentation of the model estimates. Secondly, for the RPM most frequently used in clinical practice we assessed a) the characteristics of the validation populations, and b) reported accuracy of the prognostic estimates. Thirdly, we discuss the content of the RPM reports, and assess the required literacy level to comprehend them.

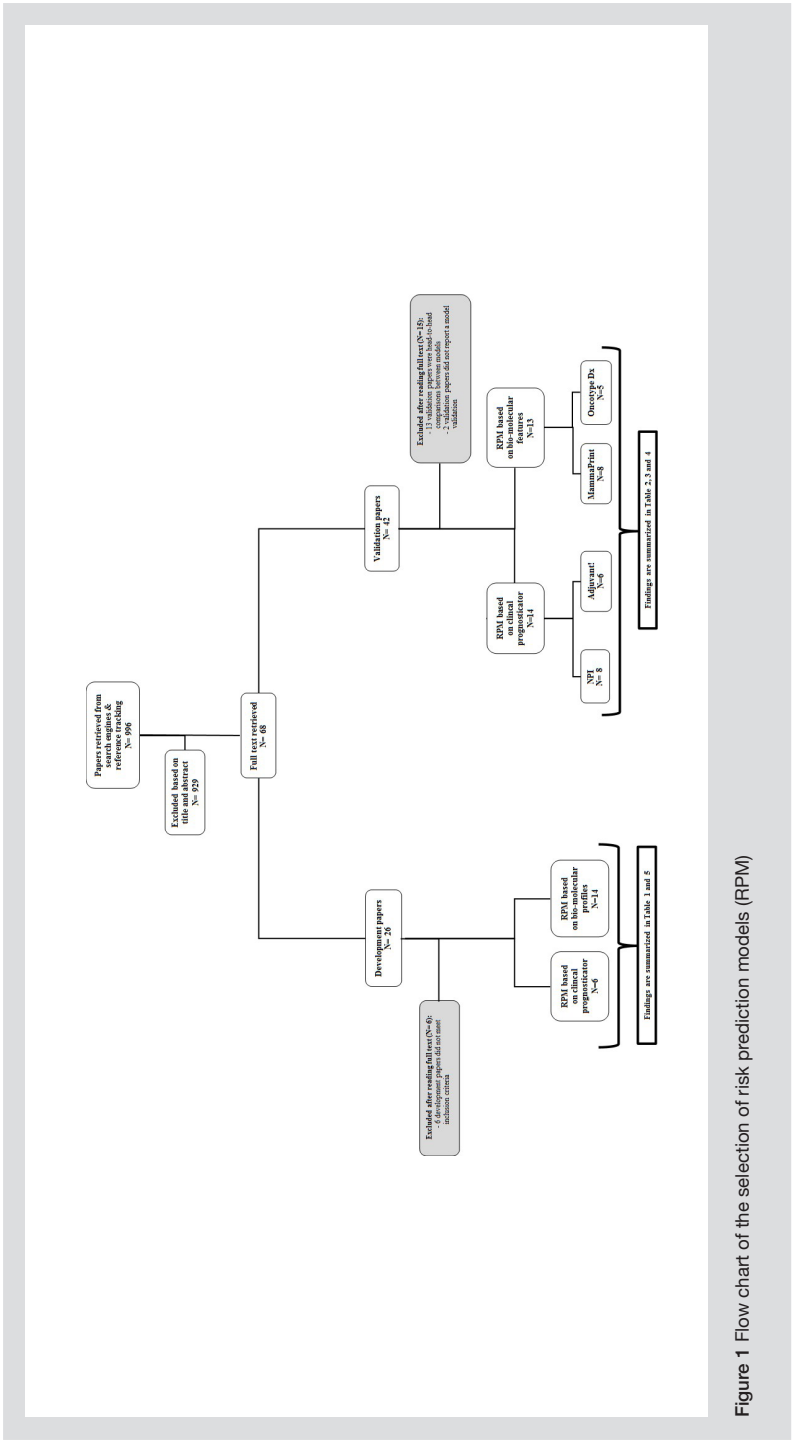

Figure 1 Flow chart of the selection of risk prediction models (RPM)

Methods

Aim 1: Systematic overview of RPM

Selection of published RPM and data extraction

Relevant papers in English were identified through searches in PUBMED, EMBASE and Web of Science, up to July 2012. We wanted to include all papers describing the development of RPM estimating breast cancer prognosis, aiming to aid the selection of patients for adjuvant systemic therapy, irrespective of whether they were based on clinical prognosticators or bio-molecular features. RPM were excluded if they a) were specifically developed for the neo-adjuvant setting, and b) only aimed to determine a single clinical or bio-molecular feature, such as tumor grade. Our search strategy consisted of search terms for a) prognostic models (including names of known prognostic models), b) breast cancer and c) adjuvant systemic therapy. **Web appendix 1** contains the terms used in each database. Two appraisers (E.G.E. and A.M.S.) independently selected papers that met the inclusion criteria based on titles and abstracts. If there was disagreement or doubt about eligibility, the paper was included in the selection for which the full-text was independently reviewed by two appraisers (E.G.E. and M.M.G.) and inclusion was determined by consensus. For included papers details on the a) aim of the model, b) development process, c) characteristics of the development and validation population(s) (if applicable), and d) reported clinical validity were retrieved.

Aim 2: Assessment of clinical validity of frequently used RPM

We define clinical validity as the accuracy of the RPM's estimate of overall (OS) or recurrence-free (RFS) survival compared to observed OS or RFS (15). When we refer to validation studies, we mean studies in which clinical validity of a RPM was assessed in a population other than the one it was developed in. Our focus is the accuracy of the prognostic estimates and not the accuracy of the RPM predictions of treatment response (if that was also an aim of the RPM).

Selection and data extraction from validation studies

We performed an extensive assessment of the RPM to which (international) clinical guidelines refer as an indication of their actual use in clinical practice. Guidelines we used were: ESMO (16); NCCN (17); NICE (18, 19); and St. Gallen (20); and the report of the consensus meeting on the influence of molecular genotyping (21). We searched PUBMED for all validation studies for the selected RPM: the NPI, Adjuvant!, MammaPrint and Oncotype Dx and consulted the references of papers retrieved and previously published reviews. Two appraisers (E.G.E. and M.M.G.) independently reviewed the papers retrieved and extracted details on a) characteristics of the validation population(s), including adjuvant treatment allocation and prevalence of recurrence, and b) clinical validity in patient subgroups.

Aim 3: Assessment of the RPM reports

Retrieval of RPM report

We sought to retrieve the report generated by each of the RPM identified by searching the manufacturer's website, Google or the link (if provided) to the model itself. If necessary, we contacted the author of the paper. We extracted information on a) the type of estimates reported, b) estimates of the uncertainty surrounding the survival estimates and c) graphical presentation formats if applicable. Moreover, to ascertain the minimal literacy level required to comprehend the RPM reports, two reviewers independently classified the use of medical or other technical jargon in the report as low, moderate or high. Disagreements in assessment of jargon use were resolved in consensus meetings. Additionally, we calculated a score for six frequently used readability indicators to provide an overall indication of the text difficulty with the Readability Test Tool (RDT) (22) (see **Web appendix 2** for an example of RDT's output and the algorithms used).

Results

Aim 1: Systematic overview of RPM

We identified 996 papers, which yielded 20 relevant RPM (Figure 1). Of the 26 development papers initially selected we excluded six after reading the full-text because the aim of the model described did not meet our inclusion criteria.

Six of the 20 RPM (7, 8, 23-26) are based solely on classical prognostic factors, while the others (9, 10, 27-38) are genetic profiles or based on novel bio-molecular factors (**Table 1**). Three (7, 8, 23) RPM based on clinicopathological features and all 14 bio-molecular signatures aim to predict relapse-free survival. Seven RPM (9, 26, 29, 30, 35, 37) are only intended for use in node-negative early stage breast cancer patients. Oncotype Dx (9), Mammostrat (34) and Theros BCI (30) are only intended for use in estrogen receptor (ER) positive patients. Of the RPM based on clinicopathological features, only CancerMath (25) and PREDICT (24, 39) take HER2-status into account when calculating prognosis estimates. All development studies identified reported that overall the clinical validity of the RPM was good or excellent in their target population (**Table 1**). Some studies did not report any limitations.

Aim 2: Assessment of clinical validity of frequently used RPM

The RPM currently most often used are: the NPI, Adjuvant!, MammaPrint and Oncotype Dx. In total we retrieved 42 validation studies (Figure 1). Two of those were excluded as they did not report a model validation. The studies retrieved reported on two types of model validations: comparisons of the estimates provided by the RPM of interest to 1) the observed survival (N=27) and/or 2) the estimates of other RPM and/or (inter) national clinical guidelines (N=13). To assess clinical validity, we restricted our in-depth analyses to validation studies that compared estimated to observed survival. Since comparisons between RPM and/or (inter) national clinical guidelines are prevalent and informative, we also briefly describe the findings of these types of comparisons (*not* incorporated in overview **Tables 1-5**).

Overview of studies comparing RPM estimates to observed survival

Table 2 provides an overview of the study design, population characteristics, and reported clinical validity for the 27 validation studies retrieved. Barring one case-control study (40), all validation studies had a retrospective design. Ten (40-49) of the validation studies were independent validation studies. The validation populations were mostly hospital-based, but Adjuvant! (50) and Oncotype Dx (51) were also validated in population-based cohorts. Also, MammaPrint was only validated on fresh frozen tissue, while Oncotype Dx was only validated on fixed paraffin-embedded tissue. Validation populations consisted mostly of patients diagnosed in the 1980s and 1990s. Only a small proportion of the patients in the validation populations were younger than 40

or older than 70 years. All validation studies retrieved, except for Buyse *et al.* (52), used patients who were treated systemically (chemotherapy and/or hormonal therapy) according to clinical guidelines applicable at the time the patients were diagnosed. Thus these validations are not 'pure validations', where RPM estimates are compared to observed survival in the absence of treatment or where treatment is allocated based on the outcome of the RPM of interest. **Table 3** presents an overview of treatment allocation and the prevalence of recurrence according to patient classification by NPI, MammaPrint and Oncotype Dx. Buyse *et al*. (52) assessed the clinical validity of MammaPrint in an untreated cohort, and reported that 16% of the patients classified as low risk and 30% of those classified as high risk developed recurrences. In the cohorts of treated patients, Oncotype Dx classified about 30% of patients as high risk, whereas MammaPrint classified about 50%-60% as high risk. MammaPrint classified 73% of the predominantly post-menopausal patients in the validation by Wittner *et al.* (49) as high risk. Oncotype Dx classified a significant proportion of patients as having an intermediate risk, but the clinical implications of this category are unclear (53-55). Figures 2a and 2b provide an overview of the variance in sensitivity, specificity and positive and negative predictive values between validation studies for MammaPrint and Oncotype Dx respectively (we do not show these estimates for the NPI, as useable data was retrieved for only 2 studies).

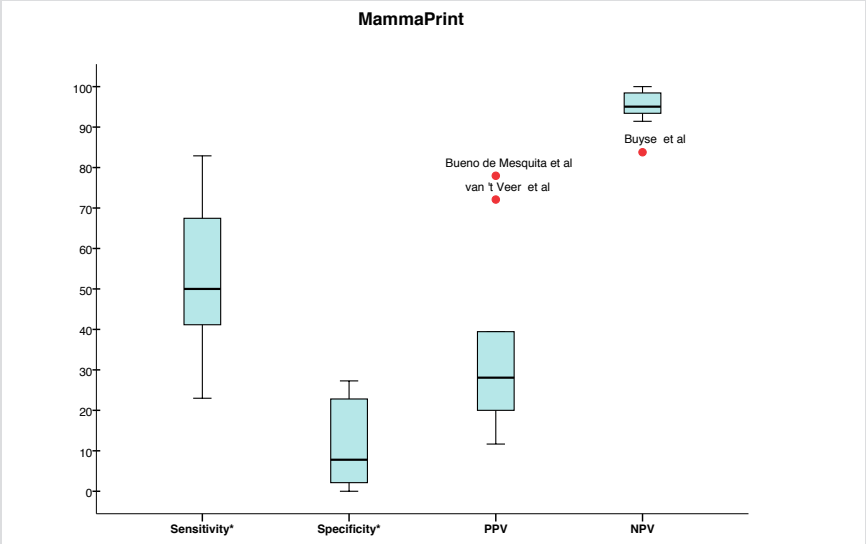

Figure 2a Variance in sensitivity, specificity and predictive value between studies for MammaPrint

Table 1 RPM based on classical prognostic factors for prognosis and/or prediction in invasive breast cancer

Characteristics	NPI	Adjuvant!	BC Nomogram	OPTIONS	PREDICT	CancerMath
Development described in:	Haybittle et al.(7)	Ravdin et al.(8)	Kattan et al.(26)	Campbell et al.(23)	Wishart et al.(24)	Michaelson et al.(25)
Publication year	1982	1996	2004	2010	2010	2011
Developed in:	UK	USA	USA	UK	UK	USA
Aims to predict*:	RFS	OS + RFS + Tx	BCSS	RFS	OS	OS + Tx
Target population particulars	NA	NA	- N0 - No prior BC	British patients	British patients	NA
Clinical prognostic factors included						
Age at diagnosis	No	Yes	Yes	Yes	Yes	Yes
Co-morbidities	No	Yes	No	No	No	No
Tumor morphology	No	No	No	No	No	Yes

* Aim of RPM: OS= Predicting overall survival ; RFS= Predicting recurrence-free survival ; BCSS= Predicting breast cancer specific survival ; Tx= Predicting systemic treatment benefit. NA = not applicable

Table 1 continued RPM based on classical prognostic factors for prognosis and/or prediction in invasive breast cancer

Characteristics	NPI	Adjuvant!	BC Nomogram	OPTIONS	PREDICT	CancerMath
Histological grade	Yes	Yes	Yes ductal vs. lobular	Yes	Yes	Yes
Tumor size	Yes	Yes	Yes	Yes	Yes	Yes
Nodal status	Yes	Yes	No	Yes	Yes	Yes
ER receptor status	No	Yes	No	Yes	Yes	Yes
Her2 receptor status	No	No	No	No	Yes	Yes
Effectiveness of systemic therapy regimens	No	Yes	No	Yes	Yes only chemo	No
Other prognostic factors	Vascular invasion	Using the "Prognostic factor impact calculator" extra factors can be incorporated	- Multifocality - LVI - Type of staining	NA	Mode of detection (screen-detected vs. symptomatic)	Specifics of loco-regional spread

* Aim of RPM: OS= Predicting overall survival ; RFS= Predicting recurrence-free survival ; BCSS= Predicting breast cancer specific survival ; Tx= Predicting systemic treatment benefit. NA = not applicable

Table 1 continued RPM based on classical prognostic factors for prognosis and/or prediction in invasive breast cancer

Characteristics	NPI	Adjuvant!	BC Nomogram	OPTIONS	PREDICT	CancerMath
Available as:	- Mobile app - Mathematical formula	- PDA-version - Website: www.adjuvantonline.com	Nomogram provided in paper (26)	- Excel sheet at: www.herc.ox.ac.uk/downloads/optionsv1/	- Website: www.predict.nhs.uk	- Website: www.lifemath.net/cancer/
The author(s) of the development study concluded:						
Predictive strengths	See Table 2	See Table 2	Overall accurate in target population	Overall accurate in target population	Overall accurate in target population	Overall accurate in target population
Predictive weaknesses	See Table 2	See Table 2	None mentioned	No patients with tumors >5cm in development population	Less accurate in patients: -<50 yrs -ER_{neg} patients -with tumors >5 cm -Grade 3 tumors ->75 yrs	No patients with tumors >5cm in study population

* Aim of RPM: OS= Predicting overall survival ; RFS= Predicting recurrence-free survival ; BCSS= Predicting breast cancer specific survival ; Tx= Predicting systemic treatment benefit. NA = not applicable

Table 2 Overview validation studies for NPI, Adjuvant!, MammaPrint and Oncotype Dx

Study characteristics	NPI	Adjuvant!	MammaPrint	Oncotype Dx
Nr. Of included studies	8 studies [41, 42, 45, 48, 66-69]	6 studies [43, 44, 46, 47, 50, 56]	8 studies [2, 49, 52, 57, 77-80]	5 studies [40, 51, 53-55]
Range of publication years	1987 – 2011	2005 – 2012	2002 – 2010	2006 – 2010
Independent validation study (yes)*	4 studies [41, 42, 45, 48]	4 studies [43, 44, 46, 47]	1 study[49]	1 study[40]
Validation study's design				
Prospective-retrospective**	8 studies [41, 42, 45, 48, 66-69]	0	0	0
Retrospective	0	6 studies [43, 44, 46, 47, 50, 56]	8 studies [2, 49, 52, 57, 77-80]	0
Case-control	0	0	0	1 study [40]
Subset from RCT population	0	0	0	5 studies [53, 54][1, 821]
Validation study noteworthy	Unclear whether cases in development dataset were also included in validation set(s)	NA	Cases from the development dataset were also included in validation set(s)	NA
Country of validation population				
North America	None	Canada [50]	USA [49]	USA [51, 53, 55]
South America	Brazil [41]	None	None	None
Europe	UK, Italy [41, 42, 45, 48, 66-69], Spain [41], Portugal [41], Denmark [42]	UK [44], France [46], Netherlands [46, 56]	France [52], Sweden [52], UK [52], Netherlands [2, 52, 77-80], Italy [79]	UK [54]
Asia and Middle-east	None	Malaysia [43]	Japan [57]	Japan [40]
		Unclear [47]		
Source of validation population				
Hospital-based cases	8 studies [41, 42, 45, 48, 66-69])	5 studies [43, 44, 46, 47, 56]	8 studies [2, 49, 52, 57, 77-80]	4 studies [40, 53-55]
General population cases	0	1 study (50)	0	1 study [51]

NPI= Nottingham Prognostic Index; UK= United Kingdom; FFPR= formalin-fixed paraffin-embedded; NA= not applicable

* We considered a validation study independent if none of the authors of the validation study was listed as an author on the development paper.

** Prospective-retrospective= a cohort of patients was included in a database for the purpose of validating the NPI, treatment allocation was to the best of our knowledge not based on the NPI results but on clinical guidelines.

Table 2 contiued Overview validation studies for NPI, Adjuvant!, MammaPrint and Oncotype Dx

Study characteristics	NPI	Adjuvant!	MammaPrint	Oncotype Dx
Validation on:				
FFPR-tissue			0	5 studies [40, 51, 53-55]
Fresh frozen tissue	NA	NA	8 studies [2, 49, 52, 57, 77-80]	0
Characteristics of study population				
Diagnosis period				
<1980 (yes)	6 studies [41, 42, 45, 67-69]	None	*Unclear* [52]	None
1980 – 2000 (yes)	8 studies [41, 42, 45, 48, 66-69]	6 studies [43, 44, 46, 47, 50, 56]	8 studies [2, 49, 52, 57, 77-80]	4 studies [51, 53-55]
> 2000 (yes)	None	None	3 studies [2, 57, 79]	1 study[40]
Nr. of cases in all validation studies (range)	13.208 (82 (48) – 9.149 (42))	12.084 (174 (47) – 5.380 (56))	1.531 (100 (49) – 964 (2))	2.479 (40 (40) – 1.231 (54))
Age at diagnosis (years)				
<40 (yes)	3 studies [41, 45, 48] *Unclear* [42, 66-68]	6 studies [43, 44, 46, 47, 50, 56]	6 studies [2, 49, 52, 77, 79, 80] *Unclear* [57]	4 studies [40, 51, 53, 55]
40-70 (yes)	5 studies [42, 45, 66-68]	6 studies [43, 44, 46, 47, 50, 56]	8 studies [2, 49, 52, 57, 77-80]	5 studies [40, 51, 53-55]
>70 (yes)	2 studies [41, 48]	4 studies [43, 44, 50, 56] *Unclear*[46]	2 studies [2, 49]	3 studies [40, 51, 54] *Unclear* [53, 55]
Not reported	1 study [69]			

NPI= Nottingham Prognostic Index; UK= United Kingdom; FFPR= formalin-fixed paraffin-embedded; NA= not applicable

* We considered a validation study independent if none of the authors of the validation study was listed as an author on the development paper.

** Prospective-retrospective= a cohort of patients was included in a database for the purpose of validating the NPI, treatment allocation was to the best of our knowledge not based on the NPI results but on clinical guidelines.

Table 2 continued Validation studies for NPI, Adjuvant!, MammaPrint and Oncotype Dx

Characteristics of study population	NPI	Adjuvant!	MammaPrint	Oncotype Dx
Nodal status				
Node negative (yes)	8 studies [41, 42, 45, 48, 66-69]	5 studies [43, 44, 46, 50, 56]	7 studies [2, 49, 52, 57, 77, 78, 80]	4 studies [40, 51, 54, 55]
1-3 positive nodes (yes)	7 studies [41, 42, 45, 48, 67-69] *Unclear* [66]	6 studies [43, 44, 46, 47, 50, 56]	3 studies [2, 79, 80]	1 study [54]
>3 positive nodes (yes)	4 studies [41, 42, 45, 67] *Unclear* [48, 66, 68, 69]	2 studies (47, 56) *Unclear* [43, 46]	1 study [80] *Unclear* [2]	1 study [53] *Unclear* [54]
Tumor size				
< 2 cm (yes)	8 studies [41, 42, 45, 48, 66-69]	6 studies [43, 44, 46, 47, 50, 56]	8 studies [2, 49, 52, 57, 77-80]	5 studies [40, 51, 53-55]
2-5 cm (yes)	8 studies [41, 42, 45, 48, 66-69]	6 studies [43, 44, 46, 47, 50, 56]	7 studies [49, 52, 57, 77-80]	5 studies [40, 51, 53-55]
>5 cm (yes)	3 studies [41, 42, 69] *Unclear* [48]	2 studies [43, 56] *Unclear* [46]	Ref. [79]: Only 3 cases with tumors >5cm	2 studies [53, 54] *Unclear* [51, 55]
Tumor grade				
Grade 1-3 (yes)	8 studies [41, 42, 45, 48, 66-69]	6 studies [43, 44, 46, 47, 50, 56]	8 studies [2, 49, 52, 57, 77-80]	5 studies [40, 51, 53-55]
Hormone receptor status				
ER-positive (yes)	3 studies [41, 45, 48]	5 studies [43, 44, 46, 50, 56]	8 studies [2, 49, 52, 57, 77-80]	5 studies [40, 51, 53-55]
ER-negative (yes)	3 studies [41, 45, 48]	5 studies [43, 44, 46, 50, 56] Ref. [47] less than 15 ER negative cases	8 studies [2, 49, 52, 57, 77-80]	NA
Not reported	5 studies [42, 66-69]	NA	NA	NA
Her2neu status (yes)	1 study [41]	1 study [46]	3 studies [2, 77, 79]	5 studies [40, 51, 53-55]

NPI= Nottingham Prognostic Index; UK= United Kingdom; FFPR= formalin-fixed paraffin-embedded; NA= not applicable

* We considered a validation study independent if none of the authors of the validation study was listed as an author on the development paper.

** Prospective-retrospective= a cohort of patients was included in a database for the purpose of validating the NPI, treatment allocation was to the best of our knowledge not based on the NPI results but on clinical guidelines.

Table 2 continued Validation studies for NPI, Adjuvant!, MammaPrint and Oncotype Dx

Characteristics of study population	NPI	Adjuvant!	MammaPrint	Oncotype Dx
Not reported	NA	4 studies [43, 44, 47, 56]	NA	3 studies [51, 54, 55]
Treatment				
Surgical treatment (+/- RT) (yes)	8 studies [41, 42, 45, 48, 66-69]	5 studies [43, 44, 46, 50, 56]	8 studies [2, 49, 52, 57, 77-80]	1 study [51]
Adjuvant systemic therapy (yes)	5 studies [41, 42, 45, 66, 68]	6 studies [43, 44, 46, 47, 50, 56]	7 studies [2, 49, 57, 77-80]	5 studies [40, 51, 53-55]
Not reported	1 study (48)	NA	NA	NA
The overall conclusions of the authors of the validation studies:				
	Stratifies target patients accurately into categories according to their risk of recurrence. **Area requiring special attention:** - Model discrimination is highly dependent on tumor grade rating by pathologist	Overall it predicts OS accurately in target population. RFS estimates less accurate across all cohorts. **Poor performance specifically in:** - patients <40 years - patients > 65 years - Her2neu overexpression - Non ductal or lobular tumors - Malaysian population - ER-negative patients	Stratifies target patients accurately into categories according to their risk of recurrence. **Area requiring special attention:** - Less discriminative in ER negative patients - *Unclear* if risk category cut-offs are applicable to Japanese cases - Not as predictive for recurrence after first 5 years	Stratifies target patients accurately into categories according to their risk of recurrence. **Area requiring special attention:** - Clinical (prognostic) significance of intermediate category *unclear* - Not as predictive for recurrence after first 5 years

NPI= Nottingham Prognostic Index; UK= United Kingdom; FFPR= formalin-fixed paraffin-embedded; NA= not applicable
* We considered a validation study independent if none of the authors of the validation study was listed as an author on the development paper.
** Prospective-retrospective= a cohort of patients was included in a database for the purpose of validating the NPI, treatment allocation was to the best of our knowledge not based on the NPI results but on clinical guidelines.

As shown in **Table 4** (also see **Figure 3**), four (44, 46, 50, 56) of the six validation studies found that Adjuvant!'s estimates were less accurate in patients ≤40 years or ≥75 years at diagnosis. OS was overestimated by 9% up to 30% for patients ≤40 years and in elderly patients (>65 years) by 12% (43, 44, 46). Two studies (44, 50) reported the difference between predicted and observed RFS. The largest discrepancies reported were a 19% underestimation of RFS for patients 76 years at diagnosis and a 14% overestimation for those <40 years at diagnosis (44, 50).

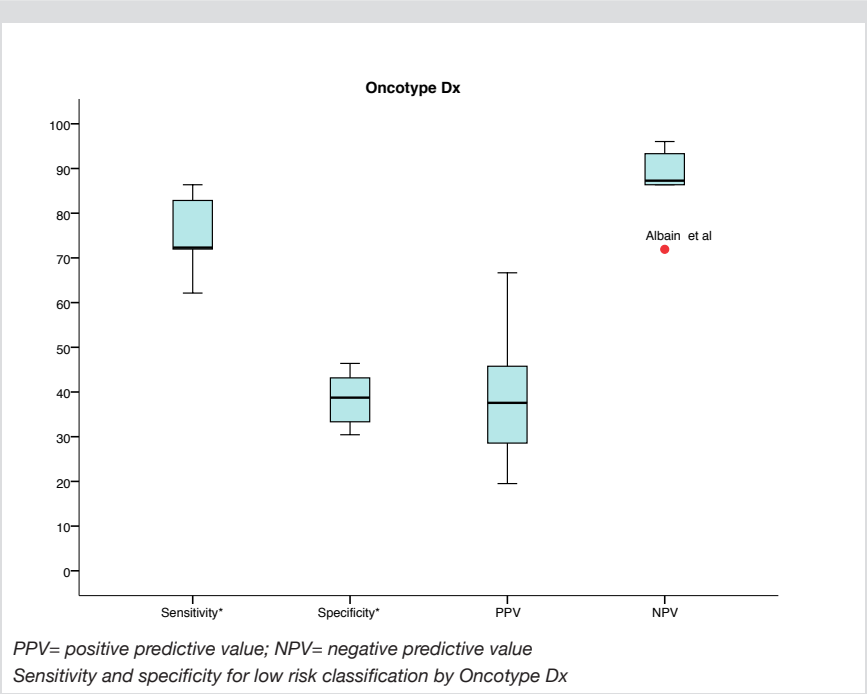

Figure 2b Variance in sensitivity, specificity and predictive value between studies for Oncotype Dx

The NPI, Adjuvant!, MammaPrint and Oncotype Dx were developed in European and/or North American populations. Clinical validity was also assessed in non-western populations (**Table 2**). A validation study (43) in a Malaysian population (N=631) found that Adjuvant! was especially overoptimistic in Malay women ≤ 40 years at diagnosis, overestimating OS by 20% (43). Oncotype Dx' performance in Japanese patients was assessed in a small case control study, that found that a higher Oncotype Dx' recurrence score (RS) was associated with disease recurrence (N= 40; RS in patients with recurrence 40.0 (95%-CI= 21.1-58.9); RS in patients without recurrence 17.8 (95%-CI= 13.8-21.9)) (40). Ishitobi *et al.* (57) reported that MammaPrint classified 80% of

patients as high risk, a greater proportion of high risk cases than reported in European validation populations (see **Table 3**). In the latter study only 18% of the high risk cases had a recurrence, however 70% of these patient received hormonal therapy and 33% received chemotherapy. It is thus unclear whether the high percentage of high risk classification is accurate and that the relatively low recurrence rate is (partly) explained by treatment, or that the current cut-offs for the MammaPrint risk categories are not valid for the Japanese population (57).

Table 3 Overview of adjuvant treatment distribution and the prevalence of recurrences for the cases that MammaPrint, Oncotype Dx and the NPI classify as low and high risk

	Study	FUP (in years)	Nr. of cases (low + high risk)	% Risk classification@		% Prevalence of recurrence in population*	Receipt of adjuvant systemic treatment				% Recurrence per risk category	
							% Chemotherapy		% Hormonal therapy			
				Low risk	High risk		Low risk	High risk	Low risk	High risk	Low risk	High risk
	Van de Vijver et al.[80]	5	295	39	61	26	38	37	15	13	5	39
MammaPrint	van 't Veer et al.[10] §	5	78	45	55	44	—	—	—	—	9	72
MammaPrint	Wittner et al.[49]	5	100	27	73	9	15	23	22	25	0	12
MammaPrint	Mook et al.[78]	5	148	61	39	15	0	0	19	18	7	28
MammaPrint	Mook et al.[2]	5	964	54	46	12	4	17	22	18	5	20
MammaPrint	Mook et al.[79]	5	241	41	59	13	39	63	80	61	2	20
MammaPrint	Bueno de Mesquita et al.[77]	6	123	52	48	38	2	29	14	8	2	78
MammaPrint	Ishitobi et al.[57]	10	102	20	80	15	10	33	85	70	0	18
MammaPrint	Buyse et al.[52]	14	302	37	63	25	0	0	0	0	16	30
MammaPrint	Paik et al.[9] §	16	519	65	35	21	—	—	100	100	13	38
Oncotype Dx	Paik et al.[55]	10	517	68	32	9	62	71	100	100	4	20
Oncotype Dx	Albain et al.[53]	10	264	55	45	36	62	60	100	100	28	46
Oncotype Dx	Dowsett et al.[54]	9	855	79	21	11	0	0	100	100	7	29
Oncotype Dx	Yorozuya et al.[40]	5	31	71	29	29	—	22	91	78	14	67

Table 3 continued Overview of adjuvant treatment distribution and the prevalence of recurrences for the cases that MammaPrint, Oncotype Dx and the NPI classify as low and high risk

	Study	FUP (in years)	Nr. of cases (low + high risk)	% Risk classification@		% Prevalence of recurrence in population*	Receipt of adjuvant systemic treatment				% Recurrence per risk category	
							% Chemotherapy		% Hormonal therapy			
				Low risk	High risk		Low risk	High risk	Low risk	High risk	Low risk	High risk
NPI$	Sidoni et al.[48]	10	43	63	37	42	—	—	—	—	26	69
	Albergaria et al.[41]	10	218	46	54	47	—	—	—	—	30	62

We only report data for studies that assessed the accuracy of these RPM prediction for recurrence-free survival compared to observed recurrence-free survival. Some studies also report performance for overall survival, yet as the main aim of these models is to predict recurrence-free survival, we opted not to report this data.
NPI= Nottingham Prognostic Index
@ NPI and Oncotype Dx also have an intermediate risk category. As the clinical significance of this category is still unclear, we did not include data on the patients classified in this category in this table. We only report proportions for the cases classified as high or low risk.
§= development study; FUP= follow-up time for recurrence; — = not reported or unclear
$= Most validation studies for the NPI used the same population. It was not always clear, but it appeared that the later studies contained the same population as used in the earlier (development and) validation studies (the Nottingham cohort), extended with the cases that had presented since the last analysis. We were unable to disentangle this so that we could present quantified data for the Nottingham cohort without duplications. Moreover, basic population characteristics are not reported in most of the papers reporting findings using the Nottingham cohort. Here we opted to only present data for 2 independent studies that used different populations.
* Prevalence of recurrence= prevalence of either loco-regional recurrence or distant metastases or both. Dependent on which had been reported by the studies; most studies combined loco-regional recurrence with distant metastasis.

Table 4 Overview of the accuracy of Adjuvant! prognostic estimates compared to observed survival in the various validation populations

	Study	N	Survival estimates for the total study population			Greatest over- or underestimation in subgroups of patients	
			Predicted (%)	Observed (%)	Difference (%)	Patient subgroup	Difference (%)
RFS estimates	Olivotto et al.[50]	4083	71	70	1	Aged 20-35 years	14
	Campbell et al.[44]	1058	72	69	3	Aged ≥76 years	-19
OS estimates	Olivotto et al.[50]	4083	72	72	0	Aged 20-35 years	9
	Bhoo-Pathy et al.[43]	631	70	64	6	Aged <40 years	20
	Hajage_F$ et al.[46]	435	85	87	-2	Aged <40 years	15
	Hajage_D# et al.[46]	247	79	66	13	Aged <40 years	30
	Campbell et al.[44]	1065	77	72	5	Aged 66-75 years	12
	Mook et al.[56]	5380	69	69	0	Mucinous carcinomas	8

OS= overall survival; RFS= recurrence-free survival; N= number of patients included in the study; CT= chemotherapy; HT= hormonal therapy; Hajage_F$= French cohort included in study; Hajage_D#= Dutch cohort included in study. The characteristics of these 2 populations vary significantly and are presented separately in the paper, therefore we also opted to present them separately.
Two validation studies (8, 47) did not report the data needed for this table, therefore they have not been incorporated.

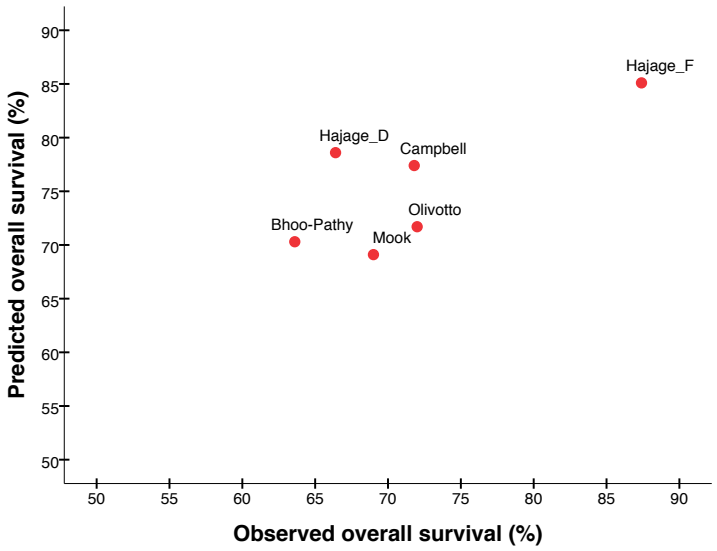

Figure 3 Overall survival predicted by Adjuvant! versus observed

Comparisons between RPM or RPM compared to clinical guidelines

Thirteen studies compared MammaPrint to NPI and Adjuvant!, and/or to existing international guidelines, such as the St. Gallen consensus guidelines and the NIH guidelines (58-61). MammaPrint was reported to provide additional prognostic information especially in ER-positive lymph node negative breast cancer patients deemed to have a low clinical risk by Adjuvant! and/or NPI (58). A small-scale study in a German population (>60 years) found a discordance rate between MammaPrint and Adjuvant! of 48% (n=60) if these RPM were used separately (60). Instead of using them separately, if MammaPrint was used in combination with the clinicopathological factors from Adjuvant!, the recommendation differed in 11 of the 60 (18%) patients in the study. This would have led to six additional patients being advised adjuvant chemotherapy and five patients being spared systemic treatment (60). Gevensleben *et al.* (59) found a similar discordance, namely of 41%, between MammaPrint and Adjuvant! in a German population (N=140) (59). They reported that combining the MammaPrint results with clinicopathological factors would have resulted in altered treatment recommendations in 41% of the patients (57 of 140). Of these patients 45 were classified as having a 'high' recurrence risk by Adjuvant!, while MammaPrint classified them as low risk; hence 41% of patients were potentially over- or undertreated (59). A small study in Korean patients (N=36) comparing MammaPrint classification to other clinicopathological classifications,

reported that MammaPrint classified almost 90% of patients as high risk, which is a significantly larger proportion than in European patient cohorts (61).

Aim 3: Assessment of the RPM reports

We retrieved the reports for 12 of the 20 RPM identified (for a description see **Table 5**). They generally consisted of the survival probability described for one or more time periods, a risk category and/or a form of graphical representation of the risk estimates. MammaPrint (10), Oncotype Dx (9) and Theros BCI (30) reports provide the confidence interval around the survival probability.

Ten of the 12 RPM for which we retrieved a report provide a graphical representation of probabilities. CancerMath (25) provides users with the option to choose in which graphical format they want the probabilities presented. Six (9, 10, 25, 30, 34, 36) models report survival curves and three molecular profiles provide technical graphs, e.g. heat maps[1] (10, 36) and normalization curves[2] (33).

Ten (8-10, 23-25, 30, 32, 34, 36) reports were intended for both oncologists and patients. Not all of these explicitly stated that they were also intended for patients. Yet, on the RPM developers' websites patients are provided tools to help them read the RPM report. On the Oncotype Dx website for example, patients can watch a video that explains what the information contained in the report means. In the disclaimer all developers urge patients to consult their oncologist to discuss the content of the RPM report.

To be able to read and comprehend any of the RPM reports , literacy at least at high school level is required (**Web appendix 2**). All the reports of the bio-molecular profiles provide information on the technical aspects of the assay, its development, validation and literature references. Especially these sections have a high use of medical jargon and technical biomedical details, which was rarely explained in lay terms. For example: "*The test is performed using a microarray-based gene expression profile. An unbiased, supervised analysis of the entire human genome, ~25,000 genes, followed by a leave-one-out cross-validation procedure …*".

[1] A heat map is a graphical representation of data where the individual values contained in a data matrix are represented as colors.

[2] Normalization means to adjust microarray data for effects which arise from variation in the technology rather than from biological differences between the RNA samples or between the printed probes (62).

Discussion

The aim of this review was to identify available RPM that intend to aid adjuvant systemic treatment selection in breast cancer, provide an overview of the reported clinical validity of their prognostic estimates, and assess how comprehensible the presentation of estimates is. We identified 20 RPM that aim to help oncologists answer the same question, namely: "*Will this specific patient potentially benefit from systemic treatment (and if so how large is the survival gain)?*". The main difference between RPM lies in the elements they utilize to generate their estimates and in how they present their results.

None of the RPM based on genetic profiles incorporates clinical factors, while there is some evidence suggesting that traditional clinicopathological variables, namely tumor size, nodal status, histologic grade, and, to a lesser extent, age at diagnosis retain independent prognostic value (54, 63). An effort to create a new model that combines the Oncotype Dx recurrence score with clinicopathological factors was reported. The resulting Recurrence Score Pathology-Clinical score (RSPC-score) was found to refine the assessment of distant recurrence risk, and, most important, reduce the number of patients classified in the intermediate risk category (64). However, the RSPC-score cannot currently be calculated for an individual patient because the model has not yet been fully specified and, most important, has not yet been externally validated in fully independent datasets (65).

The authors of the validation studies retrieved reported that their RPM showed good to excellent clinical validity. However, these validation studies were mostly retrospective validations in cohorts of patients treated according to clinical guidelines at the time they were diagnosed. We found significant variations in the prevalence of recurrences and treatment allocation between studies. Unfortunately, a number of studies used (a subset of) the same population for multiple validations (e.g. (66-69)). They did not provide sufficient data for us to be able to appropriately quantify the data on patient characteristics, which would have further facilitated comparisons. Also, we provide a graphic overview of the variation in RPM performance statistics (i.e. sensitivity, specificity, and predictive value). However, the influence of treatment on observed survival could not be taken into account, as the validation studies generally did not provide information on the distribution of recurrences within high and low risk patients stratified by treatment allocation. Thus, the RPM performance statistics should be interpreted cautiously. We realize that withholding or allocating systemic therapy based on the predictions of insufficiently validated RPM is not ethical, and it is difficult to find untreated patients nowadays. Therefore, until prospective trials where treatment is allocated according to RPM predictions become available, this is the best evidence we have, in spite of its limitations.

Two subgroups, for which the accuracy of the prognostic estimates of RPM based on clinical prognosticators are suboptimal, are women ≤40 or ≥65 years at diagnosis. Further, the clinical validity of Adjuvant!, and MammaPrint's prognostic estimates in Asian patients was inferior. Adjuvant! overestimated OS by almost 20%. MammaPrint classified ≥80% of patients as high risk, where in the European validation populations <60% of patients was classified as high risk. The observed difference in prevalence of high risk classification by MammaPrint could point to a gene disparity between Asians and Europeans (57, 61). Also, the seemingly low recurrence rate in the patients classified as high risk could be (partly) explained by systemic treatment. Large-scale studies are required to assess the validity of the prognosticators used in these RPM in Asian breast cancer patients (57, 61).

Overall, we found that the assumption that the currently available RPM's are clinically valid does not hold in certain patient subgroups, and that most RPM seem to have similar shortcomings. There are ongoing international efforts to assess the accuracy of available RPM based on clinical or molecular profiling, such as the Sage Bionetworks-DREAM Breast Cancer Prognosis Challenge.[3] These initiatives can help improve existing RPM or lead to the development of more accurate models, using the wealth of data already available.

Standardization of the terminology used in this field would also be beneficial. Varying study designs are used and the terms used as keywords vary greatly. Therefore, we might have missed some relevant papers, even though we also attempted to manually track references.

The underlying assumption of RPM is that accurately estimated probabilities improve decision-making and consequently patient outcomes. The justification of this assumption can only be assessed in impact studies, which quantify the effect of using versus not using RPM. Hornberger *et al.* (70) reviewed studies on the effect of the use of Adjuvant!, MammaPrint and Oncotype Dx on clinical recommendations and decisions. Overall, use of RPM led to a change in treatment recommendation ranging from 1% - 74%. However, there was considerable heterogeneity between studies.

RPM reports might seem straightforward as the essence of all the information contained in these reports is often summarized with a risk category, which is clearly provided. However, to truly understand what it means to be in the 'low risk' category, and to

[3] Sage Bionetworks-DREAM Breast Cancer Prognosis Challenge (http://www.the-dream-project.org/challenges/sage-bionetworks-dream-breast-cancer-prognosis-challenge): the goal of the breast cancer prognosis Challenge is to assess the accuracy of computational models designed to predict breast cancer survival, based on clinical information about the patient's tumor as well as genome-wide molecular profiling data including gene expression and copy number profiles.

be able to make a deliberate choice to undergo or forego treatment (partly) based on these results, a patient has to have insights in how large the mortality or recurrence risk associated with this category is. In their current format the content of the 12 RPM reports we assessed are too difficult to understand for most patients and it begs the question whether the addition of technical graphs (e.g. heatmaps) provides support to patients or even to oncologists. It is not advisable to provide patients with such a report without adequate explanation by a trained health professional. If developers wish for their model to be implemented in the clinical encounter and/or for patients to receive a report, they might consider creating a report specifically intended for patients containing only relevant information in lay terms. Developers should consider collaborating with cognitive and social psychologists to design risk communication and presentation strategies (71).

An advantage of RPM is that the risks are tailored to individual patient and tumor characteristics. People provided with individualized risks have been shown to become more motivated to engage in the communication process, and to have more accurate risk perception and better knowledge (72). RPM thus have the potential to empower patients by allowing them to become better informed participants in the decision-making process. However, focusing on the recurrence probabilities with and without therapy can also sidetrack patients from paying attention to side effects, which are part of the tradeoff involved in choosing therapy.

Observational studies of the communication process between oncologists and patients involving RPM are lacking, as are studies investigating patients' understanding of the uncertainties involved. In spite of the lack of research, some lessons can already be learned. Oncologists should be aware that most, but not all patients wish to receive prognostic information and that information preferences are difficult to predict (73, 74). It is therefore recommended to ask patients whether they wish to know the specific prognosis from RPM. If a patient wishes to hear the probabilities, communication of these probabilities can be optimized by using pictographs (75, 76).

Table 5 Characteristics of the output of identified risk RPMs for breast cancer prognosis and/or prediction						
Output characteristics	**MammaPrint**	**Oncotype Dx**	**MammoStrat**	**Theros BCI**	**BreastPRS**	**PAM50**
Type of output						
Quantifies survival probabilities	Yes	Yes	Yes	Yes	Yes	No
Stratifies patients according to risk	Yes	Yes	Yes	Yes	Yes	No
Risk category	High vs. Low risk	High vs. Intermediate vs. Low risk	High vs. Intermediate vs. Low risk	High vs. Intermediate vs. Low risk	High vs. Low risk	-
Target audience	Oncologists + patients	Oncologists + patients	Oncologists + patients	Oncologists + patients	Oncologists + patients	Oncologists + patients
Take home version available	Yes	Yes	Yes	Yes	No	Yes
Report content						
Benefit of treatment quantified	No	Yes	No	No	No	No
Base survival rate (without treatment) quantified	No	No	No	No	No	No
Overall survival probability reported	No	No	No	No	No	No
Disease free survival probability reported	Yes	Yes	Yes	Yes	No	No
Reported as	5-year recurrence rate in the absence of adjuvant systemic therapy	10-year recurrence rate after 5 years of Tamoxifen	3, 5, 8 and 10-year recurrence rate after Tamoxifen only	10-year distant recurrence rate	-	-

- = not applicable
$ Comprehensibility to laymen was determined using 2 methods:
a. a subjective assessment by two reviewers independently (classifying use of medical or other technical jargon in the report as low, moderate or high). Disagreements were resolved in consensus meetings. This resulted in the variable “Use of medical/technical jargon content”.
b. an objective assessment for which we used an online Readability Test Tool (http://www.read-able.com/) to calculate a score for six frequently used readability indicators in order to provide an overall indication of the difficulty of the text. This resulted in the variable “Minimal literacy level required”. We have included the report provided by the Readability Test Tool as web appendix 2.

Table 5 continued Characteristics of the output of identified risk RPMs for breast cancer prognosis and/or prediction

Output characteristics	MammaPrint	Oncotype Dx	MammoStrat	Theros BCI	BreastPRS	PAM50
Confidence interval around probability reported	Yes	Yes	No	Yes	-	-
Additional results	-	- Breast cancer recurrence score - ER, PR and Her2 score	MammoStrat risk index	Breast cancer index score	- BreastPRS index - Molecular tumor grade - Tumor subtype	Scores of markers indicative of treatment response
Type of graphical presentation	- Survival curve - Heatmap	Survival curve	Recurrence-free survival curve	Recurrence-free survival curve	- Normalization histograms - Heatmap - Recurrence-free survival curve	H&E stain image
Comprehensibility to laymen[$]						
Use of medical/technical jargon content	High	High	High	High	High	High
Minimal literacy level required	High school + specialist knowledge required	High school + specialist knowledge required	High school + specialist knowledge required	High school + specialist knowledge required	High school + specialist knowledge required	High school + specialist knowledge required

- = not applicable
$ Comprehensibility to laymen was determined using 2 methods:
a. a subjective assessment by two reviewers independently (classifying use of medical or other technical jargon in the report as low, moderate or high). Disagreements were resolved in consensus meetings. This resulted in the variable “Use of medical/technical jargon content”.
b. an objective assessment for which we used an online Readability Test Tool (http://www.read-able.com/) to calculate a score for six frequently used readability indicators in order to provide an overall indication of the difficulty of the text. This resulted in the variable “Minimal literacy level required”. We have included the report provided by the Readability Test Tool as web appendix 2.

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Web appendix 1 Search strategy per database	
Source	**Search terms**
PUBMED	(“Individualized Medicine”[Majr] OR “Personalized medicine”[tiab] OR “Decision Support Techniques”[Majr:NoExp] OR “Decision Making, Computer-Assisted”[Majr:NoExp] OR “prognostic model”[tiab] OR “prognostic software model”[tiab] OR “Prognostication”[tiab] OR “decision aid”[tiab] OR “individualized risk information”[tiab] OR “patient-specific decision aid”[tiab] OR “decision aids”[tiab] OR ((“therapeutic efficacy”[tiab] OR “therapeutic resistance”[tiab] OR “prognosis”[tiab] OR “Prognostic”[tiab] OR “Predictive”[tiab] OR “Predictor”[tiab] OR “Predictors”[tiab] OR “Prediction”[tiab] OR “Predictions”[tiab] OR “Predict”[tiab] OR “Predicts”[tiab] OR “Decision”[tiab] OR “Decide”[tiab] OR “Decides”[tiab]) AND (“tool”[tiab] OR “tools”[tiab] OR “molecular”[tiab])) OR “OncotypeDX”[tiab] OR “oncotype dx”[tiab] OR “21-gene assay”[tiab] OR “70-gene signature”[tiab] OR “mammaprint”[tiab] OR “Predict”[tiab] OR “nomogram”[tiab] OR “PAM50”[tiab] OR “MapQuant Dx”[tiab] OR “Theros Breast cancer Index SM”[tiab] OR “BLN assay”[tiab] OR “Arup breast bioclassifier”[tiab] OR “Celera Metastatic Score”[tiab] OR “Exagen Breast cancer tm”[tiab] OR “Invasive gene signature”[tiab] OR “Mammostrat”[tiab] OR “Epi/Doc”[tiab] OR “Van Nuys prognostic index”[tiab] OR “VNPI”[tiab] OR “Genomic grade index”[tiab] OR “GGI”[tiab]) AND (“breast neoplasms”[Majr] OR ((“breast”[tiab]) AND (“neoplasms”[tiab] OR “neoplasm”[tiab] OR “cancer”[tiab] OR “tumor”[tiab]OR “tumour”[tiab] OR “tumors”[tiab] OR “tumours”[tiab] OR “malignancy”[tiab] OR “malignancies”[tiab]))) AND “adjuvant therapy”[tiab]
EMBASE	(*”personalized medicine”/OR “Individualized medicine”.ti,ab. OR “Personalized medicine”.ti,ab. OR *”decision support system”/ OR “Decision Support Techniques”. ti,ab. OR “prognostic model”.ti,ab. OR “prognostic software model”.ti,ab. OR “Prognostication”.ti,ab. OR “decision aid”.ti,ab. OR “individualized risk information”. ti,ab. OR “patient-specific decision aid”.ti,ab. OR “decision aids”.ti,ab. OR ((“therapeutic efficacy”.ti,ab. OR “therapeutic resistance”.ti,ab. OR “prognosis”.ti,ab. OR “Prognostic”. ti,ab. OR “Predictive”.ti,ab. OR “Predictor”.ti,ab. OR “Predictors”.ti,ab. OR “Prediction”. ti,ab. OR “Predictions”.ti,ab. OR “Predict”.ti,ab. OR “Predicts”.ti,ab. OR “Decision”. ti,ab. OR “Decide”.ti,ab. OR “Decides”.ti,ab.) AND (“tool”.ti,ab. OR “tools”.ti,ab. OR “molecular”.ti,ab.)) OR “OncotypeDX”.ti,ab. OR “oncotype dx”.ti,ab. OR “21-gene assay”.ti,ab. OR “70-gene signature”.ti,ab. OR “mammaprint”.ti,ab. OR “Predict”.ti,ab. OR “nomogram”.ti,ab. OR “PAM50”.ti,ab. OR “MapQuant Dx”.ti,ab. OR “Theros Breast cancer Index SM”.ti,ab. OR “BLN assay”.ti,ab. OR “Arup breast bioclassifier”.ti,ab. OR “Celera Metastatic Score”.ti,ab. OR “Exagen Breast cancer tm”.ti,ab. OR “Invasive gene signature”.ti,ab. OR “Mammostrat”.ti,ab. OR “Epi/Doc”.ti,ab. OR “Van Nuys prognostic index”.ti,ab. OR “VNPI”.ti,ab. OR “Genomic grade index”.ti,ab. OR “GGI”.ti,ab.) AND (exp *”breast tumor”/OR ((“breast”.ti,ab.) AND (“neoplasms”.ti,ab. OR “neoplasm”.ti,ab. OR “cancer”.ti,ab. OR “tumor”.ti,ab.OR “tumour”.ti,ab. OR “tumors”.ti,ab. OR “tumours”. ti,ab. OR “malignancy”.ti,ab. OR “malignancies”.ti,ab.))) AND “adjuvant therapy”.ti,ab.

Web appendix 1 Search strategy per database	
Source	**Search terms**
Web of Science	TS=((“personalized medicine” OR “Individualized medicine” OR “Personalized medicine” OR “decision support system” OR “Decision Support Techniques” OR “prognostic model” OR “prognostic software model” OR “Prognostication” OR “decision aid” OR “individualized risk information” OR “patient-specific decision aid” OR “decision aids” OR ((“therapeutic efficacy” OR “therapeutic resistance” OR “prognosis” OR “Prognostic” OR “Predictive” OR “Predictor” OR “Predictors” OR “Prediction” OR “Predictions” OR “Predict” OR “Predicts” OR “Decision” OR “Decide” OR “Decides”) AND (“tool” OR “tools” OR “molecular”)) OR “OncotypeDX” OR “oncotype dx” OR “21-gene assay” OR “70-gene signature” OR “mammaprint” OR “Predict” OR “nomogram” OR “PAM50” OR “MapQuant Dx” OR “Theros Breast cancer Index SM” OR “BLN assay” OR “Arup breast bioclassifier” OR “Celera Metastatic Score” OR “Exagen Breast cancer tm” OR “Invasive gene signature” OR “Mammostrat” OR “EpiDoc” OR “Van Nuys prognostic index” OR “VNPI” OR “Genomic grade index” OR “GGI”) AND (“breast tumor” OR ((“breast”) AND (“neoplasms” OR “neoplasm” OR “cancer” OR “tumor” OR “tumour” OR “tumors” OR “tumours” OR “malignancy” OR “malignancies”))) AND “adjuvant therapy”)

Web appendix 2 Readability assessment used to compute minimal literacy in the web-based Readability Test Tool

(Source: www.read-able.com; created July 5th 2013)

The Readability Test Tool

Let's make the unreadable readable

Readability Test Results

This page has an average grade level of about 12.

It should be easily understood by 17 to 18 year olds.

Readability Indices

Flesch Kincaid Reading Ease	42.7
Flesch Kincaid Grade Level	11
Gunning Fog Score	14.2
SMOG Index	10.2
Coleman Liau Index	15.6
Automated Readability Index	11.2

Text Statistics

No. of sentences	26
No. of words	389
No. of complex words	80
Percent of complex words	20.57%
Average words per sentence	14.96
Average syllables per word	1.76

Readability Test Results

What do these results mean?

The indicator bars give a visual guide for the readability of the text. Red is a low readability score. Green is easily readable.

Flesch Kincaid Reading Ease

Based on a 0-100 scale. A high score means the text is easier to read. Low scores suggest the text is complicated to understand.

206.835 - 1.015 x (words/sentences) - 84.6 x (syllables/words)

A value between 60 and 80 should be easy for a 12 to 15 year old to understand.

Grade Level indicators

These equate the readability of the text to the US schools grade level system.

Flesch Kincaid Grade Level

0.39 x (words/sentences) + 11.8 x (syllables/words) - 15.59

Gunning Fog Score

0.4 x ((words/sentences) + 100 x (complexWords/words))

SMOG Index

1.0430 x sqrt(30 x complexWords/sentences) + 3.1291

Coleman Liau Index

5.89 x (characters/words) - 0.3 x (sentences/words) - 15.8

Automated Readability Index (ARI)

4.71 x (characters/words) + 0.5 x (words/sentences) - 21.43

Coleman Liau and ARI rely on counting characters, words and sentence. The other indices consider number of syllables and complex words (polysyllabics - with 3 or more syllables) too. Opinions vary on which type are the most accurate. It is more difficult to automate the counting of syllable as the English language does not comply to strict standards.

http://www.read-able.com/check.php[05-07-2013 10:01:33]

Chapter 3

Accuracy of the online prognostication tools PREDICT and Adjuvant! for early-stage breast cancer patients younger than 50 years

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Abstract

Importance
Online prognostication tools such as PREDICT and Adjuvant! are increasingly used in clinical practice by oncologists to inform patients and guide treatment decisions about adjuvant systemic therapy. However, their validity for young breast cancer patients is debated.

Objective
To assess first, the prognostic accuracy of PREDICT's and Adjuvant! 10-year all-cause mortality, and second, its breast cancer-specific mortality estimates, in a large cohort of breast cancer patients diagnosed <50 years.

Design
Hospital-based cohort.

Setting
General and cancer hospitals.

Participants
A consecutive series of 2,710 patients without a prior history of cancer, diagnosed between 1990-2000 with unilateral stage I-III breast cancer aged <50 years.

Main outcome measures
Calibration and discriminatory accuracy, measured with C-statistics, of estimated 10-year all-cause and breast cancer-specific mortality.

Results
Overall, PREDICT's calibration for all-cause mortality was good (predicted versus observed) $mean_{difference}$: -1.1% (95%CI: -3.2% to 0.9%) (P= 0.28)). PREDICT tended to underestimate all-cause mortality in good prognosis subgroups (range $mean_{difference}$: -2.9% to -4.8%), overestimated all-cause mortality in poor prognosis subgroups (range $mean_{difference}$: 2.6% to 9.4%), and underestimated survival in patients < 35 by -6.6%. Overall, PREDICT overestimated breast cancer-specific mortality by 3.2% (95%CI: 0.8% to 5.6%) (P= 0.007)); and also overestimated it seemingly indiscriminately in numerous subgroups (range $mean_{difference}$: 3.2% to 14.1%). Calibration was poor in the cohort of patients with the lowest and those with the highest mortality probabilities. Discriminatory accuracy was moderate-to-good for all-cause mortality in PREDICT (0.71 (95%CI: 0.68 to 0.73)) and the results were similar for breast cancer-specific mortality. Adjuvant!'s calibration and discriminatory accuracy for both all-cause and breast cancer-specific mortality were in line with PREDICT's findings.

Conclusions
Although imprecise at the extremes, PREDICT's estimates of 10-year all-cause mortality seem reasonably sound for breast cancer patients <50 years; Adjuvant! findings were similar. Prognostication tools should be used with caution due to the intrinsic variability of their estimates, and because the threshold to discuss adjuvant systemic treatment is low. Thus, seemingly insignificant mortality over- or underestimations of a few percentages can significantly impact treatment decision-making.

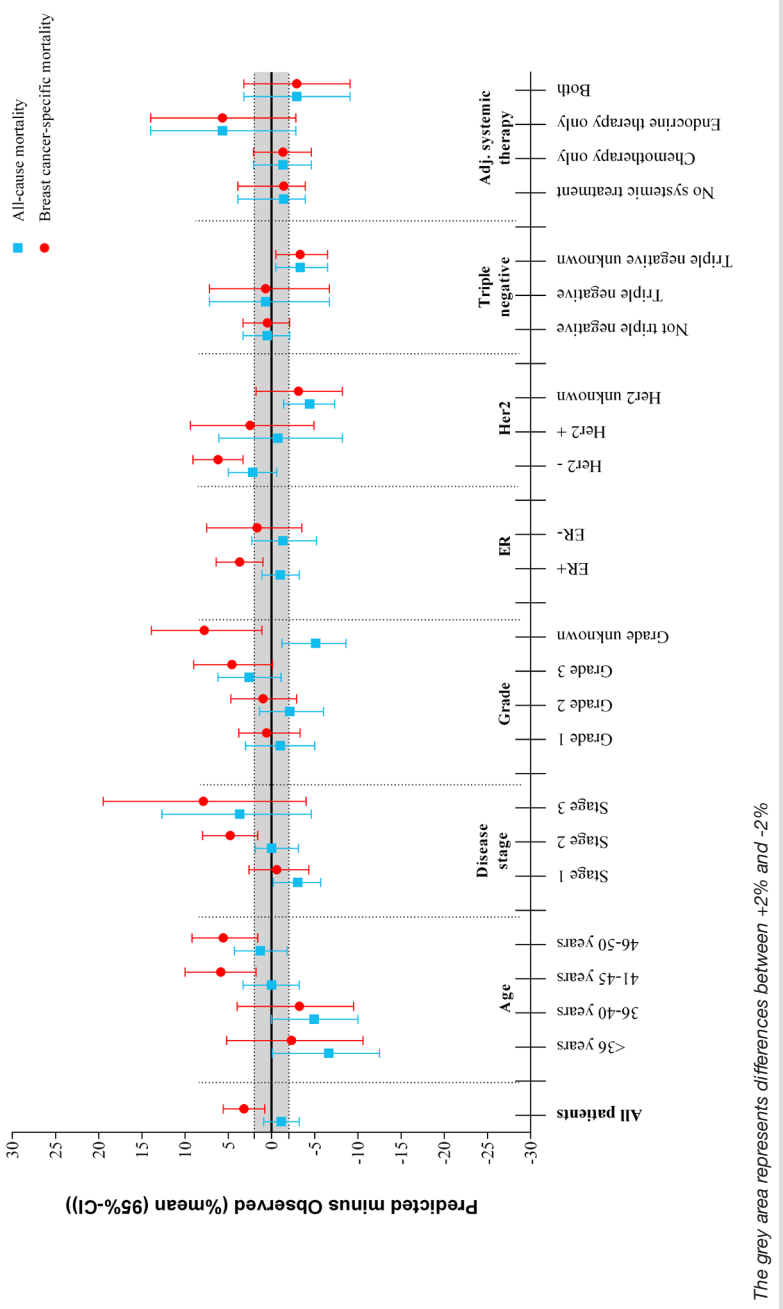
Introduction

In 2015, a total of 14,449 women were diagnosed with invasive breast cancer in The Netherlands, of which 20% were younger than 50 years at diagnosis (1). Available evidence strongly suggests that breast tumors are more aggressive in young (especially those <40 years) than in post-menopausal women (2-5). This is partly due to the over-representation of aggressive biological features (e.g., estrogen receptor (ER) negative, grade 3 in young patients (2-5). Yet, even after controlling for known biological factors indicative of tumor aggressiveness, young age in itself remains an independent predictor of poor cancer-specific survival, and strongly correlates with the risks of local recurrence and contralateral breast cancer (4,6,7). Therefore, pending better molecular characterization of tumors in young women, young age itself and classical tumor characteristics, remain important prognosticators.

Accurate quantification of long-term disease outcome and potential adjuvant systemic treatment benefit could help oncologists and patients in tailoring treatment decisions, also considering the potential side-effects of and possibly reduced quality of life during/after systemic therapy. Furthermore, adequately informing patients about such probabilities as well as the side-effects of treatment could empower them to choose the treatment option that best fits their preferences. Adjuvant! (8,9) and PREDICT (10,11) are online prognostication tools, that provide personalized 10-year all-cause and/or breast cancer-specific mortality estimates for the adjuvant treatment setting. Both tools base their predictions on patient (e.g., age) and tumor (e.g., size, nodal status, ER-status, and grade) characteristics.

Clinicians reported common use of Adjuvant! during consultations with patients (12,13); PREDICT's average user access is 10,000 per month as per February 2016, and currently probably higher as Adjuvant! has been offline for some time. Further, the Dutch national breast cancer guideline based its treatment recommendations on Adjuvant!'s estimates and leading British and American guidelines endorsed Adjuvant!'s use to quantify prognosis (14-16). Adjuvant! and PREDICT have mainly been externally validated in North American and European populations, but also in Asian populations (17-19). Generally, their estimates seem accurate for Western patients diagnosed between 50-65 years (17-19). A recent analysis within the POSH study of about 600 women diagnosed <40 years with ≥10-year follow-up has shown that overall PREDICT overestimated all cause 10-year mortality by 8%, and that in women aged 31- 35 years at diagnosis it underestimated all-cause mortality by 5%18. Overall, the evidence on Adjuvant! and PREDICT's performance in young patients is not strong, as the number of young patients (with sufficient follow-up) included in the validation studies was small; but it suggests that both tools significantly underestimate mortality in patients diagnosed <50 years, with the largest discrepancies observed in patients diagnosed ≤35 years (17-21). These

findings are concerning; especially as Adjuvant! already adjusts its mortality estimates for ER-positive breast cancer patients ≤35 years by a factor of 1.5 (9). In view of the limited evidence on their performance in patients <50 years, and the impact that these tools can have on oncologists' and patients' decision-making, our primary aim was to assess the prognostic accuracy of PREDICT and Adjuvant!'s 10-year all-cause mortality estimates in a large cohort of young breast cancer patients, and secondarily to assess the prognostic accuracy of their breast cancer-specific mortality estimates.



The grey area represents differences between +2% and -2%

Figure 1 Overview of mean difference between PREDICT's estimates and observed all-cause and breast cancer specific mortality by prognostic factors

Methods

Patient selection

We used data from a hospital-based cohort of consecutive females diagnosed <50 years of age with invasive breast cancer, identified through medical registries of participating hospitals or the Netherlands Cancer Registry. We selected all patients diagnosed between 1990-2000 with unilateral stage I-III breast cancer without a previous cancer diagnosis (except non melanoma skin cancer), for whom complete data on tumor size, nodal status, receipt of adjuvant systemic therapy, and follow-up was available (Appendix Figure 1; Appendix A).

Procedures

Data collection has been described previously (22), in short: information about diagnosis and treatment, e.g., histological tumor grade, stage, adjuvant chemotherapy and endocrine systemic treatment (before summer 2005 no adjuvant trastuzumab was administered), estrogen (ER) and progesterone receptor status (PR), Her2-neu, and angiolymphatic invasion were gathered from original pathology reports and/or determined using reviews of whole slides and staining of tumors in tissue micro arrays. Follow-up data, such as date of last follow-up, vital status, and cause of death were obtained from the medical registries from the participating hospitals and/or linkage with the Dutch municipal registry through the Netherlands Cancer Registry (last follow-up update in 2013). Patients with unknown vital status (N=16) and follow-up time ≤10 years (N=21) were excluded (Appendix Figure 1; Appendix A).

Predicted all-cause and breast cancer-specific mortality were calculated for each patient individually by entering prognosticators in PREDICT (version-1.3) and Adjuvant! (version-8.0) batch processors, with blinding to patient outcomes. After the calculation of the mortality estimates, we received a revision of the systemic therapy data which showed that for N=219 patients whether they had received systemic therapy or not, and to a lesser extent which type of systemic therapy they had received had been misclassified. We recalculated PREDICT's estimates, but not for Adjuvant!, since the latter tool was no longer available. In essence, the direction of the difference did not change, nor did our conclusions.

Adjuvant! requires data on comorbidity, which was not available, therefore we set comorbidity to minor problems (default setting). Patients <50 years at diagnosis are unlikely to have significant comorbidities, consequently the setting used will give average outcomes reflecting the general health of our sample. KI67-status was set to unknown, and mode of disease detection was set to symptomatic, in the PREDICT analyses. Also, we used the Prognostic Factor Impact Calculator incorporated in Adjuvant! to take Her2-status into account in the calculation of the all-cause and breast cancer-specific

mortality probabilities. We assumed a relative risk for high vs. low risk group of 1.5 and that on average 20% of patients had Her2-positive disease (23-25). For patients without Her2 overexpression we used the low risk probability estimates, for those with Her2 overexpression we used the high risk estimates and for those with unknown Her2-status we used the unadjusted estimates automatically generated by Adjuvant!.

Statistical analysis

PREDICT's batch processor cannot calculate prognostic estimates if ER-status is unknown, thus patients with unknown ER-status were excluded from all analyses of PREDICT's estimates, leaving 2,073 and 1,076 patients in the all-cause and breast cancer-specific mortality analyses respectively. In the all-cause mortality analyses of Adjuvant! all 2,710 patients that met the inclusion criteria were included. In the breast cancer-specific mortality analyses, hospitals for which cause of death data was missing were excluded leaving 1,535 patients in the analyses.

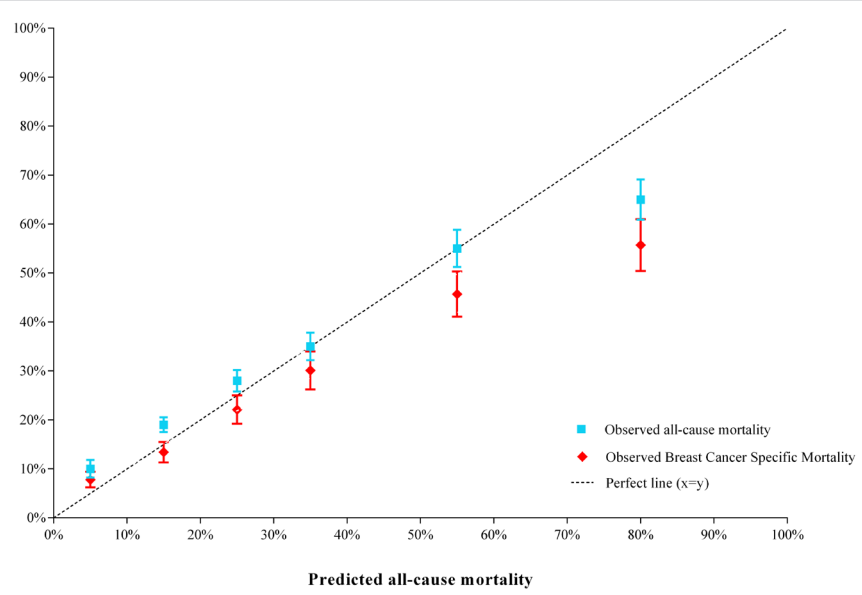


Figure 2 Observed vs. PREDICT estimates of 10-year all-cause and breast cancer specific mortality

We compared the average observed and the average predicted 10-year all-cause and breast cancer-specific mortality using one-sample T-tests for proportions. We used a

1,000 resamples bootstrap for calculation of the 95%-confidence interval, and bootstrap p-values were directly calculated from the bootstrap sampling using the percentiles and simple sampling method. The prognostication tool's average predicted mortality was the fixed value (i.e., assumed to be true based on the model used), and the average observed mortality the comparison variable. We compared the concordance between the observed and predicted estimates for the whole population and for subgroups of relevant prognostic characteristics, which were determined a priori.

Additionally, we evaluated model calibration by plotting averages of observed versus predicted mortality, grouped by deciles of predicted outcomes. If there were <100 patients in a decile, it was merged with adjacent decile(s) to ensure sufficiently large numbers in all deciles. The slope of the fitted line was compared with the slope of the line indicating a perfect relationship (y=x). We evaluated discriminatory accuracy using receiver-operator curves (ROC) and corresponding c-indices derived by calculating the area under the curve (AUC). All analyses were performed in SPSS version 20.0 software.

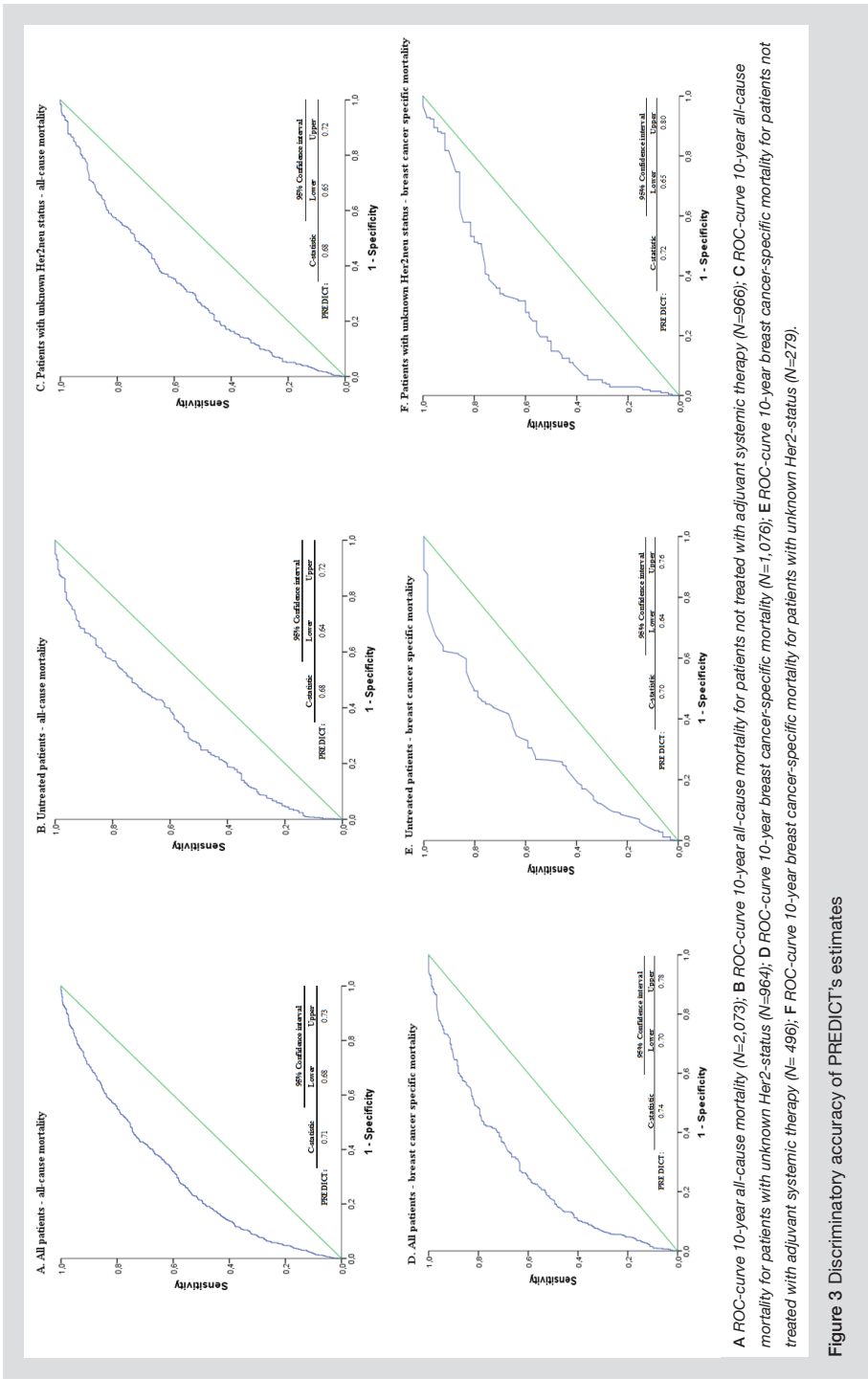
Results

Patients in the all-cause mortality analyses had a mean age of 42 years (range: 22-50) and an average of 13.5 years follow-up (Appendix Table 1). Overall, 61% of patients had stage II disease (Appendix Table 2), and on average patients ≤40 years more often had ER-negative, grade 3 and/or node-positive disease compared to those who were 41-50 years at diagnosis.

Calibration of 10-year all-cause mortality for the whole population
Calibration was assessed using the mean difference between predicted an observed mortality. PREDICT tended to underestimate all-cause mortality, but the overall difference was not statistically significant (-1.1, 95%-CI: -3.2 to 0.9; P=0.28) (Figure 1; Appendix Table 3). Adjuvant! also underestimated all-cause mortality (-2%, 95%-CI: -3.7 to -0.3; P=0.02) (Appendix Table 4). The PREDICT batch processor did not allow for inclusion of patients with unknown ER-status, therefore these patients were excluded (N= 637 (23.5%). However, Adjuvant!'s expected mortality did not change when we excluded the patients with unknown ER-status (27.0% versus 26.7%).

Calibration of 10-year all-cause mortality for key prognostic subgroups
PREDICT underestimated all-cause mortality in the two youngest age groups by -6.6% to -4.9 (Figure 1; Appendix Table 3). It also underestimated mortality in subgroups of patients with good prognosis, e.g., stage I, T1, and N0 disease, the mean range of difference was between -2.9% to -4.8%. PREDICT tended to overestimate mortality for poor prognosis subgroups (e.g., N1, stage III, T3) by 2.6% to 9.4%. PREDICT also overestimated mortality in the Her2-negative subgroup by 2.2%. Adjuvant!'s performance was comparable to PREDICT's (Appendix Figure 2; Appendix Table 4). Neither PREDICT nor Adjuvant! take angiolymphatic invasion into account, but we did evaluated the prognosis estimates for subgroups in our dataset. Both tools underestimated mortality in patients with extensive angiolymphatic invasion (range mean difference: -4.0% to -9.3%) (Appendix Tables 3-4).

Calibration of 10-years breast cancer-specific mortality estimates
PREDICT overestimated breast cancer-specific mortality by 3.2% (95%-CI: 0.8 to 5.6; P=0.007) (Figure 1; Appendix Table 3). Adjuvant!'s estimates did not significantly differ from observed breast cancer-specific mortality (P=0.23) (Appendix Figure 3; Appendix Table 4). However, both PREDICT and Adjuvant! seemed to indiscriminately overestimate rates across subgroups (range mean difference: 3.0% to 14.1%) (Figure 1; Appendix Figure 3; Appendix Table 3-4).



A *ROC-curve 10-year all-cause mortality (N=2,073);* **B** *ROC-curve 10-year all-cause mortality for patients not treated with adjuvant systemic therapy (N=966);* **C** *ROC-curve 10-year all-cause mortality for patients with unknown Her2-status (N=964);* **D** *ROC-curve 10-year breast cancer-specific mortality (N=1,076);* **E** *ROC-curve 10-year breast cancer-specific mortality for patients not treated with adjuvant systemic therapy (N= 496);* **F** *ROC-curve 10-year breast cancer-specific mortality for patients with unknown Her2-status (N=279).*

Figure 3 Discriminatory accuracy of PREDICT's estimates

Calibration curves

The calibration curves for PREDICT and Adjuvant! were similar, and showed that overall both tools' predictions of all-cause mortality were accurate for patients with 20% to 40% mortality probability (Figure 2; Appendix Figure 4). However, the fit was inferior in the cohort of patients with the best (<20% mortality probability) and poorest (>40% mortality probability) prognosis (Figure 2; Appendix Figure 4). We found a similar pattern for breast cancer-specific mortality probability estimates for both tools (Figure 2; Appendix Figure 4).

Discriminatory accuracy

PREDICT's discriminatory accuracy for all-cause (C-statistic: 0.71) and breast cancer-specific mortality (C-statistic: 0.74) was moderate in the whole population (Figure 3: panel-A, panel-D). To assess the discriminatory accuracy in the absence of a treatment effect, we ran these analyses in untreated patients. Patients with relatively good prognosis were overrepresented in this subgroup; there were more patients with ER-positive (72%), grade 1 (22%), T1 tumors (62%), N0 status (85%) and stage I (58%) disease (compared to whole cohort: see Appendix-Table 2). The discriminatory accuracy in the subgroup of untreated patients was moderate (Figure 3: panel-B, panel-E). Adjuvant!'s discriminatory accuracy is in line with PREDICT in the whole population and in the cohort of untreated patients (Appendix Figure 5).

In our analyses we accounted for Her2-status, which is not automatically done by Adjuvant!. To gauge Adjuvant!'s discriminatory accuracy in a subgroup where we did not use this adjustment, we ran these analyses in patients with unknown Her2-status. Adjuvant! and PREDICT discriminatory accuracy for all-cause and breast cancer-specific mortality in this subgroup was also moderate (Figure 3: panel-C, panel-F; Appendix Figure 5).

Discussion

The prognostic accuracy of PREDICT and Adjuvant!'s 10-year all-cause and breast cancer-specific mortality estimates were evaluated in a large cohort of Dutch patients diagnosed <50 years of age between 1990 and 2000. We mainly focus on PREDICT's results as Adjuvant! has been offline for some time, therefore we were unable to update it estimates after receiving new data about adjuvant systemic therapy. However, the updated data about adjuvant systemic therapy did not lead to differences in the direction of the under- or overestimation by PREDICT, therefore, we used the Adjuvant! results to substantiate our findings in PREDICT. Overall, PREDICT tended to underestimate all-cause mortality, but the difference was not statistically significant. It did significantly underestimated all-cause mortality for patients ≤40 years by up to -6.6%. Further, PREDICT underestimated all-cause mortality for patients with good prognosis, and overestimated it for those with poor prognostic characteristics. Adjuvant!'s calibration and discriminatory accuracy in our population was in line with PREDICT's. Although the absolute differences observed were small, they might nonetheless be clinically relevant. Given that the minimum treatment benefit generally required to be eligible for adjuvant systemic treatment is only 3-5%, an absolute overestimation of treatment benefit of 2% may already affect treatment decisions, and reflects a relative overestimation of almost 30%.

Many young patients (especially those ≤35 years) with favorable prognostic characteristics (e.g., N0 or T1) had a high tumor grade. This could partly explain PREDICT's (and Adjuvant!'s) underestimation of all-cause mortality in the good prognosis subgroups. Also, it has been described that tumors in young patients have a greater tendency to metastasize, even in case of favorable prognostic characteristics (4). Given the high probability of poor outcomes in patients ≤40 years, it has been argued that most or all are candidates for adjuvant chemotherapy, solely based on age at diagnosis (4). Indeed, treating all patients diagnosed ≤40 years with adjuvant chemotherapy seems to be the tendency in clinical practice, which inevitably means that a substantial proportion of patients only experience side-effects and no treatment benefit. Current guidelines (14-16) stipulate that independent of intrinsic tumor subtype, all breast cancer patients ≤35 years with tumors >1cm should receive chemotherapy, and for those who are Her2neu-positive (irrespective of age) chemotherapy in combination with trastuzumab is also indicated in case of tumors 5-10 mm (T1b). The first international consensus guidelines for the treatment of breast cancer in patients ≤40 years, however, strongly advocated that age should not be the sole reason to prescribe more aggressive treatment and that tumor biology should be the overriding factor (26). This underscores the importance of well-validated tools including all relevant tumor characteristics.

Contrary to our findings that both prognostication tools tended to overestimate all-cause

mortality in subgroups with poor prognosis, we found that both tools underestimate all-cause mortality especially for patients with extensive angiolymphatic invasion by as much as 9.3%. Currently, neither tool takes angiolymphatic invasion into account. This is perhaps understandable as angiolymphatic invasion is one of the features that pathologists have difficulty scoring in a reproducible manner, which has somewhat limited its usefulness when assessing prognosis. However, in view of our findings, it might be relevant to investigate whether this factor adds prognostic information.

Further, PREDICT (and Adjuvant!) tended to underestimate the impact of endocrine therapy on survival. As relatively few young patients have ER-positive breast cancer, and before 1995 endocrine therapy was not administered to premenopausal patients, they are probably underrepresented in the trials on which the treatment effect estimates are based. However, nowadays substantially more young patients are treated with adjuvant systemic therapy (Appendix Figure 6), including endocrine therapy in case of hormone-positive disease, as there is evidence that endocrine therapy is equally effective in young/premenopausal and older/postmenopausal patients (27). Our findings highlight that these tools need to be updated from time to time, as is currently the case for Adjuvant!.

In this young age group, all-cause mortality is likely a close representation of breast cancer-specific mortality. Based on our smaller dataset with known cause of death, PREDICT significantly overestimated breast cancer-specific mortality, and it (like Adjuvant!) seemed to generally indiscriminately overestimate breast cancer-specific mortality across subgroups. For a large proportion of our population, data on cause of death was not available, limiting the number of patients available for the breast cancer-specific mortality analyses and leading to wide confidence intervals in many subgroup analyses. Also, where cause of death was known, for 37% of patients in our sample it was classified as not breast cancer-related. Considering that these were young women, it seems unlikely that such a large proportion of patients would have pre-existing comorbid conditions, i.e., competing causes of death. It seems more likely that cause of death was not missing at random, and/or at least for a proportion of these breast cancer patients and/or the late effects of treatment were the true underlying cause of death. Indeed, bias through misclassification of cause of death is a well-known problem when assessing cancer-specific mortality (28-30). Moreover, differences may exist between health care provided in the Netherlands versus the United States and United Kingdom. Therefore, our cancer-specific mortality findings should be interpreted cautiously.

A clear strength of our study is our large cohort with complete data about tumor size, nodal status and receipt of adjuvant therapy. However, a weakness is that mode of disease detection (PREDICT) was missing (but population-based screening starts at 50

years), and that Her2neu and KI67-status were not routinely determined at diagnosis, and Her2-status was only assessed by immunohistochemistry. Also, we excluded patients diagnosed prior to 1990, which reduced our sample size considerably. We opted to exclude these patients from our analyses as patients diagnosed during this time period had significantly poorer survival compared to those diagnosed between 1990-2000. Therefore, the findings in this subgroup would not be comparable to those of currently diagnosed/treated patients. Further, we cannot disentangle the effect of adjuvant systemic treatments on outcome, as treatment decisions were not or not always based on PREDICT (or Adjuvant!) estimates, but on local treatment guidelines and patient preferences. Yet, since half of our population did not receive adjuvant systemic treatment, they can be viewed as a proxy for a validation unbiased by treatment effect. In this subgroup PREDICT (like Adjuvant!) performed well with regard to all-cause mortality. Additionally, some of the differences observed between the tools might be due to differences in exposure to risk factors and/or factors associated with poor survival between the populations in which they were developed (31-33), i.e., British for PREDICT and American for Adjuvant!. Finally, in order to allow for sufficient follow-up time we used a cohort of patients diagnosed up to 2000 in which absolute survival might not completely reflect that of recently diagnosed patients (Appendix Figure 7).

PREDICT's all-cause mortality estimates seem reasonably sound for young breast cancer patients, but further adjustments are especially needed for patients ≤40 years and for those in the best and poorest prognosis subgroups. Our data underscores that it is important to remain aware of the fact that these tools provide average estimates which in certain patients and patient groups might not be accurate, also in view of the variability of the disease. These estimates, therefore, are intended to supplement, and not to replace clinical judgement and doctor-patient communication, when advising patients about adjuvant systemic therapy.

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Appendix A supplemental information on the methods used

Number of patients per participating hospital

Included patients were treated between 1990 and 2000 at the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (N=683), Erasmus Medical Center-Daniel den Hoed Clinic (N=320), which are cancer centers; Leiden University Medical Center (N=205), an academic hospital; and Medisch Spectrum Twente Hospital (N=839), PAMM Laboratories (N=221), Albert Schweitzer Hospital (N=191), Rijnland Hospital (N=86), Viecuri Hospital (N=74), Diaconessenhuis Leiden (N=50), and Elkerliek Hospital (N=41), which are regional hospitals.

An update of the clinical and follow-up data revealed that 19 patients included in the current study were 50 years at diagnosis, and therefore did not meet the eligibility criterion of below 50 years. This shift in age was due to adjustment of the date of diagnosis (histological confirmation). Given the small number of patients concerned and the fact that the results remained the same irrespective of whether these patients were included or not, we decided to keep them in the analyses.

Procedures

Data categorization: age at diagnosis (continuous), tumor size (continuous for PREDICT and for Adjuvant! categorized as: 0.0-1.0 cm, 1.1-2.0 cm, 2.1-3.0 cm, 3.1-5.0 cm or >5.0 cm), tumor grade (categorized as: Grade 1, Grade 2, Grade 3 or undefined if missing), number of positive axillary lymph nodes (continuous for PREDICT and for Adjuvant! categorized as: 0 positive nodes, 1-3 positive nodes, 4-9 positive nodes or >9 positive nodes), ER-status (categorized as: positive, negative or undefined if missing).

For Adjuvant! if tumor diameter (in mm) was missing, patients were categorized using pathological T-stage if available (T1 was categorized as having a tumor of 1.1-2.0 cm, T2 was categorized as having a tumor of 3.1-5.0 cm and T3 was categorized as having a tumor of >5.0 cm). For Adjuvant! patients with missing data on the number of positive axillary lymph nodes were categorized using pathological N-stage if available (N0 was categorized as having 0 positive nodes, N1 was categorized as having 1-3 positive nodes, N2 was categorized as having 4-9 positive nodes and N3 was categorized as having >9 positive nodes). We used weighed mean imputed values to calculate PREDICT survival estimates for missing values of grade (imputed value: 2.25), tumor size in mm (if pT1a-b: 5mm; pT1c: 1.5mm; pT2: 40mm; pT3: 50mm), and number of positive axillary lymph nodes (if pN1: 2 positive nodes; pN2: 7 positive nodes; pN3: 10 positive nodes). The T, N, and M were determined according to Dutch guidelines at the time of diagnosis; for combining these three factors in the stage variable, the AJCC TNM staging guidelines of 2002 were used.

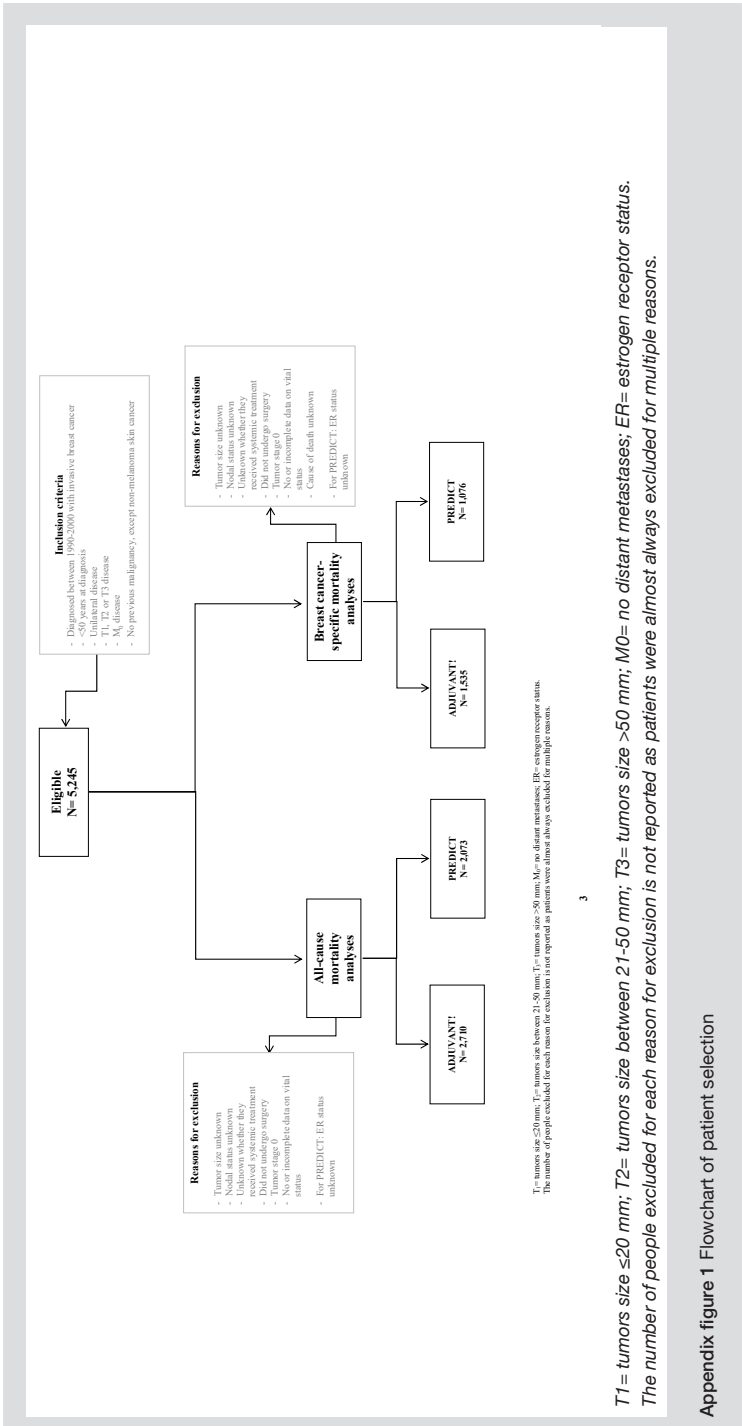
According to the clinical cut-off points endorsed in the Dutch breast cancer guideline for immunohistochemical staining of receptors, a tumor was considered receptor negative using the following cut-offs: ER= ≤10%; PR= ≤10%; Her2-score= 0 or 1+)) (21;26;27). Receptor status data was included from Tissue Micro Arrays (TMA) if data from pathology reports was not available, for ER the data source was N_{TMA}= 757 and $N_{pathology\ reports}$= 1316, and for Her2 data source was N_{TMA}= 817 and $N_{pathology\ reports}$= 308. Patients with a tumor that did not express ER, PR and Her2 were considered to have a triple negative tumor. Within the time period that patients in this cohort had been diagnosed (i.e. 1990-2000), it was not yet standard practice to routinely assess cell-surface Her2 protein expression by immunohistochemistry (Her2-status missing for N= 1,639 (60%)). Her2 was mostly included from analyses of TMA using Her2 immunohistochemistry, however, the number of copies of the Her2-gene was not quantified using an in situ hybridization technique (e.g., FISH, CISH or SISH) for patients with an equivocal Her2 immunohistochemistry (i.e. 2+ score) to definitively determine Her2-status (N= 60 (2%)). We opted to include patients with equivocal Her2 immunohistochemistry in our analyses and treat them as having Her2-negative disease, based on Kaplan-Meier curves analyses that showed that their survival pattern was similar to those with immunohistochemistry Her2-negative disease (data not shown).

Angiolymphatic-invasion, i.e., tumor formation in blood and/or lymph blood vessels, was only available for reviewed tumor H&E slides. A breast pathologist (H. Peterse, NKI-AVL) scored the tumors as follows: 0=none, 1=1-3 vessels in the whole slide, 2=more than three vessels in the whole slide.

Adjuvant systemic treatment was categorized as: none, first generation (if treated with cyclophosphamide - methotrexate - fluorouracil (CMF), cyclophosphamide - doxorubicin or epirubicin (AC or EC) (four cycles) or if type chemotherapy regime was unknown and the patient also received endocrine therapy) and second generation (if treated with fluorouracil (5FU) - doxorubicin or epirubicin - cyclophosphamide (FEC or FAC) (six cycles), others). In the Adjuvant! analysis sample (N=2,710), in total 1,058 patients received first generation chemotherapy and 47 patients received second-generation chemotherapy. In the PREDICT analysis sample (N=2,073), in total 800 patients received first generation chemotherapy and 24 patients received second-generation chemotherapy. In this population, endocrine treatment only consisted of Tamoxifen.

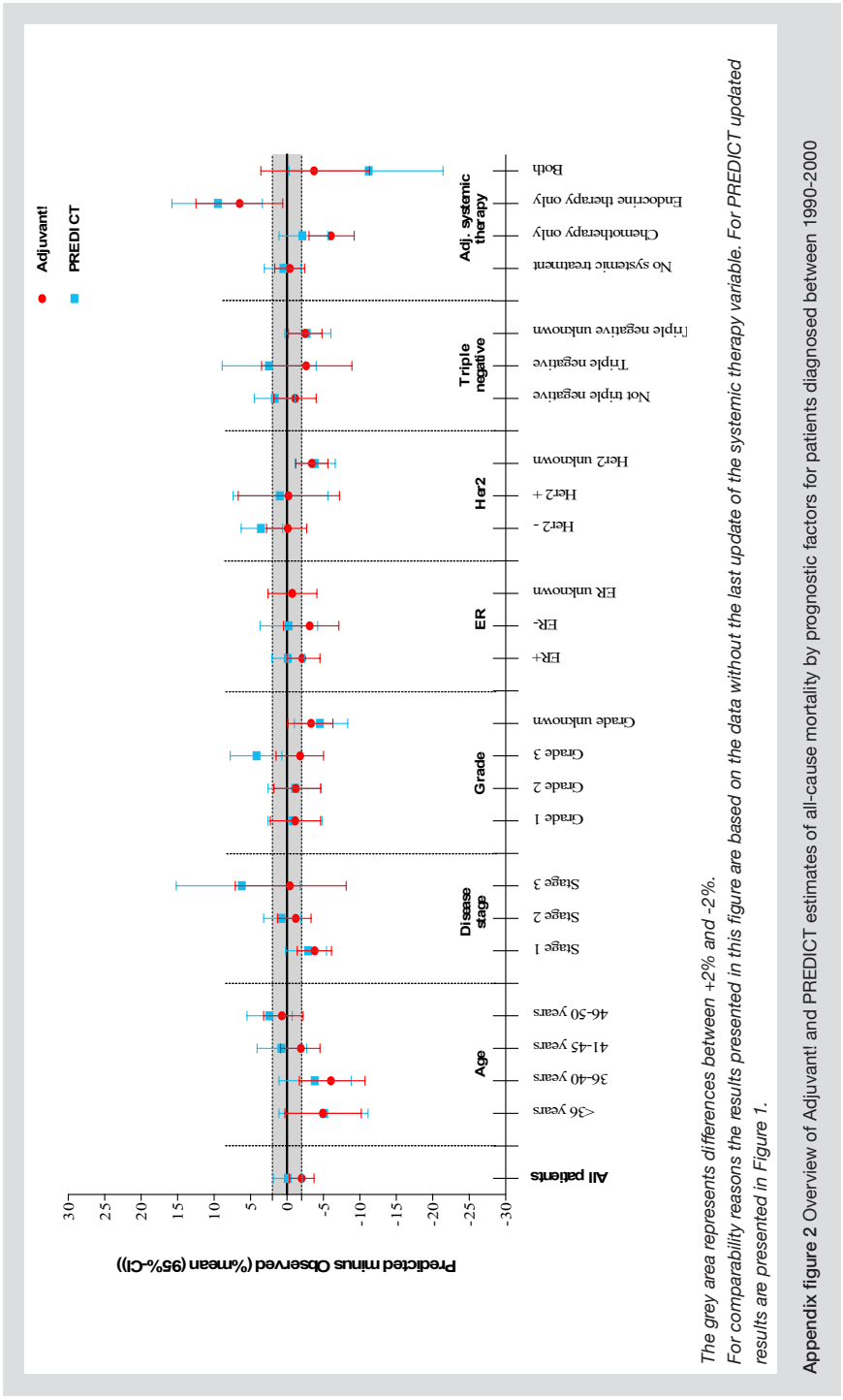
Analyses

The following hospitals had no data on cause of death and were thus excluded from the breast cancer-specific mortality estimates, namely: Elkerliek (N=41), Viecuri (N=74), PAMM Laboratories (N=221) and Medisch Spectrum Twente (N=839).



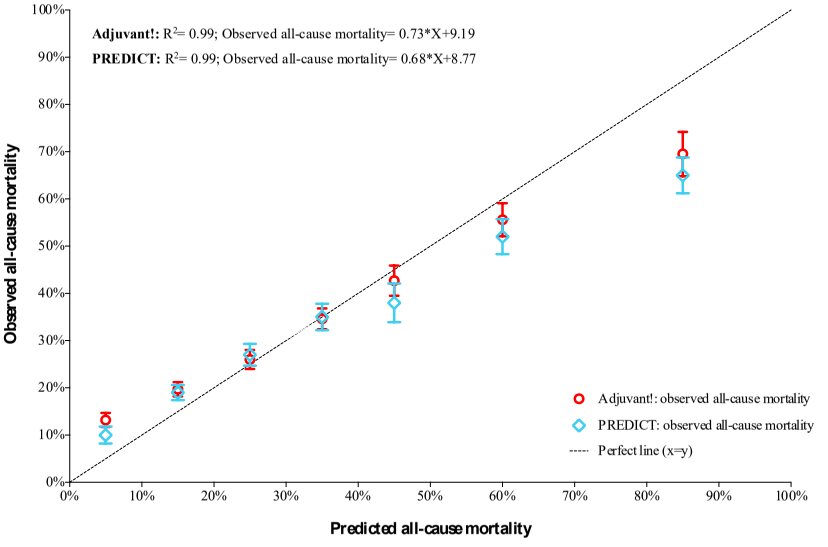
T1= tumors size ≤20 mm; T2= tumors size between 21-50 mm; T3= tumors size >50 mm; M0= no distant metastases; ER= estrogen receptor status.
The number of people excluded for each reason for exclusion is not reported as patients were almost always excluded for multiple reasons.

Appendix figure 1 Flowchart of patient selection



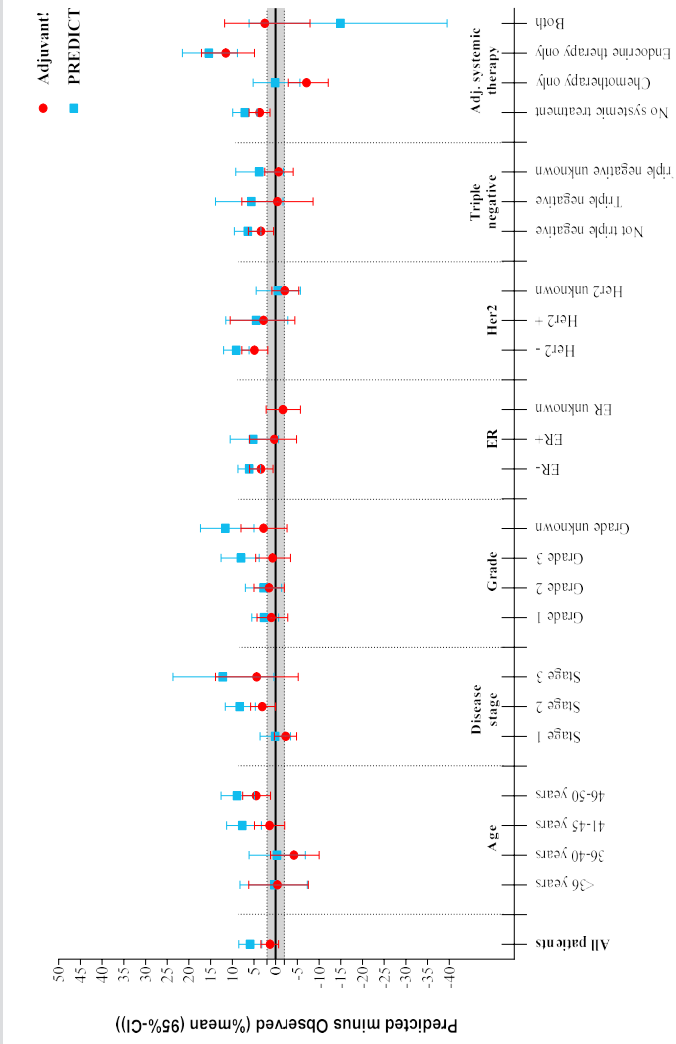
The grey area represents differences between +2% and -2%.
For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 1.

Appendix figure 2 Overview of Adjuvant! and PREDICT estimates of all-cause mortality by prognostic factors for patients diagnosed between 1990-2000



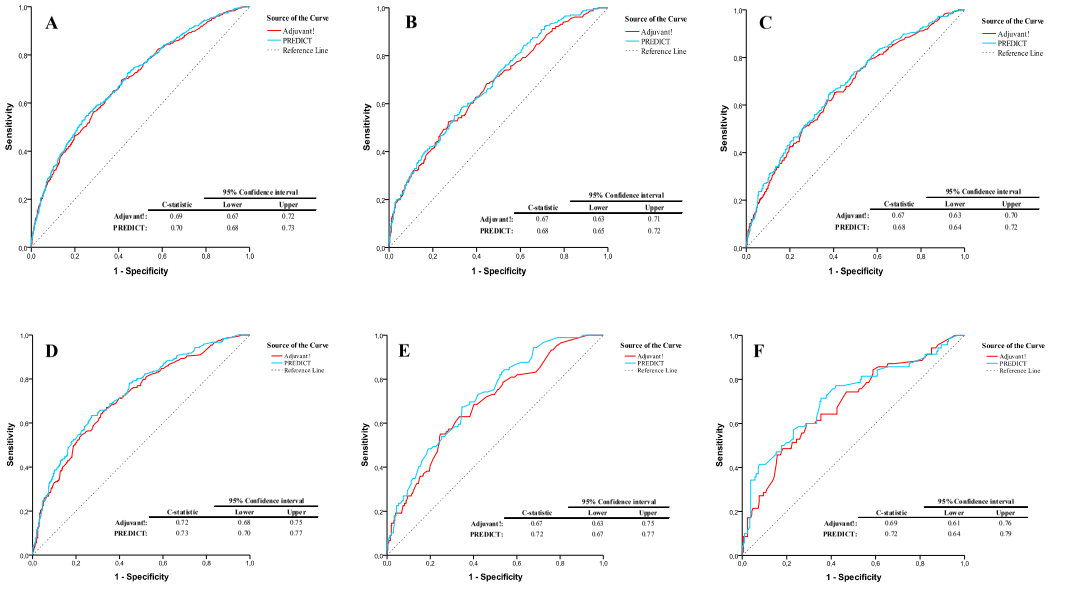
The grey area represents differences between +2% and -2%.
For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 1.

Appendix figure 3 Overview of Adjuvant! and PREDICT's estimates of breast cancer-specific mortality by prognostic factors for patients diagnosed between 1990-2000



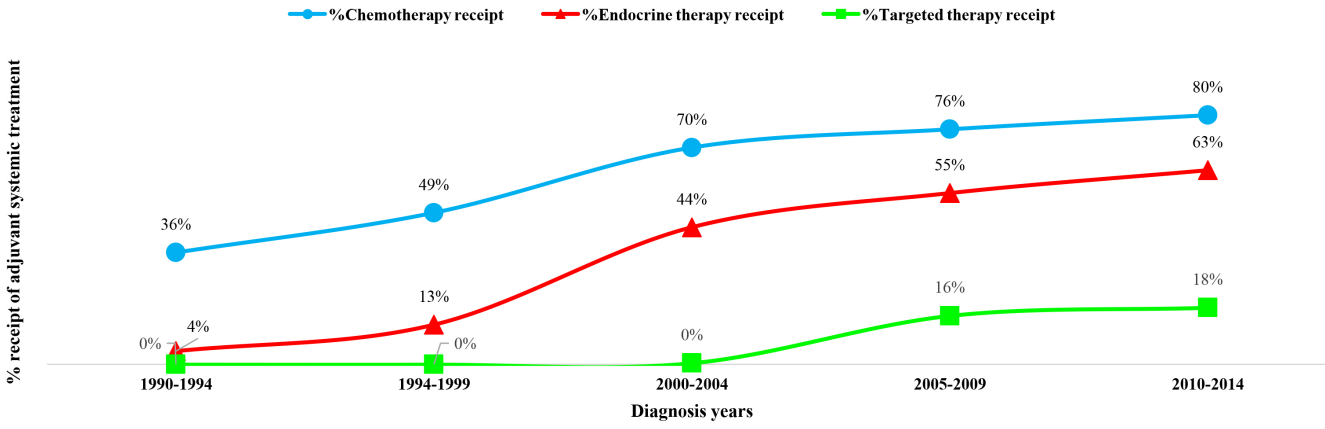
The analysis of Adjuvant!'s calibration contains N= 1,535 patients, and in the PREDICT analysis we included N= 1,076 patients. Deciles with <100 patients were merged, namely 40% to 60% and 60% to 100%. Error bars are standard errors (SE). For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 2.

Appendix figure 4 Observed vs. Predicted 10-year all-cause and breast cancer-specific mortality for patients diagnosed between 1990-2000 (without updated adjuvant systemic therapy receipt data)



All ROC-curves are based on patients diagnosed between 1990 up to 2000 included in the PREDICT analyses (N=2,073). For comparability reasons the results presented in this figure are based on the data without the last update of the systemic therapy variable. For PREDICT updated results are presented in Figure 3.
A *ROC-curve 10-year all-cause mortality (N=2,073);* **B** *ROC-curve 10-year all-cause mortality for patients not treated with adjuvant systemic therapy (N=1,061);* **C** *ROC-curve 10-year all-cause mortality for patients with unknown Her2-status (N=964);* **D** *ROC-curve 10-year breast cancer-specific mortality (N=1,076); E ROC-curve 10-year breast cancer-specific mortality for patients not treated with adjuvant systemic therapy (N= 591); F ROC-curve 10-year breast cancer-specific mortality for patients with unknown Her2-status (N=279).*

Appendix figure 5 Discriminatory accuracy of Adjuvant! and PREDICT in patients diagnosed between 1990-2000

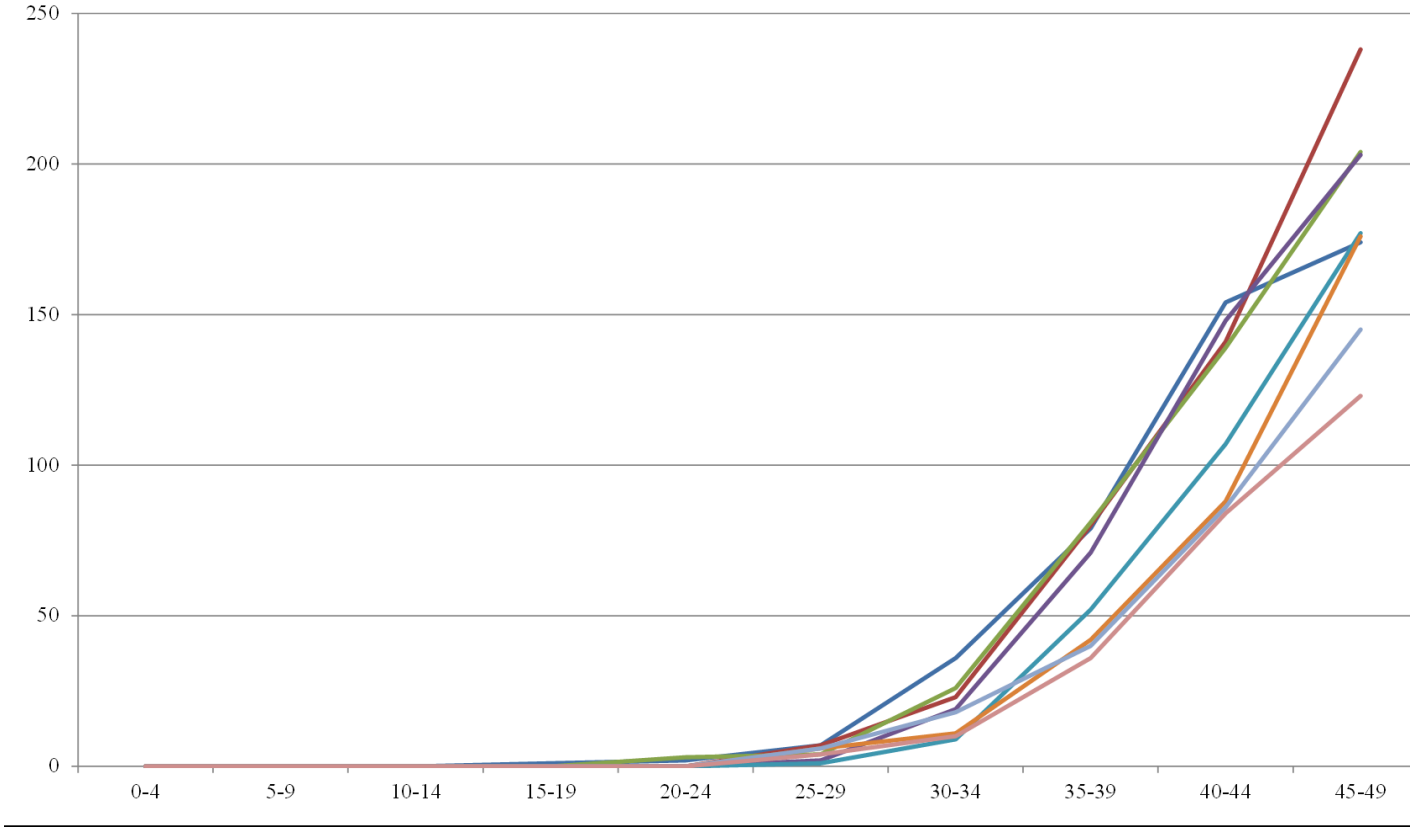


Source: Netherlands Cancer Registry, managed by Netherlands Comprehensive Cancer Organisation (IKNL)© March 2016

Appendix Figure 6 Netherlands Cancer Registry data on the trends in use of adjuvant systemic therapy among stage I-III breast cancer patients aged <50 years diagnosed between 1990-2014

		Total number of patients who received:								
Diagnosis years	*Total population*	*Neo-adjuvant chemotherapy*	*Adjuvant chemotherapy*	*Neo-adjuvant and adjuvant chemotherapy*	*Neo-adjuvant endocrine therapy*	*Adjuvant endocrine therapy*	*Neo-adjuvant and adjuvant endocrine therapy*	*Neo-adjuvant targeted therapy*	*Adjuvant targeted therapy*	*Neo-adjuvant and adjuvant targeted therapy*
1990-1994	10.269	109	3.582	9	4	438	0	0	0	0
1994-1999	11.451	207	5.357	29	18	1.449	0	0	0	0
2000-2004	12.907	599	8.374	42	18	5.684	4	1	58	0
2005-2009	13.983	1.555	8.933	101	30	7.674	14	239	1.888	72
2010-2014	13.887	3.215	7.749	184	71	8.592	25	633	1.722	191

Source: Netherlands Cancer Registry, managed by Netherlands Comprehensive Cancer Organisation (IKNL)© March 2016



Source: Netherlands Cancer Registry, managed by Netherlands Comprehensive Cancer Organisation (IKNL) © January 2016

Appendix figure 7 Netherlands Cancer Registry data on mortality rates among breast cancer patients for the period 1990-2014

Appendix Table 1 Overview of subsets used in the analyses

	Adjuvant! analyses		PREDICT analyses	
	Subset diagnosed between 1990-2000		Subset diagnosed between 1990-2000	
	all-cause mortality	*breast cancer-specific mortality*	*all-cause mortality*	*breast cancer-specific mortality*
Number of patients:	2,710	1,535	2,073	1,076
Mean FUP in years (SE):	13.5 (0.12)	8.7 (0.07)	13.5 (0.14)	8.6 (0.08)
FUP range in years:	0 to 23	0 to 10	0 to 23	0 to 10
Mean age in years (SE):	42 (0.10)	43 (0.14)	42 (0.12)	43 (0.17)
Age in years (range):	23 to 50	23 to 50	23 to 50	23 to 50
Number of patients per age category (%):				
<35	328 (12)	189 (12)	254 (12)	132 (12)
36-40	447 (17)	255 (17)	353 (17)	183 (17)
41-45	936 (35)	538 (35)	716 (35)	379 (35)
46-50	999 (37)	553 (36)	750 (36)	382 (36)
Number of patients per stage (%):				
1	925 (34)	534 (35)	690 (33)	365 (34)
2	1,614 (60)	891 (58)	1,256 (61)	638 (59)
3	171 (6)	110 (7)	127 (6)	73 (7)
unknown	0	0	0	0

Appendix Table 2 Distribution of prognostic characteristics by age at diagnosis for patients diagnosed between 1990-2000 (N (row%))

	≤35 years N_{col}= 254	36-40 years N_{col}= 353	41-45 years N_{col}= 716	46-50 years N_{col}= 750	N_{row}	P*
ER-status						
ER +	127 (9)	225 (16)	517 (36)	581 (40)	1,450	**<0.001**
ER -	127 (20)	128 (21)	199 (32)	169 (27)	623	
Unknown	0	0	0	0	0	
Her2-status						
Her2 -	105 (12)	155 (17)	307 (34)	331 (37)	898	0.093
Her2 +	36 (17)	41 (19)	70 (33)	64 (30)	211	
Unknown	113	157	339	355	964	
Tumor grade						
Grade 1	16 (6)	36 (14)	88 (34)	121 (46)	261	
Grade 2	46 (9)	86 (17)	180 (35)	206 (40)	518	**<0.001**
Grade 3	123 (17)	145 (20)	246 (34)	215 (30)	729	
Unknown	69	86	202	208	565	
Tumor size						
0.1-1.0 cm	29 (11)	47 (19)	86 (34)	92 (36)	254	
1.1-2.0 cm	85 (11)	132 (17)	279 (35)	300 (38)	796	
2.1-3.0 cm	54 (12)	85 (18)	168 (36)	162 (35)	469	0.326
3.1-5.0 cm	64 (15)	63 (15)	142 (33)	159 (37)	428	
>5 cm	22 (18)	26 (21)	41 (33)	37 (29)	126	
Unknown	0	0	0	0	0	

ER= estrogen receptor; Her2= Her2neu receptor
This table is based on the patients included in the PREDICT analyses (N= 2,073). It is based on updated adjuvant systemic treatment data. In the new data patients were mainly reallocated to having received systemic treatment instead of not having done so, and having received chemotherapy instead of only endocrine therapy.
If row percentage does not add up to 100%, this is due to the rounding at the first decimal.
*P-values for Chi-square tests (not including unknown).

Appendix Table 2 continued Distribution of prognostic characteristics by age at diagnosis for patients diagnosed between 1990-2000 (N (row%))

	≤35 years N_{col}= 254	36-40 years N_{col}= 353	41-45 years N_{col}= 716	46-50 years N_{col}= 750	N_{row}	P*
Positive nodes						
0	122 (12)	149 (15)	372 (37)	360 (36)	1,003	
1-3	77 (11)	134 (19)	220 (32)	258 (37)	689	**0.046**
4-9	36 (13)	49 (18)	98 (36)	90 (33)	273	
>9	19 (18)	21 (19)	26 (24)	42 (39)	108	
Unknown	0	0	0	0	0	
Disease stage						
Stage 1	72 (10)	108 (16)	260 (38)	250 (36)	690	
Stage 2	164 (13)	216 (17)	413 (33)	463 (37)	1,256	0.085
Stage 3	18 (14)	29 (23)	43 (34)	37 (29)	127	
Unknown	0	0	0	0	0	
Surgery						
Breast conserving	104 (10)	192 (18)	377 (36)	380 (36)	1,053	**0.032**
Mastectomy	150 (15)	160 (16)	338 (33)	369 (36)	1,017	
Unknown	0	1	1	1	3	
Adjuvant systemic treatment						
None	104 (11)	144 (15)	369 (38)	349 (36)	966	
Chemotherapy only	125 (16)	157 (20)	257 (33)	249 (32)	788	**<0.001**
Endocrine therapy only	3 (3)	6 (6)	26 (26)	66 (65)	101	
Both	22 (10)	46 (21)	64 (29)	86 (39)	218	
Unknown	0	0	0	0	0	

ER= estrogen receptor; Her2= Her2neu receptor

This table is based on the patients included in the PREDICT analyses (N= 2,073). It is based on updated adjuvant systemic treatment data. In the new data patients were mainly reallocated to having received systemic treatment instead of not having done so, and having received chemotherapy instead of only endocrine therapy.

If row percentage does not add up to 100%, this is due to the rounding at the first decimal.

*P-values for Chi-square tests (not including unknown).

Appendix Table 3 Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P	N (%)	Observed	Predicted	Predicted minus Observed (95-C.I.)	P
Overall	2073 (100)	27.2	28.3	-1.1 (-3.2 to 0.9)	0.28	1076 (100)	22.6	25.8	3.2 (0.8 to 5.6)	**0.007**
Age (years)										
≤ 35	254 (12)	26.6	33.2	-6.6 (-12.5 to -0.1)	**0.04**	132 (12)	33.0	30.7	-2.3 (-10.6 to 5.2)	0.52
36-40	353 (17)	25.3	30.2	-4.9 (-10.0 to 0.0)	0.06	183 (17)	31.1	27.9	-3.2 (-9.5 to 4.0)	0.35
41-45	716 (35)	27.5	27.5	0.0 (-3.2 to 3.3)	0.99	379 (35)	19.8	25.7	5.9 (1.8 to 10.0)	**0.003**
46-50	750 (36)	27.7	26.4	1.3 (-1.8 to 4.3)	0.39	382 (36)	17.5	23.1	5.6 (1.6 to 9.2)	**0.01**
Her2-status										
Negative	898 (43)	29.9	27.7	2.2 (-0.6 to 5.0)	0.15	628 (58)	18.3	24.5	6.2 (3.3 to 9.1)	**0.001**
Positive	211 (10)	38.9	39.6	-0.7 (-8.2 to 6.1)	0.85	169 (16)	34.3	36.8	2.5 (-4.9 to 9.4)	0.49
Unknown	964 (47)	21.9	26.3	-4.4 (-7.3 to -1.4)	**0.01**	279 (26)	25.1	22.0	-3.1 (-8.2 to 1.8)	0.22
ER-status										
Positive	1450 (70)	23.5	24.5	-1.0 (-3.2 to 1.1)	0.38	785 (73)	18.2	21.9	3.7 (1.0 to 6.4)	**0.01**
Negative	623 (30)	35.9	37.2	-1.3 (-5.2 to 2.3)	0.52	291 (27)	34.4	36.1	1.7 (-3.5 to 7.5)	0.54
Triple negative										
Not triple negative	971 (47)	28.7	28.2	0.5 (-2.1 to 3.3)	0.72	727 (68)	20.9	25.1	4.2 (1.0 to 6.9)	**0.01**
Triple negative	207 (10)	37.6	36.9	0.7 (-6.7 to 7.2)	0.84	136 (13)	33.1	34.9	1.8 (-6.7 to 9.1)	0.64
Unknown	895 (43)	23.1	26.4	-3.3 (-6.5 to -0.5)	**0.03**	213 (20)	21.6	22.0	0.4 (-5.4 to 5.9)	0.89

Table is based on updated adjuvant systemic treatment data.
ER= estrogen receptor; Her2= Her2neu receptor
[a] = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.
- = Due to the small number of cases, we were unable to calculate this value.
* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 3 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

				10-year all-cause mortality					*10-year breast cancer-specific mortality*	
Tumor Grade										
Grade 1	261 (13)	9.1	10.1	-1.0 (-5.0 to 3.0)	0.63	176 (16)	6.3	6.9	0.6 (-3.3 to 3.8)	0.72
Grade 2	518 (25)	19.5	21.6	-2.1 (-6.0 to 1.4)	0.25	342 (32)	17.5	18.5	1.0 (-2.9 to 4.7)	0.63
Grade 3	729 (35)	44.0	41.4	2.6 (-1.1 to 6.2)	0.16	442 (41)	35.3	39.9	4.6 (-0.1 to 9.0)	**0.05**
	N (%)	**Observed**	**Predicted**	**Predicted minus Observed (95-C.I.)**	**P**	**N (%)**	**Observed**	**Predicted**	**Predicted minus Observed (95-C.I.)**	**P**
Unknown	565 (27)	20.8	25.9	-5.1 (-8.6 to -1.2)	**0.01**	116 (11)	13.8	21.6	7.8 (1.1 to 13.9)	**0.02**
Stage										
Stage 1	690 (33)	11.0	14.0	-3.0 (-5.7 to -0.2)	**0.04**	365 (34)	12.9	12.3	-0.6 (-4.3 to 2.6)	0.77
Stage 2	1256 (61)	32.8	32.8	0.0 (-3.1 to 1.9)	0.62	638 (59)	25.4	30.2	4.8 (1.6 to 8.0)	**0.01**
Stage 3	127 (6)	64.9	61.2	3.7 (-4.6 to 12.7)	0.42	73 (7)	46.6	54.5	7.9 (-4.0 to 19.5)	0.17
Tumor size										
0.1-1.0 cm	254 (12)	8.7	12.8	-4.1 (-8.8 to 0.5)	**0.09**	155 (14)	11.0	9.8	-1.2 (-6.8 to 3.4)	0.64
1.1-2.0 cm	796 (38)	14.9	19.7	-4.8 (-7.9 to -1.9)	**0.001**	358 (33)	19.0	17.5	-1.5 (-5.8 to 2.3)	0.47
2.1-3.0 cm	469 (23)	31.0	31.7	-0.7 (-5.4 to 3.2)	0.74	261 (24)	24.1	29.4	5.3 (0.0 to 10.7)	**0.06**
3.1-5.0 cm	428 (21)	44.5	40.7	3.8 (-0.8 to 8.4)	0.11	224 (21)	29.0	36.4	7.4 (1.0 to 13.8)	0.27
>5 cm	126 (6)	68.0	58.6	9.4 (0.3 to 18.0)	**0.04**	78 (7)	38.5	52.6	14.1 (3.2 to 25.5)	**0.02**
Positive nodes										
0	1003 (48)	14.1	17.0	-2.9 (-5.4 to -0.5)	**0.02**	544 (51)	15.4	15.2	-0.2 (-3.5 to 2.9)	0.85

Table is based on updated adjuvant systemic treatment data.
ER= estrogen receptor; Her2= Her2neu receptor
[a] = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.
- = Due to the small number of cases, we were unable to calculate this value.
[*] P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 3 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

				10-year all-cause mortality					*10-year breast cancer-specific mortality*	
1-3	689 (33)	28.3	29.6	-1.3 (-4.9 to 1.8)	0.44	380 (35)	23.9	29.5	5.6 (0.6 to 9.6)	**0.02**
4-9	273 (13)	53.6	49.7	3.9 (-2.0 to 9.8)	0.20	112 (10)	38.4	48.5	10.1 (1.2 to 19.3)	**0.03**
>9	108 (5)	75.1	70.9	4.2 (-4.1 to 12.8)	0.36	40 (4)	62.5	69.8	7.3 (-7.5 to 23.3)	0.32
Morphology										
IDC	1569 (76)	27.8	29.5	-1.7 (-3.8 to 0.6)	0.15	812 (75)	24.3	27.5	3.2 (0.2 to 6.1)	**0.03**
ILC	204 (10)	21.3	25.1	-3.8 (-9.8 to 2.3)	0.23	105 (10)	21.0	20.0	-1.0 (-9.3 to 6.7)	0.81
IL/DC	109 (5)	32.4	29.5	2.9 (-6.7 to 11.2)	0.50	52 (5)	15.4	24.4	9.0 (-1.7 to 17.7)	**0.09**
Tubular carcinoma	64 (3)	13.8	10.0	3.8 (-3.0 to 8.4)	0.22	25 (2)	0.0	5.6	-	-
Mucinous carcinoma	23 (1)	31.0	24.2	6.8 (-11.1 to 19.4)	0.39	14 (1)	14.3	20.0	5.7 (-15.7 to 14.4)	0.57
Medular	46 (2)	44.6	28.8	15.8 (4.4 to 24.5)	**0.02**	25 (2)	16.0	27.4	11.4 (-4.4 to 22.6)	0.14
Comedo carcinoma	23 (1)	26.5	32.8	-6.3 (-27.2 to 12.8)	0.55	14 (1)	21.4	26.9	5.5 (-17.8 to 20.7)	0.60
Other	35 (2)	16.0	22.3	-6.3 (-23.4 to 8.8)	0.42	29 (3)	24.1	19.0	-5.1 (-21.5 to 9.6)	0.52
Angiolymphatic invasion										
No angiolymphatic invasion	502 (24)	26.5	24.9	1.6 (5.3 to -2.3)	0.40	336 (31)	17.0	20.2	3.2 (-1.0 to 7.1)	0.12
Angiolymphatic invasion in up to 3 vessels	278 (13)	25.9	28.6	-2.7 (-8.1 to 2.7)	0.36	68 (6)	22.1	28.6	6.5 (-4.3 to 15.8)	0.21
Extensive angiolymphatic invasion	140 (7)	36.2	40.6	-4.4 (-13.1 to 4.4)	0.32	36 (3)	47.2	47.3	0.1 (-17.6 to 16.5)	0.99
Unknown	1153 (56)	26.7	28.2	-1.5 (-4.3 to 1.0)	0.26	636 (59)	24.2	27.2	3.0 (-0.1 to 6.2)	**0.07**
Type of surgery										
Breast conserving surgery	1053 (51)	19.0	21.8	-2.8 (-5.5 to -0.3)	**0.04**	575 (53)	20.0	19.8	-0.2 (-3.5 to 3.3)	0.93

Table is based on updated adjuvant systemic treatment data.
ER= estrogen receptor; Her2= Her2neu receptor
[a] = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.
- = Due to the small number of cases, we were unable to calculate this value.
* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 3 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and PREDICT estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

				10-year all-cause mortality					*10-year breast cancer-specific mortality*	
Mastectomy	1017 (49)	35.6	35.0	0.6 (-2.5 to 3.6)	0.70	500 (46)	25.6	32.7	7.1 (2.7 to 10.7)	**0.001**
Unknown	3 (0.1)	7.7	20.5	-	-	1 (0)	0.0	11.3	-	-
Radiotherapy										
No	450 (22)	22.2	24.3	-2.1 (-6.2 to 2.0)	0.30	225 (21)	20.9	23.1	2.2 (-3.4 to 7.7)	0.43
Yes	1623 (78)	28.5	29.4	-0.9 (-3.1 to 1.4)	0.45	851 (79)	23.0	26.5	3.5 (0.6 to 6.3)	**0.03**
Systemic treatment										
None	966 (47)	18.4	19.8	-1.4 (-3.9 to 3.9)	0.28	496 (46)	13.3	16.9	3.6 (0.4 to 6.7)	**0.03**
Chemotherapy only	788 (38)	35.5	36.8	-1.3 (-4.6 to 2.1)	0.46	377 (35)	35.0	36.1	1.1 (-3.7 to 5.7)	0.63
Endocrine therapy only	101 (5)	38.1	32.4	5.7 (-2.8 to 14.0)	0.20	62 (6)	14.5	25.9	11.4 (1.4 to 19.4)	**0.02**
Endocrine therapy and chemotherapy	218 (11)	30.0	32.9	-2.9 (-9.1 to 3.2)	0.40	141 (13)	25.5	29.2	3.7 (-3.6 to 10.8)	0.32

Table is based on updated adjuvant systemic treatment data.
ER= estrogen receptor; Her2= Her2neu receptor
[a] = PREDICT is unable to provide estimates if ER-status is unknown. Hence, all patients with an unknown ER-status, were excluded from the analyses.
- = Due to the small number of cases, we were unable to calculate this value.
* P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 4 Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
All patients	2,710 (100)	26.7	28.7 (0.9)	-2.0 (-3.7 to -0.3)	**0.023**	1,535 (100)	24.3	23.0 (1.1)	1.3 (-0.7 to 3.4)	0.232
Age (years)										
≤ 35	328 (12.1)	34.4	39.3 (2.6)	-4.9 (-10.2 to 0.3)	0.066	189 (12.3)	33.1	33.5 (3.5)	-0.4 (-7.5 to 6.2)	0.908
36-40	447 (16.5)	28.0	34.0 (2.3)	-6.0 (-10.7 to -1.7)	**0.009**	255 (16.6)	26.2	30.4 (2.8)	-4.2 (-10 to 1.2)	0.136
41-45	936 (34.5)	25.1	27.0 (1.4)	-1.9 (-4.5 to 0.9)	0.182	538 (35.0)	22.9	21.5 (1.8)	1.4 (-2.1 to 4.9)	0.459
46-50	999 (36.9)	25.1	24.4 (1.4)	0.7 (-2.2 to 3.2)	0.638	553 (36.0)	21.8	17.3 (1.7)	4.5 (1.2 to 7.6)	**0.009**
Her2-status										
Negative	911 (33.6)	25.4	25.5 (1.4)	-0.1 (-2.7 to 2.8)	0.964	633 (41.2)	22.5	17.6 (1.5)	4.9 (1.8 to 7.8)	**0.002**
Positive	214 (7.9)	40.5	40.7 (3.4)	-0.2 (-7.2 to 6.7)	0.963	170 (11.1)	37.5	34.7 (3.7)	2.8 (-4.4 to 10.5)	0.447
Unknown	1,585 (58.5)	25.6	29.0 (1.1)	-3.4 (-5.6 to -1.2)	**0.004**	732 (47.7)	22.8	24.9 (1.6)	-2.1 (-5.3 to 0.9)	0.179
ER-status										
Positive	1,450 (53.5)	23.4	25.5 (1.1)	-2.1 (-4.5 to 0.0)	0.062	785 (51.1)	21.1	17.7 (1.4)	3.4 (0.6 to 6.0)	**0.017**
Negative	623 (23.0)	35.4	38.5 (2.0)	-3.1 (-7.1 to 0.5)	0.106	291 (19.0)	33.7	33.4 (2.8)	0.3 (-4.8 to 6.0)	0.915
Unknown	637 (23.5)	25.7	26.4 (1.8)	-0.7 (-4.1 to 2.6)	0.717	459 (29.9)	23.8	25.5 (2.0)	-1.7 (-5.7 to 2.2)	0.422
Triple negative										
Not triple negative	972 (35.9)	26.6	27.7 (1.5)	-1.1 (-4.0 to 1.8)	0.466	727 (47.4)	23.8	20.4 (1.5)	3.4 (0.5 to 6.3)	**0.029**
Triple negative	207 (7.6)	33.6	36.2 (3.3)	-2.6 (-8.9 to 3.5)	0.456	136 (8.9)	31.7	32.1 (3.9)	-0.4 (-8.6 to 7.8)	0.918

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˙P-values for one-sample t-tests for proportions are bootstrap p-values directly calculated from the bootstrap sampling.

Appendix Table 4 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
Unknown	1,639 (60.5)	25.8	28.3 (1.2)	-2.5 (-4.8 to -0.2)	0.034	672 (43.8)	23.3	24.0 (1.7)	-0.7 (-4.0 to 2.5)	0.653
Tumor Grade										
Grade 1	328 (12.1)	10.8	11.9 (1.8)	-1.1 (-4.6 to 2.3)	0.540	229 (14.9)	8.1	7.1 (1.7)	1.0 (-2.8 to 4.3)	0.555
Grade 2	644 (23.8)	21.9	23.1 (1.7)	-1.2 (-4.6 to 1.8)	0.465	459 (29.9)	19.2	17.7 (1.8)	1.5 (-2.0 to 5.0)	0.412
Grade 3	915 (33.8)	35.8	37.6 (1.7)	-1.8 (-5.0 to 1.5)	0.286	607 (39.5)	34.1	33.4 (2.0)	0.7 (-3.4 to 4.6)	0.746
Unknown	823 (30.4)	26.6	29.9 (1.6)	-3.3 (-6.3 to -0.1)	**0.040**	240 (15.6)	24.8	22.0 (2.7)	2.8 (-2.6 to 8.0)	0.307
Stage										
Stage 1	925 (34.1)	11.6	15.4 (1.2)	-3.8 (-6.1 to -1.4)	**0.005**	534 (34.8)	9.8	12.1 (1.4)	-2.3 (-4.8 to 0.3)	0.093
Stage 2	1,615 (59.6)	32.4	33.6 (1.2)	-1.2 (-3.3 to 1.3)	0.315	892 (58.1)	29.8	26.7 (1.5)	3.1 (0.0 to 5.8)	**0.042**
Stage 3	170 (6.3)	54.9	55.3 (3.9)	-0.4 (-8.1 to 7.1)	0.915	109 (7.1)	50.7	46.3 (4.7)	4.4 (-5.2 to 13.9)	0.337
Tumor size										
0.1-1.0 cm	363 (13.4)	10.2	14.9 (1.9)	-4.7 (-8.4 to -0.9)	**0.015**	221 (14.4)	7.0	11.0 (2.2)	-4.0 (-8.5 to -0.1)	0.061
1.1-2.0 cm	1,036 (38.2)	17.9	22.8 (1.3)	-4.9 (-7.5 to -2.4)	**0.002**	540 (35.2)	15.3	17.4 (1.6)	-2.1 (-5.3 to 1.2)	0.193
2.1-3.0 cm	582 (21.5)	33.2	33.2 (1.9)	0.0 (-3.9 to 3.7)	0.987	347 (22.6)	30.6	25.9 (2.4)	4.7 (0.2 to 9.5)	0.053
3.1-5.0 cm	560 (20.7)	38.3	37.9 (2.0)	0.4 (-3.4 to 4.3)	0.823	314 (20.5)	35.0	31.8 (2.7)	3.2 (-2.3 to 8.2)	0.238
>5 cm	169 (6.2)	55.3	49.1 (4.0)	6.2 (-2.1 to 13.7)	0.121	113 (7.4)	52.4	40.0 (4.8)	12.4 (2.9 to 21.5)	**0.014**
Positive nodes										

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Appendix Table 4 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
0	1,348 (49.7)	16.0	19.4 (1.1)	-3.4 (-5.6 to -1.3)	**0.002**	544 (26.2)	15.6	15.1 (1.5)	0.5 (-2.4 to 3.4)	0.748
1-3	869 (32.1)	28.7	30.8 (1.6)	-2.1 (-5.3 to 0.9)	0.171	380 (18.3)	31.9	22.7 (2.1)	9.2 (4.8 to 13.3)	**0.001**
4-9	347 (12.8)	46.4	45.5 (2.7)	0.9 (-4.6 to 6.3)	0.740	112 (5.4)	55.1	37.8 (4.7)	17.3 (7.7 to 25.6)	**0.001**
>9	146 (5.4)	67.0	61.6 (4.1)	5.4 (-3.4 to 13.3)	0.189	40 (1.9)	77.5	62.5 (7.8)	15.0 (0.1 to 30.3)	0.066
Morphology										
IDC	2,038 (75.2)	28.9	30.7 (1.0)	-1.8 (-3.9 to 0.2)	0.081	812 (39.2)	29.7	23.6 (1.5)	6.1 (3.2 to 9.0)	**0.003**
ILC	272 (10)	25.0	26.5 (2.6)	-1.5 (-6.7 to 3.4)	0.584	105 (5.1)	22.1	19.4 (4.0)	2.7 (-5.2 to 10.4)	0.477
IL/DC	129 (4.8)	25.8	25.6 (3.8)	0.2 (-7.2 to 7.5)	0.960	52 (2.5)	26.9	15.4 (5.0)	11.5 (1.4 to 21.1)	**0.048**
Tubular carcinoma	78 (2.9)	10.3	6.4 (2.8)	3.9 (-2.1 to 8.9)	0.196	25 (1.2)	5.7	-	-	-
Mucinous carcinoma	31 (1.1)	19.9	16.1 (6.6)	3.8 (-10.1 to 15.4)	0.581	14 (0.7)	20.0	14.3 (9.3)	5.7 (-20.0 to 14.4)	0.566
Medular	58 (2.1)	27.4	12.1 (4.3)	15.3 (6.6 to 23.3)	**0.016**	25 (1.2)	27.8	16.0 (7.4)	11.8 (-5.5 to 23.6)	0.125
Comedo carcinoma	40 (1.5)	26.7	37.5 (7.5)	-10.8 (-25.7 to 3.4)	0.161	14 (0.7)	26.9	21.4 (10.8)	5.5 (-19.7 to 20.7)	0.624
Other	49 (1.8)	21.5	26.5 (6.3)	-5.0 (-17.4 to 7.5)	0.444	29 (1.4)	19.3	24.1 (8.1)	-4.8 (-22.4 to 10.6)	0.541
Unknown	15 (0.6)	24.9	13.3	-	-	0	-	-	-	-
Angiolymphatic invasion										
No angiolymphatic invasion	557 (20.6)	22.4	23.0 (1.8)	-0.6 (-4.4 to 2.5)	0.747	336 (16.2)	20.6	16.0 (2.0)	4.6 (0.6 to 8.7)	**0.030**
Angiolymphatic invasion in up to 3 vessels	355 (13.1)	26.7	28.7 (2.5)	-2.0 (-7.0 to 2.6)	0.404	68 (3.3)	29.0	22.1 (4.9)	6.9 (-3.4 to 16.5)	0.165

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Appendix Table 4 continued Overview of baseline characteristics for patients diagnosed between 1990 and 2000 and Adjuvant! estimates versus observed 10-year all-cause and breast cancer-specific mortality (in mean%)

		10-year all-cause mortality					*10-year breast cancer-specific mortality*			
	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P	N (%)	Predicted	Observed (SE)	Predicted minus Observed (95%-C.I.)	P
Extensive angiolymphatic invasion	159 (5.9)	36.0	45.3 (3.9)	-9.3 (-16.9 to -1.5)	**0.013**	36 (1.7)	48.7	45.7 (8.7)	3.0 (-13.8 to 19.4)	0.729
Unknown	1,639 (60.5)	27.3	29.0 (1.1)	-1.7 (-3.9 to 0.5)	0.127	636 (30.7)	30.2	23.7 (1.7)	6.5 (3.3 to 9.8)	**0.001**
Type of surgery										
Breast conserving surgery	1,365 (50.4)	20.6	23.7 (1.1)	-3.1 (-5.3 to -0.8)	**0.008**	575 (27.7)	20.7	19.6 (1.6)	1.1 (-2.2 to 4.3)	0.503
Mastectomy	1,340 (49.4)	33.0	33.9 (1.3)	-0.9 (-3.5 to 1.8)	0.494	500 (24.1)	35.9	24.7 (2.0)	11.2 (7.1 to 14.9)	**0.001**
Unknown	5 (0.2)	18.6	20.0	-	-	1 (0.1)	-	-	-	-
Radiotherapy										
No	614 (22.7)	23.0	25.2 (1.7)	-2.2 (-5.6 to 1.2)	0.188	225 (10.9)	24.0	19.8 (2.6)	4.2 (-1.3 to 9.0)	0.120
Yes	2,096 (77.3)	27.8	29.7 (1.0)	-1.9 (-3.9 to 0.0)	0.059	851 (41.1)	28.8	22.5 (1.5)	6.3 (3.6 to 9.4)	**0.001**
Systemic treatment										
None	1,395 (51.5)	20.3	20.7 (1.1)	-0.4 (-2.4 to 1.7)	0.693	591 (28.5)	21.7	14.6 (1.5)	7.1 (4.3 to 9.9)	**0.001**
Chemotherapy only	935 (34.5)	33.5	39.5 (1.6)	-6.0 (-9.2 to -3.0)	**0.001**	317 (15.3)	35.7	35.6 (2.7)	0.1 (-5.6 to 5.2)	0.965
Endocrine therapy only	210 (7.7)	33.6	27.1 (3.0)	6.5 (0.6 to 12.5)	**0.036**	149 (7.2)	35.0	19.6 (3.2)	15.4 (8.8 to 21.5)	**0.001**
Endocrine therapy and chemotherapy	170 (6.3)	33.4	37.1 (3.7)	-3.7 (-11.3 to 3.6)	0.310	19 (0.9)	27.2	42.1 (11.7)	-14.9 (-39.5 to 6.1)	0.239

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Part III

Oncologists' attitudes towards and use of tools to communicate the benefits of adjuvant systemic therapy for early-stage breast cancer

Chapter 4

Oncologists' weighing of the benefits and side effects of adjuvant systemic therapy: *has it changed over time?*

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Introduction

The use of adjuvant chemotherapy and endocrine therapy for early-stage breast cancer has substantially increased. The presentation of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analyses of adjuvant systemic treatment effectiveness, late-1990s, led to a paradigm shift where adjuvant systemic treatment was no longer reserved for patients with (locally) advanced disease, but also became available to node negative patients (1). New insights in prognostic factors and improvements in treatment have led to further easing of the eligibility criteria for adjuvant systemic treatment over time. For example, according to the American National Comprehensive Cancer Network (NCCN) breast cancer guidelines, some form of adjuvant systemic treatment could be considered for all breast cancer patients with invasive ductal or lobular tumors larger than 0.5 cm. If a patient has Her2-positive disease, adjuvant systemic treatment could also be considered for tumors smaller than 0.5 cm (2). Going by these NCCN and other (inter)national guidelines, a proportion of early-stage breast cancer patients with a clinical indication for adjuvant systemic treatment have a potential overall survival benefit of as little as 1% - conversely, 99% of these patients potentially only experience side-effects and no survival gain. With the exception of patient subgroups deemed at high risk of recurrence and breast cancer mortality (e.g., Her2-positive patients or those 40 years or younger at diagnosis), the general rule of thumb applied in the Netherlands is that adjuvant systemic treatment is advised if treatment reduces the patient's risk of breast cancer death by at least 4% (absolute). This easing of the eligibility criteria for adjuvant systemic treatment is also reflected in the substantial increase in its use in Dutch clinical practice from 1990-2011. Where between 1990-1997 only 37% of early-stage breast cancer patients received adjuvant systemic therapy, in 2011 an average of 70% of early-stage breast patients received adjuvant systemic treatment (3, 4).

In 2000, just after the publication of the first EBCTCG meta-analysis, a survey amongst Dutch oncologists reported that the majority felt that adjuvant chemotherapy should minimally yield 6-10% overall survival benefit to make it worthwhile for patients with node negative disease (5). To date no studies have assessed what survival benefit makes endocrine treatment worthwhile according to oncologists. Yet, endocrine treatment duration has been extended more and more (from 2.5 to 5 years and an extension to 10 years is currently topic of debate), whilst studies show non-adherence and/or premature discontinuation of treatment of as much as 40% (6-8).

It has been over a decade since Stiggelbout et al. conducted their survey of oncologists' views on the survival benefit that makes adjuvant chemotherapy treatment worthwhile. As patients are increasingly diagnosed at earlier stages the benefits adjuvant chemotherapy and endocrine therapy can yield are often small, whereas the potential for

side-effects remains undiminished (4). In view of the substantial increase in adjuvant systemic treatment use in the past decades, we replicated our study assessing how much treatment benefit, given the potential side-effects, Dutch oncologists require to tip the scale in favor of adjuvant systemic treatment.

Methods

Recruitment of participants

This study was conducted as part of a larger project investigating oncologists' views on risk prediction models and their use in clinical practice to guide adjuvant systemic treatment decisions (9). Medical and surgical oncologists were eligible to participate in the current study. The Comprehensive Cancer Center the Netherlands (IKNL) sent out an invitation to complete the anonymous online-survey on our behalf to the members of all the medical oncology and breast cancer working parties. IKNL has a nationwide coverage, facilitating the recruitment of our target. A reminder was sent four weeks later.

Measures and data analyses

To determine the minimal adjuvant systemic treatment 10-years overall survival benefit participants deemed sufficient, they were asked: "What is the minimal percentage treatment benefit that in your opinion makes treatment X worthwhile, given the side-effects?". This was a multiple choice question, where participants could choose from the following categories: "1-5%", "6-10%", "11-20%" or "more than 20%". If they indicated that the treatment benefit they required was between 1-5%, they were asked to provide us with the exact percentage. We also assessed some background characteristics such as age, type of hospital they work at and level of experience. All analyses were performed using SPSS 20.

Results

We included forty-two oncologists, of whom half were surgeons. Participants were 49 years on average (range, 31-64 years), 58% were male and 80% worked in a teaching hospital (general or academic) (Table 1). For privacy reasons we could not access data on the size and composition of the IKNL working parties approached for this study; hence, we are unable to estimate our response rate.

Chemotherapy

Half of surgical and medical oncologists indicated that between 6-10% survival gain is the minimal percentage benefit that offsets the potential side-effects due to treatment (Figure 1). Of the 16 (38%) oncologists who indicated that 1-5% was sufficient survival gain, the minimally required benefit ranged from 3% (N=2, 13%) to 5% (N=9, 56%).

Table 1: Oncologists' characteristics (N (%))

		Surgical oncologists	Medical oncologists
		N= 20	N=22
Age	≤ 50 years	10 (59)	13 (62)
	> 50 years	7 (41)	8 (38)
Gender	Male	12 (71)	10 (48)
Experience treating breast cancer	< 5 years	1 (4)	3 (12)
	6-10 years	7 (28)	12 (46)
	> 10 years	17 (68)	11 (42)
Type of hospital	General	3 (18)	4 (18)
	Training	10 (59)	12 (55)
	UMC	4 (24)	6 (27)

Participants do not add up to 42 due to missing data.; Differences between surgical and medical oncologists were not significant. UMC= University Medical Center

Endocrine therapy

Medical oncologists tended to require greater survival benefits from endocrine therapy than surgical oncologists, but the difference was not statistically significant (Figure 1). If oncologists (N=21, 50%) thought that 1-5% overall survival benefit was sufficient to justify endocrine treatment, the minimally required benefit threshold ranged from 3% (N= 9, 43%) to 5% (N=7, 24%).

Generally, younger (<50 years) and female oncologists more often indicated that a minimal overall survival benefit (1-5%) was sufficient to offset potential treatment side-effects for both chemotherapy and endocrine therapy (data not shown; differences not statistically significant).

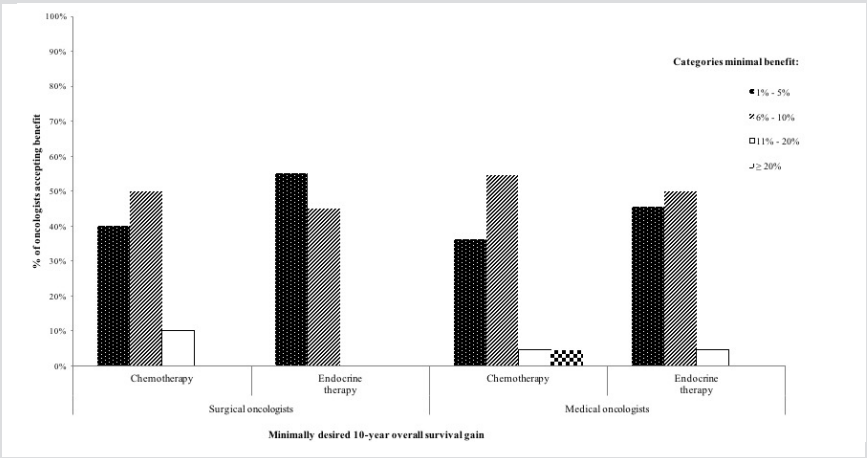

Figure 1 Minimal overall survival gain oncologists deem sufficient to justify adjuvant systemic treatment

Discussion

There was a wide range in the benefit required from adjuvant systemic treatment within both surgical and medical oncologists. Most oncologists required 6-10% survival benefit to recommend adjuvant chemotherapy. When it came to endocrine therapy most surgical oncologists had a lower required benefit threshold (1-5%) compared to medical oncologists (6-10%).

The current study is the first to explore oncologists' minimally desired treatment benefit of endocrine therapy. Although a larger proportion of medical compared to surgical oncologists require an overall survival benefit equal to that of chemotherapy, half of our respondents required less treatment benefit to justify endocrine treatment which suggests that there is a tendency to underestimate the impact of endocrine therapy. Although often perceived as less aggressive, there is substantial non-adherence to endocrine therapy, moreover, although side effects may be less severe, treatment lasts for a substantially longer time. A recent study showed that overall, patients consider the efficacy of treatment to be the most important factor, but it was closely followed by side-effects joint and muscle pain and risk of endometrial cancer. About one in six patients even felt that the treatment benefits did not outweigh the side-effects (10). This illustrates the importance of taking patients' values into account when deciding about treatment.

Interestingly, even though the eligibility criteria for adjuvant systemic treatment have become broader, oncologists' minimally required benefit from adjuvant chemotherapy remains unchanged compared to the findings reported by Stiggelbout et al. well over a decade ago. Perhaps this lack of change, is a sign of the overriding sense that by casting such a wide net, i.e. having such broad guidelines, more harm is done than good, as the vast majority (>60%) of patients currently undergoing adjuvant systemic treatment, probably do not need it (11). Unfortunately, the currently available tools are not yet sensitive enough to help clinicians determine which patients can forego treatment, without negatively affecting their (recurrence-free) survival (12).

Regrettably, our sample is small; nonetheless, our findings indicate that for both chemotherapy and endocrine therapy, most oncologists agree that treatment is worthwhile if the potential survival benefit is 10% or more. There only seems to be a difference of opinion if the potential benefit is less than 10%. Oncologists that participated in the current study require greater survival benefits from adjuvant systemic treatment, than the threshold indicated in the Dutch breast cancer guideline (i.e., ≥ 4%), to deem treatment worthwhile. Over the past decades patients are diagnosed at earlier stages and have a good prognosis a priori. The fact that during the same period the use of adjuvant systemic treatment has virtually doubled, suggests that oncologists do

not adhere to their own minimally-desired treatment benefit when recommending treatment to patients. This stresses the imperative for oncologists and patients to critically mull over whether the potential treatment benefits are worthwhile in light of the side-effects associated with treatment. Especially when the potential treatment benefit is small, patient preferences could be the overriding factor when deciding about treatment. However, to make this possible, patients should be adequately informed about all the relevant treatment options (including forgoing treatment), their potential benefits and (main) side-effects, and afforded the opportunity to freely discuss their thoughts, concerns and any doubts about treatment with their oncologist. Such an open exchange of information (oncologist) and considerations (patients) could help patients and their oncologists to decide on the best course of action with which both parties feel comfortable.

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Chapter 5

Breast cancer specialists' views on and use of risk prediction models in clinical practice: *a mixed methods approach*

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Abstract

Purpose

Risk prediction models (RPM) in breast cancer quantify survival benefit from adjuvant systemic treatment. These models (e.g. Adjuvant! Online (Adjuvant!)) are increasingly used during consultations, despite their not being designed for such use. As still little is known about oncologists' views on and use of RPM to communicate prognosis to patients, we investigated if, why, and how they use RPM.

Methods

We disseminated an online questionnaire that was based on the literature and individual and group interviews with oncologists.

Results

Fifty-one oncologists (partially) completed the questionnaire. Adjuvant! is the best known (95%) and most frequently used RPM (96%). It is used to help oncologists decide whether or not to recommend chemotherapy (>85%), to inform (86%) and help patients decide about treatment (>80%), or to persuade them to follow the proposed course of treatment (74%). Most oncologists (74%) believe that using Adjuvant! helps patients understand their prognosis.

Conclusion

RPM have found a place in daily practice, especially Adjuvant!. Oncologists think that using Adjuvant! helps patients understand their prognosis, yet studies suggest that this is not always the case. Our findings highlight the importance of exploring whether patients understand the information that RPM provide.

Introduction

Deciding about adjuvant systemic therapy for breast cancer can be a difficult balancing act between potential survival gains and side-effects. Many risk prediction models (RPM) have been developed to primarily aid oncologists' decision-making about adjuvant systemic treatment (1). RPM seem to meet a need and appear to have been widely adopted in clinical practice. For example, the Dutch breast cancer adjuvant systemic treatment guidelines are largely based on Adjuvant! survival and treatment benefit estimates (2). The American National Comprehensive Cancer Network (NCCN) guidelines have incorporated Oncotype Dx in their adjuvant systemic treatment decision-making algorithm (2,3). The British National Institute for Health and Clinical Excellence (NICE) has incorporated the Nottingham Prognostic Index in their decision algorithm and both NICE and NCCN endorse the use of Adjuvant! to support estimations of individual prognosis and absolute benefit of adjuvant treatment (4,3).

A 2005 questionnaire amongst American medical oncologists found that 80% had ever used Oncotype Dx, and that 78% used Adjuvant! (5). A small questionnaire study amongst 25 British medical oncologists from 13 oncology centers found that 96% of the participants used Adjuvant! to calculate mortality estimates and 36% also used it to calculate relapse probabilities. Most participants (≥84%) were confident that Adjuvant! estimates are accurate (6).

Most RPM offer graphical representations of prognostic information, and this increases their appeal for use in the consultation to convey prognostic information to patients. The UK-based questionnaire found that 92% of participants regularly discussed the survival probabilities and treatment benefit estimates from Adjuvant! with their patients, and a quarter also said they provided patients with the printout from Adjuvant! (6). Not much is known about such use of RPM during the consultation (i.e., frequency and reason for use) and similarly, little is known about how well patients understand prognostic information from RPM. The information these models provide is complex and could cause confusion if risk communication is not done properly, and increase patients' anxiety. Patients tend to have problems understanding probabilities, in part due to limited understanding of health statistics (7,8). Two small studies (<30 patients) assessing patients' understanding of prognostic information before and after receiving results from Adjuvant! reported that 43% - 65% were not able to accurately recall recurrence-free (RFS) and/or overall survival (OS) immediately after the consultation with their medical oncologist (9,10). In a few patients the use of Adjuvant! printouts led to heightened confusion and decreased comprehension (10). Simplifying Adjuvant!'s printout resulted in significantly more accurate recall (11), although at the cost of information loss.

A drawback of RPM is that the point estimates they provide reflect average outcome probabilities derived from groups of similar patients (7). Adjuvant! provides survival estimates as point estimates without the confidence interval surrounding the estimates. Knowing the width of the confidence interval could help oncologists gauge how robust Adjuvant!'s survival estimates are. Yet, it is unknown if oncologists are interested in this type of information and if and how they would disclose the associated uncertainty to their patients. Many patients have difficulties understanding uncertainty (7); and the effect of and how best to share uncertainty with patients is unknown (12,13).

Given the lack of information on the use of RPM to communicate prognosis to patients, and the pitfalls if not done appropriately, we assessed oncologists' a) familiarity with and use, b) reasons for use, for themselves and with patients, c) views on the (dis) advantages of RPM, and d) wish for uncertainty estimates and views about communicating these to patients.

Methods

Questionnaire development

Given the limited literature on this subject, we first conducted semi-structured interviews (N=10) with surgical and medical oncologists. We aimed to conduct a minimum of 10 interviews, and during the analysis process we also observed that after 10 interviews new categories, themes or explanations stopped emerging (data saturation). Subsequently, we held two online focus groups with a new group of surgical and medical oncologists (8 active participants out of 20 who agreed to participate). Oncologists attending the 2011 Dutch Medical Oncology congress and members of the Comprehensive Cancer Centre The Netherlands (IKNL) medical oncology and breast cancer working parties were invited to participate via e-mail, if they wanted to participate they indicated their preference for either an interview or focus group. IKNL has a nationwide coverage, facilitating the recruitment of our target population throughout The Netherlands.

The themes explored in the interviews were oncologists' a) familiarity with and use, b) reasons for use, both for themselves and with patients, c) views on the (dis)advantages of RPM, and d) wish for uncertainty estimates and views about communicating these to patients. We used the information obtained in the interviews to formulate statements, which we posted on a website especially created for these online focus groups. The online focus group participants were asked to post their views about the statements during a four-week period. They were also able to respond to other participants' posts. Participants were not aware of each other's identity. The data from the interviews and online focus groups were independently coded by two researchers using NVivo 9 software, and an open coding system. Discrepancies in coding were resolved by consensus.

Next, we used the data from the interviews and online focus groups to develop an online questionnaire. With the online questionnaire we explored all the themes (a-d) described above (Appendix 1). We also assessed participants' a) characteristics, and b) general reluctance to disclose uncertainty (14). To limit participants' time investment, most questions were multiple choice; answering categories were based on the findings of our qualitative analyses. Participants were also offered the option of providing open answers.

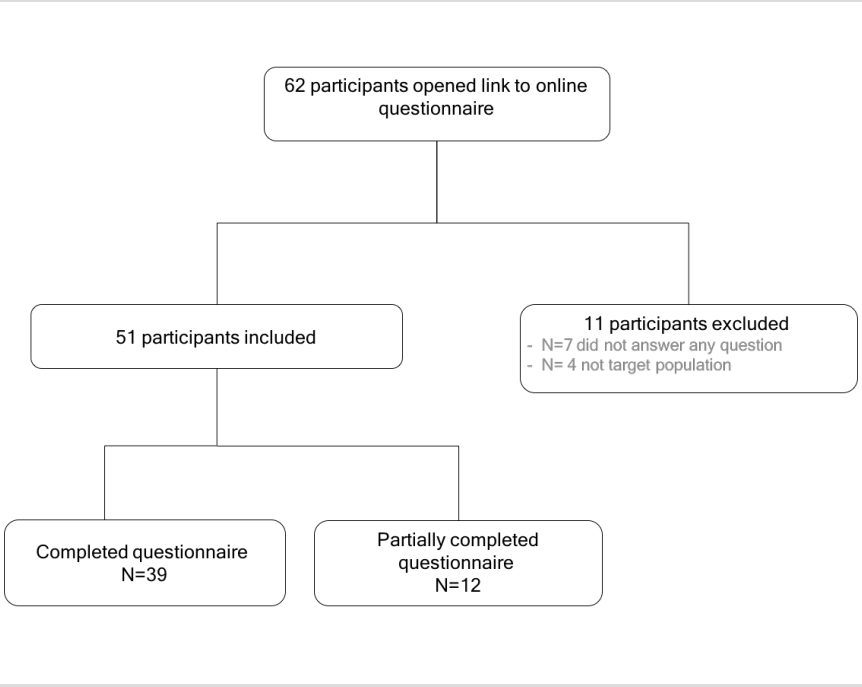

Figure 1 Flowchart of participants

Recruitment of participants online questionnaire

The Comprehensive Cancer Centre The Netherlands sent out an invitation on our behalf to the members of all regional medical oncology and breast cancer working parties. Medical and surgical oncologists were eligible to participate in the current study. Participants could anonymously complete the questionnaire online or on paper. Four weeks after sending the initial invitation, a reminder was sent to the working parties.

Data analysis

For privacy reasons we could not access data on the size and composition of the working parties; and are unable to estimate the response rate. The proportion of surgical and medical oncologists in our sample was similar to the distribution of the specialties in a reference sample of IKNL-working parties across The Netherlands. Participants who only partially completed the online questionnaire were included in the analyses if they had answered at least the questions on the (dis)advantages of RPM in general. Descriptive analyses were performed, as well as comparisons between groups, using Chi Squared or Fisher's Exact Tests for categorical variables and Student's T-test for continuous variables, all using SPSS 20.

In the results we will focus on the RPM that the majority of oncologists use most frequently, illustrate oncologists' views on and how they use RPM in general. Further, we will present quotes from the interviews and online focus groups to illustrate the quantitative findings.

Results

Fifty-one participants were included (Figure 1) and 77% of them completed all questions. There were no significant differences between the participants who had fully or partly completed the questionnaire (Appendix Table 1). On average the participants were 49 years old, 44% were female, and 82% worked in teaching hospitals (general or university) (Table 1). We found no significant difference in socio-demographic and work-related characteristics between surgeons and medical oncologists.

Familiarity with and use of RPM in clinical practice

The best-known RPM amongst oncologists were Adjuvant! (95%) and MammaPrint (88%). About one-third were familiar with Oncotype Dx and 19% with the Nottingham Prognostic Index. Overall, 71% of surgical oncologists reported to sometimes or regularly use RPM, compared to 100% of medical oncologists (p= 0.004; Fisher's exact test) (Table 2). Of those who use RPM, medical (100%) and surgical (95%) oncologists indicated that they most frequently use Adjuvant!. If MammaPrint was used, in most cases it was to supplement Adjuvant!. For example, if the patient and/or the oncologist were leaning towards foregoing chemotherapy, the MammaPrint results were decisive in determining the probability that forgoing chemotherapy would negatively affect RFS.

We asked participants which estimates, 10-year OS or RFS, they most frequently consulted a) before and b) during consultations with patients. Both surgical (63%) and medical (71%) oncologists reported that they usually consulted both estimates before the consultation. If only one was consulted, it most frequently was OS (21%). The majority indicated that they preferred OS because the main aim of adjuvant systemic treatment is to improve OS. There were also some concerns about the robustness of the relapse estimates, as in Adjuvant! no distinction is made between loco-regional and distant recurrences. One in three oncologists indicated that they habitually showed patients only the OS estimates and about half reported to show patients both the OS and RFS estimates. Oncologists indicated that Adjuvant! estimates are not too difficult to show to patients (Table 3). Some think that estimates from Adjuvant! should always be disclosed to patients, except if the patient strongly objects to hearing this information. Most medical (63%) and surgical (74%) oncologists indicated that one should ask patients if they want to hear Adjuvant! estimates, and if so, provide them with the estimates.

Table 1 Participants' characteristics (N=51)*

	Surgeons *N (%)*	Medical oncologists *N (%)*
Average age in years (range)	50 (37-64)	48 (31-62)
Age unknown	8 (32)	5 (19)
Gender		
Male	12 (71)	10 (48)
Experience with breast cancer care in years		
<5	5 (20)	10 (39)
6-10	9 (36)	9 (35)
>10	11 (44)	7 (27)
Number of consultations with early-stage breast cancer patients per month		
1-5	1 (4)	3 (12)
6-10	7 (7)	12 (46)
>10	17 (68)	11 (42)
Type of hospital		
General teaching hospital	10 (59)	12 (55)
University medical center	4 (24)	6 (27)
General non-teaching hospital	3 (18)	4 (18)
Total	25 (49)	26 (51)

* = Participants do not add up to 51 due to missing data; No significant differences between surgical and medical oncologists, hence p-values not reported.

Of medical oncologists, 42% indicated that they ask patients if they want a printout to take home, compared to 11% of surgical oncologists (p= 0,04); Fisher's exact test). Most surgical oncologists (61%) indicated that they do not actively offer a printout, but provide it if asked. Moreover, many participants (63% of medical and 47% of surgical oncologists) feel that oncologists should disclose Adjuvant! estimates to patients even if they forecast a bleak outlook. As an oncologist said: "Before I disclose Adjuvant!'s estimates I tell patients that the estimates could be quite hard to stomach and check whether they still want to hear it…. if they still do, I discuss them".

Table 2 Frequency of RPM use (in *N (%)*)			
	Surgeons *N= 24**	Medical oncologists *N=25**	P [#]
Never	4 (17)	0	0.007
Ever	3 (13)	0	
Sometimes	9 (38)	7 (28)	
Regularly	8 (33)	18 (72)	

*= Participants do not add up to 51 due to missing data; [#] = Comparison made using Fisher's exact test

Reasons for using RPM for themselves or with patients

More than 90% of oncologists sometimes use Adjuvant! to prepare the consultation; one in four medical oncologists always use Adjuvant! to prepare the consultation. Oncologists predominantly consult Adjuvant! before the consultation, to decide whether or not to recommend chemotherapy alone (87%) or in combination with endocrine therapy (91%). Adjuvant! is also consulted to decide about endocrine monotherapy (60%). Up to one in four oncologists (surgical more often than medical oncologists) also use Adjuvant! to decide about neo-adjuvant systemic therapy. Overall, 85% of surgical and 76% of medical oncologists indicated that their treatment preference sometimes changed after consulting a RPM. If there was a shift in medical oncologists' treatment preference, it was caused by either viewing the results of Adjuvant! alone (42%) or in combination with MammaPrint (58%).

Table 3 Oncologists' views on using Adjuvant! Online (Adjuvant!) during the consultation (in %)						
	Surgical oncologists (*N =19*[$])			Medical oncologists (*N =24*[$])		
Oncologists should:	*Disagree*	*Neutral*	*Agree*	*Disagree*	*Neutral*	*Agree*
not show Adjuvant! estimates to patients as it is too difficult for them	84	16	0	83	17	0
not show Adjuvant! estimates to patients as people cling too much to the estimates	53	47	0	75	21	4
never show Adjuvant! estimates to patients, it is best to use verbal labels[#] instead	42	42	16	71	21	8
not show Adjuvant! estimates to patients if these estimates are too hard to face	47	32	21	63	12	25

Table 3 Oncologists' views on using Adjuvant! Online (Adjuvant!) during the consultation (in %)

	Surgical oncologists ($N = 19^{\$}$)			Medical oncologists ($N = 24^{\$}$)		
Oncologists should:	*Disagree*	*Neutral*	*Agree*	*Disagree*	*Neutral*	*Agree*
only show Adjuvant! estimates to highly educated patients as they are best capable of understanding this information	63	21	16	83	12	4
offer to show Adjuvant! estimates to patients and show the estimates if the patient wants to see it	16	10	74	17	20	63
always show Adjuvant! estimates, unless the patient absolutely does not want to hear this	53	26	21	79	8	13
always show Adjuvant! estimates to breast cancer patients ≤ 40 years, as this information is most relevant for these patients	53	36	11	71	16	13
always show Adjuvant! estimates if the patient asks for information on prognosis	0	32	68	17	8	75

$ Participants do not add up to 51 due to missing data; # Verbal labels are terms used to denote likelihoods, e.g. "small chance that x will happen" or "it is likely that x will happen"; The category "*disagree*" comprises of those that selected either "*totally disagree*" or "*disagree*". And the category "*agree*" comprises of those that selected either "*agree*" or "*totally agree*"; No significant differences between surgical and medical oncologists were found, hence p-values Fisher's exact test are not reported.

Surgical oncologists indicated to regularly use Adjuvant! to help patients decide whether or not undergoing chemotherapy is worthwhile (73%) (Table 4). Medical oncologists stated to use Adjuvant! to provide patients with prognostic information (100%) and/or to help patients decide whether or not to undergo chemotherapy (96%). Additionally, 75% of medical oncologists indicated that they sometimes/regularly use Adjuvant! to convince patients that undergoing chemotherapy is not necessary and 83% also use it occasionally to convince patients of the benefit of their proposed treatment plan.

Medical (96%) and surgical (75%) oncologists reported that the output of RPM not only influenced their own decisions, but also those of their patients. In all, 56% of surgical and 70% of medical oncologists indicated that they frequently observe hesitation with regard to chemotherapy, yet after seeing Adjuvant!'s prognostic estimates patients change their minds.

Over 70% of oncologists think that Adjuvant! helps patients to understand their prog-

nosis better. Conversely, about 14% think that Adjuvant! does not make it easier for patients to understand their prognosis, but makes it easier for them to discuss prognosis with patients.

Views on the (dis)advantages of RPM

The two most frequently cited concerns about RPM were a) estimates only provide insights at a group level (34%) and b) those based on genetic profiles, e.g. MammaPrint or Oncotype Dx, are not yet sufficiently validated for use in clinical practice (36%). Twelve percent of medical oncologists indicated that another important drawback of RPM is that they give patients a false sense of security: "As you can imagine, when people who feel the need to keep a tight grip on their illness or their life find themselves in a situation in which all certainties have been taken away, that they desperately look for something to cling to… it's very hard to get them to put these estimates in perspective".

We asked oncologists to indicate their main concerns with regard to Adjuvant! specifically. They consistently indicated that Adjuvant! is one of the best RPM currently available, but far from perfect. The accuracy of Adjuvant!'s estimates in some patient populations, e.g. in the elderly (>65 years), is possibly suboptimal. Some felt that it would be informative, especially for younger patients and those with hormone receptor positive disease, if Adjuvant! were to provide prognostic estimates up to 20-years follow-up, instead of only 10-year estimates. The majority (85%) indicated that Adjuvant! is currently missing important prognostic factors, particularly her2neu receptor status. Also, preferably Adjuvant! should take the effect of Trastuzumab into account. More than three quarter indicated that the way prognostic factors are categorized in Adjuvant! is not ideal, or that it is unclear how the categories should be interpreted. Many felt the categorization of nodal status too crude (i.e., 0 positive; 1-3 positive; 4-9 positive and > 9 positive nodes). "A patient with one positive node would reasonably be expected to have a better prognosis than a patient with three positive nodes." It is currently unclear how to classify patients with micro-metastases; classifying them as node negative might yield prognostic estimates that are too optimistic, but classifying them as having 1-3 positive nodes seems to be a gross exaggeration.

It was often mentioned as an asset that Adjuvant! takes comorbid conditions into account, but most participants do not know how to interpret the categories Adjuvant! uses (i.e., perfect health; minor problems; average for age; major problem +10; major problem +20 and major problem +30). "If a patient has well-managed diabetes, is that a minor problem or is it a major problem?". Over 80% of oncologists indicated that they tend to use the default setting, namely "minor problems". However, if a patient has significant comorbidities, choosing a comorbidity category is often a bit of guesswork; oncologists try out multiple categories to see what happens with the estimates, and stick with the one they think yields the most realistic survival estimates.

Views on communicating uncertainty around the estimates from RPM
One in three (37%) thought that a confidence interval would be of no added value to them, with most indicating that they assume that Adjuvant!'s estimates are sufficiently accurate because the Dutch breast cancer guidelines are partly based on Adjuvant!. Half (49%) would want to know the width of the confidence intervals to determine for themselves how much credence they should give the estimates.

One in five oncologist are highly reluctant to disclose uncertainty to patients; yet, 95% of surgical and 100% medical oncologists discuss the uncertainty associated with Adjuvant!'s estimates with their patients in general terms. One oncologist said: "Uncertainties are a part of consultations with patients. We should not shy away from communicating them." Using an open-ended question, we asked oncologists to describe how they communicate uncertainty around Adjuvant!'s estimates to patients. The two most frequently reported methods were: a) telling patients that the estimates do not say anything about an individual, they are true at a group level (46%) and b) telling patients the estimates are based on statistics (14%). If they were available, over 75% of oncologists would disclose the confidence interval surrounding Adjuvant!'s estimates to patients, whom they think are capable of understanding this. A medical oncologist pointed out: "Sometimes I think patients can't handle uncertainty, but doctors probably struggle with it even more…".

Discussion

We assessed oncologists' views on RPM and their use of these tools. Adjuvant! is the most frequently used RPM, with many oncologists using it to prepare their consultation and use Adjuvant! in the encounter to inform and/or help patients decide about treatment. About half sometimes use Adjuvant! to convince patients of the merits of the proposed treatment plan. Surgical and medical oncologists' role in decision-making about adjuvant systemic treatment differs, hence we found some differences in frequency and motivation for using RPM.

Unexpectedly, we found that up to a quarter of oncologists also used Adjuvant! to decide about neo-adjuvant systemic therapy. Adjuvant! has not been validated for this purpose, and it is not known whether the estimates hold in the neo-adjuvant setting.

MammaPrint was the best-known RPM based on a gene profile, but was rarely used. Most oncologists indicated that such RPM do not yet have sufficient scientific underpinning to guide treatment decision-making. Many indicated that they are awaiting the results of the Mindact trial[1] and TAILORx trial[2], to know whether high risk patients according to Adjuvant! but low risk according to MammaPrint or Oncotype Dx, respectively can be spared chemotherapy without negatively affecting RFS.

Oncologists expressed concern about the validity of Adjuvant!'s estimates in specific subgroups and felt some key prognosticators were missing, inappropriately categorized or it is difficult to categorize patients into. These views are in agreement with the results of our recent systematic review (1). In spite of these limitations, most felt that Adjuvant! is a helpful tool and that no matter how complete the RPM, it will always be impossible to provide patients with a 100% certainty about disease outcome or treatment effect.

Most felt that using Adjuvant! during consultations helped patients understand their prognosis better. Moreover, in general oncologists did not think that the complex nature of Adjuvant!'s estimates and the fact that these estimates could be hard to hear for patients, are reasons not to use Adjuvant! during consultations. Oncologists even reported high willingness to communicate about the uncertainty surrounding the estimates of RPM to patients.

There are not many studies we can compare our findings to. A study that assessed the communication of uncertainty about risks and benefits of various treatments in

1 The MINDACT (Microarray In Node negative and 1-3 positive lymph node Disease may Avoid ChemoTherapy): http://www.agendia.com/clinical-trials-mindact/; Date last accessed: 27-05-2014.
2 The TAILORx trial (Trial Assigning IndividuaLized Options for Treatment (Rx)): http://www.cancer.gov/clinicaltrials/noteworthy-trials/tailorx; Date last accessed: 27-05-2014.

outpatient clinics found that uncertainty was discussed in about 1% up to 16% of consultations depending on the difficulty of the decision at hand (15). It would be interesting to get insights in how and how often oncologists actually discuss uncertainty in daily practice, since there are no guidelines available on how uncertainty should best be communicated (12). Moreover, it is unclear to what extent patients understand the uncertainty around RPM estimates and how information on uncertainty affects them personally as well as their final treatment decision.

Unfortunately, we were unable to determine our response rate. Also, the number of participants was relatively small. This is partly explained by the fact that we recruited participants via the IKNL-working parties which consist of a highly motivated, yet relatively small subgroup of experienced oncologists.

In conclusion, RPM have found their way into the consultation. It is encouraging that oncologists are driven to obtain the best possible prognostic estimates to guide their own decision-making and to communicate this information to patients, which in turn may facilitate patient participation in decision-making. However, clinicians assume that using RPM during consultations helps patients understand their prognosis better. Studies on patient understanding of prognosis (10,9) suggest that using Adjuvant! does not necessarily facilitate or improve patient understanding. Large observational studies of the communication process between oncologists and patients involving RPM are urgently needed to get insight into whether patients indeed understand the risks communicated during the consultation, and whether this enhances their participation. Additionally, studies assessing patients' understanding and acceptance of communication about uncertainties are needed to guide practice on communicating uncertainties.

Table 4 Oncologists' reasons for using Adjuvant! Online (Adjuvant!) (in %)

	Surgical oncologists (*N* =19[$])					Medical oncologists (*N* =24[$])					
	Never	Rarely	Sometimes	Often	Always	Never	Rarely	Sometimes	Often	Always	P [#]
Oncologists use Adjuvant! before the consultation to:											
prepare for the consultation	11	21	37	26	5	8	8	25	33	25	-
Oncologists use Adjuvant! during the consultation to:											
inform patients	16	16	53	16	0	0	0	38	50	13	< 0.01
inform patients who ask about prognosis	16	16	26	37	5	0	4	21	54	21	-
present the survival probabilities graphically	16	16	47	11	11	4	30	22	39	4	-
convince patients that undergoing chemotherapy is not necessary	42	11	26	21	0	4	21	63	8	4	< 0.01
help patients decide whether or not to undergo chemotherapy	21	5	47	26	0	4	4	25	63	4	0.05
convince patients of the benefits of my treatment plan	32	5	42	21	0	0	17	58	21	4	< 0.05

[$] Participants do not add up to 51 due to missing data; [#] = Comparison made using Fisher's exact test; - = not significant

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Appendix Table 1: Participants' characteristics of by completion of the questionnaire (N=51)

	The questionnaire was:	
	Completed N (%)	Partially completed N (%)
Average age in years (range)	49 (31-64)	unknown
Gender (male)	22 (56)	unknown
Specialty		
Surgeon	17 (44)	8 (67)
Medical oncologist	22 (56)	4 (33)
Experience with breast cancer care in years		
<5	4 (10)	0
6-10	15 (39)	4 (33)
>10	20 (51)	8 (67)
Number of consultations with early-stage breast cancer patients per month		
1-5	11 (28)	4 (33)
6-10	15 (39)	3 (25)
>10	13 (33)	5 (42)
Type of hospital		
General teaching hospital	22 (56)	
University medical center	10 (26)	unknown
General non-teaching hospital	7 (18)	
Total	39 (77)	12 (24)

No significant differences between surgical and medical oncologists, hence p-values Fisher's exact test are not reported

Appendix 1: Oncologists' views on and use of risk prediction models

Fill in date

Please first fill in today's date? (day/month/year)

☐☐/☐☐/☐☐☐☐

1. What is your specialism?

   - ❑ Surgical oncologist
   - ❑ Medical oncologist
   - ❑ Surgical oncologist in training
   - ❑ Medical oncologist in training
   - ❑ Other, namely:

     ……..

2. Approximately how many new breast cancer patients do you see per month, where initially the treatment intent is curative?

   - ❑ 1−2 patients
   - ❑ 3−5 patients
   - ❑ 6−10 patients
   - ❑ 11−15 patients
   - ❑ >15 patients

3. How many years experience do you have treating breast cancer patients?

   - ❑ < 2 years
   - ❑ 2−5 years
   - ❑ 6−10 years
   - ❑ > 10 years

With the following questions we want to ascertain which risk prediction models you are familiar with, which you may use and what you think of them.

4. With which of the risk prediction models below are you familiar?
   (*multiple answers possible*)

   - ❑ Adjuvant! Online
   - ❑ MammaPrint
   - ❑ Nottingham Prognostic Index
   - ❑ Oncotype Dx
   - ❑ Other, namely: ……

Below are a few arguments against the use of risk prediction models that are sometimes made by clinicians. Will you indicate for each statement the extent to which you are in agreement.

5. Information from risk prediction models:

	Totally Disagree	Disagree	Neither disagree nor agree	Agree	Totally Agree
is of no added value to me in the clinic	❑	❑	❑	❑	❑
is not sufficiently scientifically supported for use in the clinic	❑	❑	❑	❑	❑
is not user friendly	❑	❑	❑	❑	❑
gives false assurances, onto which patients unduly cling	❑	❑	❑	❑	❑
does not say anything about individual patients, as it applies to groups	❑	❑	❑	❑	❑
is too complicated	❑	❑	❑	❑	❑
makes patients unnecessarily anxious	❑	❑	❑	❑	❑
based on genetic profiles, such as MammaPrint, is <u>not</u> sufficiently scientifically supported	❑	❑	❑	❑	❑

I (also) have other arguments against the use of risk prediction models, namely:

.....

6. Do you sometimes use a risk prediction model (RPM)?

- ❑ No, I have never used a RPM ☞ **Go to question 28**
- ❑ Yes, I have *ever* used a RPM before
- ❑ Yes, I sometimes use a RPM ☞ **Go to question 7**
- ❑ Yes, I often use a RPM

7. Which of the risk prediction models below do you use or have you used before?
(multiple answers possible)

- ❑ Adjuvant! Online
- ❑ MammaPrint
- ❑ Nottingham Prognostic Index
- ❑ Oncotype Dx
- ❑ Other, namely: .....

8. If you do not use Adjuvant!Online, please indicate here the reasons you do not use Adjuvant!Online?
I do not use Adjuvant! Online because: .....

9. Does your preference for whether or not to give adjuvant systemic therapy ever change in response to the outcome of a risk prediction model?

- ❑ No ☞ **Go to question 12**
- ❑ Yes ☞ **Go to question 10**

10. You have indicated that your preference for adjuvant systemic therapy sometimes changes based on the outcome of a risk prediction model. For which risk prediction model(s) does this apply? *(multiple answers possible)*

- ❑ Adjuvant! Online
- ❑ MammaPrint

- ❑ Nottingham Prognostic Index
- ❑ Oncotype Dx
- ❑ Other, namely: .....

11. To which choice does this usually apply?

- ❑ whether or not to give chemotherapy
- ❑ whether or not to give endocrine therapy
- ❑ whether or not to add chemotherapy to the endocrine treatment

From interviews with oncologists we found that the prediction model Adjuvant! Online is predominantly used in the Netherlands. As you perhaps know, the choice of whether or not to give adjuvant treatment in the Dutch breast cancer guidelines is based on the tables from Adjuvant! Online.

12. Which risk prediction model do you use most frequently?

- ❑ Adjuvant! Online
- ❑ MammaPrint
- ❑ Nottingham Prognostic Index
- ❑ Oncotype Dx
- ❑ Other, namely: .....

13. For which of the treatment decisions (or considerations) below do you (sometimes) use Adjuvant!Online?

	Never	Seldom	Sometimes	Often	Always
Whether or not to give adjuvant chemotherapy?	❑	❑	❑	❑	❑
Whether or not to give adjuvant endocrine therapy?	❑	❑	❑	❑	❑
Whether or not to include adjuvant chemotherapy to adjuvant endocrine treatment?	❑	❑	❑	❑	❑
Which adjuvant chemotherapy regime gives the highest survival gains?	❑	❑	❑	❑	❑
Which adjuvant endocrine therapy (or combination of) gives the highest survival gains?	❑	❑	❑	❑	❑
Whether or not to give neo-adjuvant chemotherapy?	❑	❑	❑	❑	❑
Whether or not to give neo-adjuvant endocrine therapy?	❑	❑	❑	❑	❑

14. Below you find a few statements about the use of Adjuvant! Online. Please indicate for each statement the extent to which it applies to you?

I currently use Adjuvant! Online:

	Never	Seldom	Sometimes	Often	Always
to prepare for the consultation	❑	❑	❑	❑	❑
during the consultation in order to inform patients	❑	❑	❑	❑	❑
to inform patients *if* they ask for information about their prognosis	❑	❑	❑	❑	❑
to convince patients about the usefulness of the treatment plan I am proposing	❑	❑	❑	❑	❑
to convince patients that chemotherapy is not necessary	❑	❑	❑	❑	❑
if I think that patients can cognitively and emotionally deal with the prognosis estimates	❑	❑	❑	❑	❑

to also present the chances graphically	❑	❑	❑	❑	❑
to help patients to make a decision on whether or not to undergo chemotherapy	❑	❑	❑	❑	❑

Will you indicate the extent to which you think Adjuvant! Online influences the patient's therapy preference?

Adjuvant! Online influences patients in their preference of whether or not to undergo systemic therapy	❑	❑	❑	❑	❑

Will you indicate how often the situations below occur in clinical practice?
A patient who according to the guideline is eligible to receive chemotherapy:

Wants to undergo chemotherapy, but after looking at Adjuvant! Online she does not want to undergo chemotherapy anymore	❑	❑	❑	❑	❑
does not want to undergo chemotherapy, but after looking at Adjuvant! Online she does want to undergo chemotherapy	❑	❑	❑	❑	❑

I use Adjuvant! Online (also) for other reasons, namely:

.....

.....

15. The estimates from Adjuvant! Online can be helpful when communicating prognosis to patients. But, how do you determine which patients you do or do not show the estimates from Adjuvant! Online to? Below you find a few statements from clinicians about this.
Please indicate for each statement the extent to which you are in agreement?

Regarding the estimates from Adjuvant! Online, clinicians should:

	Totally Disagree	Disagree	Neither disagree nor agree	Agree	Totally Agree
always show them, unless patients absolutely do not want this	❑	❑	❑	❑	❑
offer them to patients and show Adjuvant! Online depending on whether the patient wants to know or not	❑	❑	❑	❑	❑
always show them if patients ask about prognosis	❑	❑	❑	❑	❑
not show them if they are too hard to hear	❑	❑	❑	❑	❑
not show them, they are better off using verbal labels (e.g. possible, probable, seldom) to explain prognosis	❑	❑	❑	❑	❑
always show younger breast cancer patients (younger than 50 years old), because these figures are most informative for them	❑	❑	❑	❑	❑
not show them, it is too difficult for patients	❑	❑	❑	❑	❑
not show them, because the majority of patients get hung up on the numbers	❑	❑	❑	❑	❑
only show them to the higher educated patients, because they can at least understand them	❑	❑	❑	❑	❑

The questions below refer specifically to the prognostic factors upon which Adjuvant! Online bases its estimates.

16. In your opinion, does Adjuvant! Online include all the important prognostic factors?

    - ❑ Yes
    - ❑ No, I miss specifically:

      .....

      .....

17. Almost all the prognostic factors in Adjuvant! Online are split into categories. Are the categories used, in your opinion, clinically relevant categories?

    - ❑ Yes
    - ❑ No, the following prognostic factors and/or category segments are *not relevant*, *incomplete* or *incorrect*:

      .....

      .....

18. How do you fill in the variable about comorbidity?

    - ❑ I always let the variable about comorbidity remain on the default setting (i.e. minor problems)
    - ❑ Patients with severe comorbidity are not referred for adjuvant systemic therapy, therefore the variable on morbidity is not relevant.

    Unless the patient has severe comorbidity, whereby I need to estimate for myself into which category she best fits, I always set the comorbidity variable on:

    - ❑ Perfect health
    - ❑ Minor problems
    - ❑ Average for age

The questions below refer specifically to the output from Adjuvant! Online.

19. Which results do you usually look at?

    - ❑ Mortality estimates
    - ❑ Relapse estimates
    - ❑ Both

20. If you do not usually look at the relapse estimates, for what reason(s) don't you look at the output?

    - ❑ I am not convinced of the accuracy of the relapse estimates
    - ❑ By adjuvant systemic treatment the mortality estimates are the most relevant
    - ❑ Other, namely: .....

21. Which output do you let patients see?

    - ❑ I don't show the output
    - ❑ Mortality estimates (usually)
    - ❑ Relapse estimates (usually)
    - ❑ Both (usually)

22. Do you give out a printout of the Adjuvant! Online output?

    - ❑ No, never
    - ❑ Yes, if the patient asks for it
    - ❑ Yes, if I think the patient is interested in it
    - ❑ Yes, I always ask patients if they would like to take it with them
    - ❑ Other, namely:

      .....

.....

Do you have suggestions to improve Adjuvant! Online's output?

.....

.....

For some patients it can be difficult to understand risk information. How can you actually check if the patient has understood the information out of Adjuvant! Online during the consultation? Is it necessary to check patient understanding?

23. During the consultation my method of determining whether the patient has understood the information is:

.....

.....

24. Below you find a few statements from clinicians about checking patient understanding. *Please indicate for each statement the extent to which you are in agreement*.

Checking whether patients have understood the information from Adjuvant! Online:

	Completely disagree	Disagree	Neutral	Agree	Completely agree
is not necessary, because I only show Adjuvant! Online if I think she will understand the information	❑	❑	❑	❑	❑
is not necessary if I take the time to explain everything to her	❑	❑	❑	❑	❑
is not necessary, because if she doesn't ask questions then it is clear	❑	❑	❑	❑	❑
cannot be done, clinicians can tell whether a patient has understood the information	❑	❑	❑	❑	❑
I do it by asking her if she has understood everything	❑	❑	❑	❑	❑
I do it by asking her to repeat the information in her own words	❑	❑	❑	❑	❑

25. In your opinion, does using Adjuvant! Online make it easier for patients to understand the information about prognosis?

- ❑ No, it does not become easier with Adjuvant! Online
- ❑ It does not become easier for patients to understand the information, but it is easier for the clinician to clearly present the information
- ❑ Yes, Adjuvant! Online usually makes it easier for the patient to understand the information about prognosis
- ❑ Other, namely: .....

Risk prediction models, such as Adjuvant! Online, quantify the chance of a recurrence and of survival. On the one hand, this can give more insight into the prognosis of an individual patient. However, these are estimates surrounded a confidence interval. Adjuvant! Online, for example, does not report the confidence intervals around its estimates.

26. Would you personally want to know the confidence intervals around the estimates from Adjuvant! Online?

- ❑ No, it is of no added value to me because we do not currently have better estimates anyway
- ❑ No, I know that it involves estimates. How wide the confidence intervals are is not important
- ❑ No, the recommendations in the national breast cancer guideline are based on this, therefore I assume that the estimates are accurate (enough)
- ❑ Yes, then I can determine how much I can rely upon Adjuvant! Online's estimates
- ❑ Yes, that is important to know because the recommendations in the national breast cancer guideline are based on this
- ❑ Other, namely:.....

27. Supposing Adjuvant! Online would indeed provide the confidence intervals around its estimates. Would you show this to patients?

- ❑ No, absolutely not. That is too complex for most patients
- ❑ Sometimes, if I think that patients could understand it
- ❑ Yes, along with my explanation most patients could understand this
- ❑ Other, namely:.....

Regardless of whether you use a risk prediction model or not:

28. If you communicate prognosis estimates to the patient, do you talk about the uncertainty around these estimates?

- ❑ Never ☞ **Go to question 30**
- ❑ Sometimes
- ❑ Often ☞ **Go to question 29**
- ❑ Always

29. You indicated that you (sometimes) discuss the uncertainty around the prognosis estimates with your patients. Can you briefly indicate below how you explain this?
I then say: .....

Each doctor has his/her own preference when it comes to making treatment decisions, and everyone has their own way of dealing with the uncertainty which comes with patient care. We would really like to know your thoughts about this. With the following two questions, we gain further insight into how you prefer to make decisions and how you deal with uncertainty.

30. After being informed about their illness and the possible treatment, some patients prefer to let the doctor make the treatment decision, others would prefer to jointly decide. Which statement best fits your ideal?

- ❑ The doctor should decide based on everything that is known about the treatments
- ❑ The doctor should decide, but also seriously take the patient's opinion into account
- ❑ The doctor and the patient should decide together, as equals
- ❑ The patient should decide, but also seriously take the doctor's opinion into account
- ❑ The patient should decide based upon everything that the patient knows or has heard about the treatments

31. Will you indicate for the questions below the extent to which you are in agreement?

	Disagree			Agree		
	Strongly	moderately	slightly	slightly	moderately	strongly
When physicians are uncertain of a diagnosis, they should share this information with their patients.	❑	❑	❑	❑	❑	❑
I always share my uncertainty with my patients	❑	❑	❑	❑	❑	❑
If I shared all of my uncertainties with my patients, they would lose confidence in me	❑	❑	❑	❑	❑	❑
Sharing my uncertainty improves my relationship with my patients	❑	❑	❑	❑	❑	❑
I prefer patients not know when I am uncertain of what treatments to use	❑	❑	❑	❑	❑	❑

Your answers will be analyzed anonymously. For the research it is important to have insight into the characteristics of the participants. Therefore, we ask you to fill in the questions below.

32. In which region do you practice?

- ❑ Regio North (i.e. Groningen, Friesland, Drenthe)
- ❑ Regio East (i.e. Gelderland, Overijssel, Flevoland)
- ❑ Regio West (i.e. Noord-Holland, Zuid-Holland, Utrecht)
- ❑ Regio South (i.e. Zeeland, Brabant, Limburg)
- ❑ I prefer not to disclose this

33. What is your gender?

- ❑ Male
- ❑ Female

34. What is your age? .....years

35. In what type of hospital do you work?

- ❑ General hospital (non-teaching)
- ❑ General hospital (teaching)
- ❑ University medical center
- ❑ Specialized oncology center
- ❑ Other, namely .....

If you have any comments, please leave them below.

Part IV

Communicating the benefits and harms of adjuvant systemic therapy for early-stage breast cancer during patient consultations

Chapter 6

Information provision about the benefits and side-effects of adjuvant systemic therapy for breast cancer in clinical practice: *does the use of Adjuvant! facilitate communication?*

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Abstract

Background

Adjuvant systemic therapy for early-stage breast cancer may improve survival, but has side-effects impacting patients' quality of life. Knowing the magnitude of treatment benefits can facilitate oncologists' and patients' decision-making. Prediction tools such as Adjuvant! may help, but little is known about their use and the implications thereof. We assessed a) the prevalence and determinants of Adjuvant! use, b) information provision about treatment benefits and side-effects overall and by Adjuvant! use, and c) whether Adjuvant! use is associated with the likelihood of reaching a decision.

Methods

We audiotaped consecutive patient consultations about adjuvant systemic therapy. We assessed prevalence of Adjuvant! use in the whole sample (N=287), and determinants of use in N=217, excluding consultations by oncologists who *always* or *never* used Adjuvant!. We assessed differences in information provision and decision-making in a random subset of consultations with and without Adjuvant! (N=211).

Findings

The oncologists used Adjuvant! *prior* to 70% of consultations, and also or only *during* 67% of consultations. Use was less likely the higher the disease stage (P=0.002) and the older the oncologist (P=0.03). Relapse reduction probabilities were the most frequently communicated treatment benefit (96%). In 39/214 (18%) consultations it was unclear to what outcome communicated probabilities related. Generally, fewer side-effects were communicated for endocrine therapy (Md.=4 (range: 0-9) than for chemotherapy (Md.=7 (range: 1-13), irrespective of Adjuvant! use. Communication about side-effects was generally inconsistent. Decision-making was more often postponed if Adjuvant! was used (P=0.005).

Conclusion

Adjuvant! was frequently used during consultations with patients, however, its probabilities were not always clearly communicated. Also, there was great disparity in information provision about side-effects. Critical assessment of prediction model use in risk communication and guidance on information provision about side-effects are needed to ensure clear and balanced information in treatment decision making.

Introduction

Decisions about adjuvant systemic treatment for stage I-III breast cancer are often not straightforward given the impact that side-effects (e.g., alopecia, nausea, loss of appetite, fatigue and neuropathy) can have on patients' short- and long-term quality of life (1-4). Current clinical guidelines generally endorse discussing adjuvant systemic treatment with early-stage breast cancer patients if the expected absolute survival gain is minimally 3-5% (5-7). This also implies that roughly 9 out of 10 patients treated either undergo treatment without gain or die in spite of treatment. There generally is no 'best' treatment option in this setting, thus, treatment decisions need to be guided by patients' informed preferences.

When weighing the benefits of treatment against its harms, it is helpful to know the magnitude of the expected treatment benefit. Prediction tools have been developed for this purpose, such as Adjuvant! and PREDICT. Adjuvant! was the most often used tool in the Netherlands before being taken offline by the end of 2015 for updates (8). It quantifies 10-year recurrence and mortality probabilities with and without adjuvant systemic treatment (9,10). Clinical guidelines recommend using Adjuvant! to support clinicians in obtaining personalized prognostic information for their patients (5-7). Small self-report surveys amongst oncologists suggest that Adjuvant! is regularly used during consultations with patients (8,11,12). Three-quarters of oncologists indicated in a survey that they felt that using Adjuvant! during consultations helps patients to better understand their prognosis (8). Available studies reported though that fewer than half of the patients provided with prognostic estimates from Adjuvant! were able to comprehensibly articulate their prognosis after the consultation (13,14).

Unfortunately, evidence on whether and how Adjuvant! use influences information provision during real-time consultations is lacking. Yet, the use of Adjuvant! may have several important implications. For example, Adjuvant! only provides probabilities of the potential benefits of treatment, it does not incorporate information about nor probabilities of the potential side-effects. Adjuvant! use during consultations could therefore shift the focus of the consultation towards discussing prognosis with and without treatment, at the expense of discussing treatment side-effects. Effective communication about side-effects may be further complicated by a lack of guidance as to which side-effects of adjuvant systemic therapy for breast cancer minimally need to be communicated to patients. Available evidence suggests that Adjuvant! not only influences oncologists' treatment recommendations, but also patients' treatment preferences (15,16). If the information provision about benefits and side-effects is unbalanced, the potential treatment benefits (i.e., relapse probability reduction and mortality reduction) may primarily drive patients' treatment preferences and ultimately decision-making, rather than a trade-off between the benefits and side-effects (17).

This may simplify decision-making, but it calls into question the informed nature of the decision. Receiving information about treatment benefit and harms might make patients aware that there is no obvious choice, and that undergoing therapy does not guarantee a good outcome.

The aim of the current study was to provide insight in information provision about the benefits and harms of adjuvant systemic therapy for breast cancer during patient consultations, and the impact of Adjuvant! use on information provision and decision-making during these consultations. We specifically investigated 1) the prevalence, and 2) determinants of Adjuvant! use in clinical practice, 3) information provision about treatment benefits and side-effects overall and by Adjuvant! use, and 4) whether Adjuvant! use influenced the likelihood of reaching a decision.

Methods

Design

Patient sample

Breast cancer patients with stage I-III disease from 7 outpatient clinics were invited to participate if they a) did not have a prior history of cancer for which they had received systemic therapy, b) were eligible to receive adjuvant systemic chemotherapy and/or endocrine therapy, and c) were fluent in Dutch. Patients were recruited between July 2012 and February 2015. Medical ethics boards of the participating hospitals approved the study protocol.

Procedures and measures

The procedure was as follows: (1) consultations were audiotaped after obtaining informed consent from patients, (2) after each consultation oncologists completed a checklist, and (3) patients completed a survey, (4) after the recruitment ended oncologists completed a survey, and (5) additional tumor and treatment characteristics were collected from the medical charts, with patients' consent.

Half of the consultations were transcribed verbatim, the remaining were coded directly from audio. Due to time constraints, it proved impossible to transcribe all consultations. To ensure the reliability of coding directly from audio, each coder coded a sample of consultations (N=13-16) that had already been coded from transcript, minimally three months after the original coding. The agreement between coding from audio and transcripts was high (81% and 83%, respectively; kappa for all items ≥0.6). Consultations were double-coded by 2 trained research assistants until an inter-rater kappa of minimally 0.6 was reached for all items, then one research assistant performed final coding.

Below we describe per research question (RQ) in detail which data was collected in each of the steps described above.

RQ1: Frequency and mode of use of Adjuvant!

After each consultation, oncologists indicated whether Adjuvant! had been used during the consultation (no/yes), and if so, when (prior to/during the consultation/both prior and during). Further, if oncologists had used Adjuvant! during the consultation, we asked *how* they had used the model (only providing the prognostic information orally/orally and visually (via the computer screen and/or a printout of Adjuvant!'s output)).

Table 1 Characteristics of whole study population and subsets used in analyses (N (%))

		Subset	
	Whole population N= 287 (100%)	determinants sample* N= 217 (76%)	information provision sample# N= 211 (74%)
Patients characteristics			
Average age in years (range)	59 (32-90)	58 (33-90)	59 (35-90)
Education level			
Low	44 (19.5)	27 (15.7)	31 (18.2)
Intermediate	114 (50.4)	92 (53.5)	83 (48.8)
High	68 (30.1)	53 (30.8)	56 (32.9)
Unknown	61	45	41
Numeracy level			
Low	51 (22.4)	35 (20.1)	39 (22.7)
Intermediate	59 (25.9)	45 (25.9)	45 (26.2)
High	118 (51.8)	94 (54.0)	88 (51.2)
Unknown	59	43	39
Tumor characteristics			
TNM stage			
Stage I	127 (44.6)	96 (44.4)	92 (44.0)
Stage II	141 (49.5)	107 (49.5)	104 (49.8)
Stage III	17 (6.0)	13 (6.0)	13 (6.2)
Unknown	2	1	2
Consultation characteristics			
Median duration in minutes (range)	27 (6-80)	26 (6-80)	28 (6-80)
Treatment discussed			
Chemotherapy only	35 (12.2)	24 (11.1)	28 (13.3)
Endocrine therapy only	35 (12.2)	23 (10.6)	23 (10.9)
Chemotherapy & endocrine therapy	217 (75.6)	170 (78.3)	160 (75.8)
Use of Adjuvant! during consultation			
Not used	96 (33.4)	57 (26.3)	92 (43.6)
Used	191 (66.6)	160 (73.7)	119 (56.4)

* In the determinants sample we only included consultations by oncologists who: a) had included at least five patients to the study population, and b) did not *always* or *never* use Adjuvant! during the consultation.
# In the information provision sample we included a random sample of all consultations consisting of approximately an equal number of consultations with and without Adjuvant!.

Table 1 continued Characteristics of whole study population and subsets used in analyses (N (%))			
Oncologist characteristics			
Number of oncologists	30	24	28
Median number of patients included	6 (1-40)	5 (1-39)	4 (1-30)
Average age in years (range)	46 (30-66)	41 (30-66)	41 (30-66)
Gender			
Male	13 (43.3)	10 (41.7)	12 (42.9)
Female	17 (56.7)	14 (58.3)	16 (57.1)
Experience treating breast cancer			
Less than 5 years	11 (50.0)	9 (47.4)	10 (47.6)
Between 5-10 years	2 (9.1)	2 (10.5)	2 (9.5)
More than 10 years	9 (40.9)	8 (42.1)	9 (42.9)
Unknown	9	5	7
Type of hospital			
Academic	16 (53.3)	12 (50.0)	14 (50.0)
General teaching	14 (46.7)	12 (50.0)	14 (50.0)

[*] In the determinants sample we only included consultations by oncologists who: a) had included at least five patients to the study population, and b) did not *always* or *never* use Adjuvant! during the consultation.
[#] In the information provision sample we included a random sample of all consultations consisting of approximately an equal number of consultations with and without Adjuvant!.

If the checklist was missing, we used the audiotapes of the consultation to determine use of Adjuvant! (yes/no/unclear). Use of Adjuvant! was coded as 'Yes' if: a) prognostic probabilities from Adjuvant! were discussed during the consultation irrespective of whether Adjuvant!'s output was shown to patients, or b) Adjuvant!'s output was used to graphically illustrate the potential treatment effect, irrespective of whether the oncologist mentioned the probabilities.

RQ2: Determinants of Adjuvant! use

The potential determinants assessed were characteristics of a) the patient (age, education level, numeracy, and preference to receive prognostic probabilities), b) the disease (TNM stage, grade, estrogen receptor (ER) status, triple negative disease and/or Her2 status), and c) the oncologist (age, level of experience, type of hospital). If oncologists asked patients whether they wanted to receive prognostic probabilities, we coded patients' response to this question (yes/no/patient did not respond). If only a companion indicated an opinion, this was taken as the patients' opinion if she did not contradict it. After the consultation patients completed a survey covering, first, their education level (low (i.e., up to lower vocational education)/medium (i.e., up to secondary vocational education)/high (i.e., university of applied sciences and higher)). Secondly, their objective numeracy, i.e., their ability to understand and use numbers, was assessed using

the seven expanded numeracy items proposed by Lipkus *et al*.(18) Scores (range: 0-7) were divided into three categories (low numeracy= 0-2; intermediate numeracy= 3-5; high numeracy= 6-7). We assessed oncologists' socio-demographic characteristics in a short survey disseminated after the patient recruitment period closed (age, number of years of experience with treating breast cancer patients (<5 years/6-10 years/ >10 years) and type of hospital (general teaching/academic medical center)). Patient charts were examined to obtain tumor size (in cm), number of axillary lymph nodes, ER status and tumor grade. Tumor size and nodal status were used to determine TNM stage according to the American Joint Committee on Cancer definition, 7th edition (19).

RQ3: Communication of benefits and side-effects of treatment overall and by use of Adjuvant!
From the consultations we extracted data on: a) which disease outcomes (mortality/ relapse probability reduction) were discussed, b) whether benefit discussion included explicit disclosure of probabilities (yes/no), c) whether side-effects were communicated (yes/no), d) which side-effects were communicated, and e) comprehensiveness of the description of the side-effects (side-effect only mentioned (basic)/side-effect mentioned including information on the course of the symptoms/side-effect mentioned including the probability of occurrence).

RQ4: Association between use of Adjuvant! and decision-making
From all consultations, we extracted data on whether a treatment decision was made (made/postponed/made for only one of the treatments discussed in case both chemotherapy and endocrine therapy had been discussed), and what was decided (forego/ undergo/treatment postponed).

Statistical analyses
The participation rate was 358 out of 500 (72%) patients. Patient consultations were excluded if the audiotaping had failed (N=71/358 (20%)). This resulted in a sample of 287 consultations for analysis (see Figure 1 for a flowchart). Descriptive analyses were performed and we assessed the prevalence of Adjuvant! use in the whole sample (N=287) (RQ1). To determine whether and which patient, oncologist and disease characteristics influenced the use of Adjuvant! during consultations, we selected consultations by oncologists who had included minimally five patients into the study population and who did not *always* or *never* use Adjuvant! during the consultation (N=217) (RQ2). The association between the use of Adjuvant! and the determinants was assessed using χ^2 tests or Fisher's Exact Test, as appropriate.

The assessment of information provision about treatment benefits and side-effects (RQ3), and of whether a decision had been reached during the consultation (RQ4) required more extensive content analyses of the consultations. For reasons of feasibility

we used a random subset of approximately equal number of consultations with (N= 92) and without (N= 119) Adjuvant!. Differences in information provision are depicted graphically. The association between use of Adjuvant! and decision-making was assessed using a χ^2 test or Fisher's Exact Test as appropriate. Analyses were performed in SPSS 20. Significance testing was done two-sided at α=0.05.

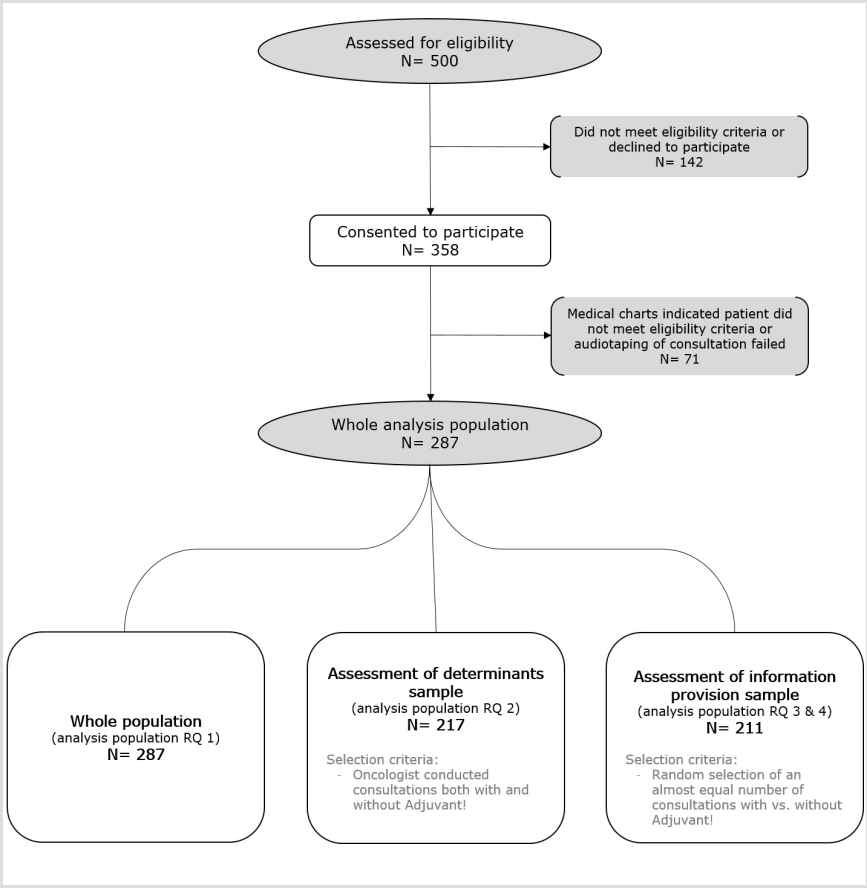


Figure 1 Flowchart of selection and analysis population

Results

Thirty oncologists (mean age: 46 years (range: 30-66 years)) included a median of 6 (range: 1-40) patients (Table 1). Patients (n= 287) were on average 59 years (range: 32-90 years), and they mostly had stage I (45%) or stage II (50%) disease. In three-quarters of the consultations both chemotherapy and endocrine therapy were discussed.

RQ1: Frequency and mode of use of Adjuvant!

Oncologists indicated in 70% of consultations that they had consulted Adjuvant! *prior* to the consultation. Oncologists with >10 years experience consulted Adjuvant! significantly less often prior to the consultation than those with ≤10 years experience (53% vs. 96% (P<0.001)). Adjuvant! was used *during* 191 (67%) of the patient consultations. In 74% of these 191 consultations, Adjuvant! was also reported to have been visually displayed either on the computer screen and/or using a printout of its output. If Adjuvant! was consulted prior to the consultation, it was subsequently used in 84% of those consultations.

RQ2: Determinants of Adjuvant! use during the consultation

Experienced oncologists used the model less frequently in the consultation than their less experienced counterparts (P= 0.03, (Table 2)). The higher the patient's TNM stage, the less frequently Adjuvant! was used during the consultation (P= 0.002). No other patient, oncologist, or disease characteristics were associated with Adjuvant! use.

RQ3: Information provision about treatment benefits and side-effects of treatment by use of Adjuvant! and by treatment

Communication about benefits

Figure 2 shows which benefits were presented during the consultations, by use of Adjuvant! and by treatment. In 183 of the 188 (97%) consultations in which chemotherapy was discussed, at least one benefit of chemotherapy was mentioned. In the remaining 3% of chemotherapy consultations patients could only assume a treatment benefit. In 96% of chemotherapy consultations relapse probability reduction was presented, and in 26% mortality reduction was (also) presented. If Adjuvant! was used, mortality reduction was discussed more often than if Adjuvant! was not used (P<0.001).

Table 2 Use of Adjuvant! by patient, disease, consultation and oncologist characteristics (col%)

	Adjuvant! Online *not* used* N= 57	Adjuvant! Online used* N= 160	P#
Patients characteristics			
Age			
younger than 50 years	17 (30)	29 (18)	0.10
50-70 years	29 (51)	105 (66)	
older than 70	11 (19)	25 (16)	
Education level			
Low	7 (16)	20 (16)	0.97
Intermediate	25 (56)	67 (53)	
High	13 (29)	40 (32)	
Numeracy level			
Low	11 (24)	24 (19)	0.62
Intermediate	12 (27)	33 (26)	
High	22 (49)	72 (56)	
Preference for hearing survival probabilities			
does not want probabilities	20 (91)	4 (8)	**<0.001**
wants probabilities	2 (9)	49 (93)	
Disease characteristics			
TNM stage			
Stage I	15 (26)	81 (51)	**0.002**
Stage II/III	42 (74)	78 (49)	
Grade			
Grade 1	6 (11)	17 (11)	0.97
Grade 2	30 (55)	83 (53)	
Grade 3	19 (35)	57 (36)	
ER status			
ER negative	5 (9)	22 (14)	0.48
ER positive	52 (91)	137 (86)	
Triple negative			
Not triple negative	53 (95)	147 (93)	0.76
Triple negative	3 (5)	12 (8)	

*Numbers do not always add up to column totals due to missing data.
#P-values from χ^2 tests or Fisher's Exact Tests (as appropriate).

Table 2 continued Use of Adjuvant! by patient, disease, consultation and oncologist characteristics (col%)			
	Adjuvant! Online *not* used* N= 57	Adjuvant! Online used* N= 160	P#
Her2neu status			
Negative	46 (84)	138 (87)	0.65
Positive	9 (16)	21 (13)	
Consultation characteristics			
Treatment discussed			
Chemotherapy only	4 (7)	20 (13)	0.11
Endocrine therapy only	10 (18)	13 (8)	
Chemotherapy & endocrine therapy	43 (75)	127 (79)	
Oncologist characteristics			
Gender			
Male	23 (40)	84 (53)	0.13
Female	34 (60)	76 (48)	
Experience treating breast cancer			
Less than 5 years	12 (22)	58 (38)	**0.03**
5-10 years	2 (4)	13 (9)	
More than 10 years	41 (75)	81 (53)	
Type of hospital			
Academic	44 (77)	117 (73)	0.60
General teaching	13 (23)	43 (27)	

*Numbers do not always add up to column totals due to missing data.
#P-values from χ^2 tests or Fisher's Exact Tests (as appropriate).

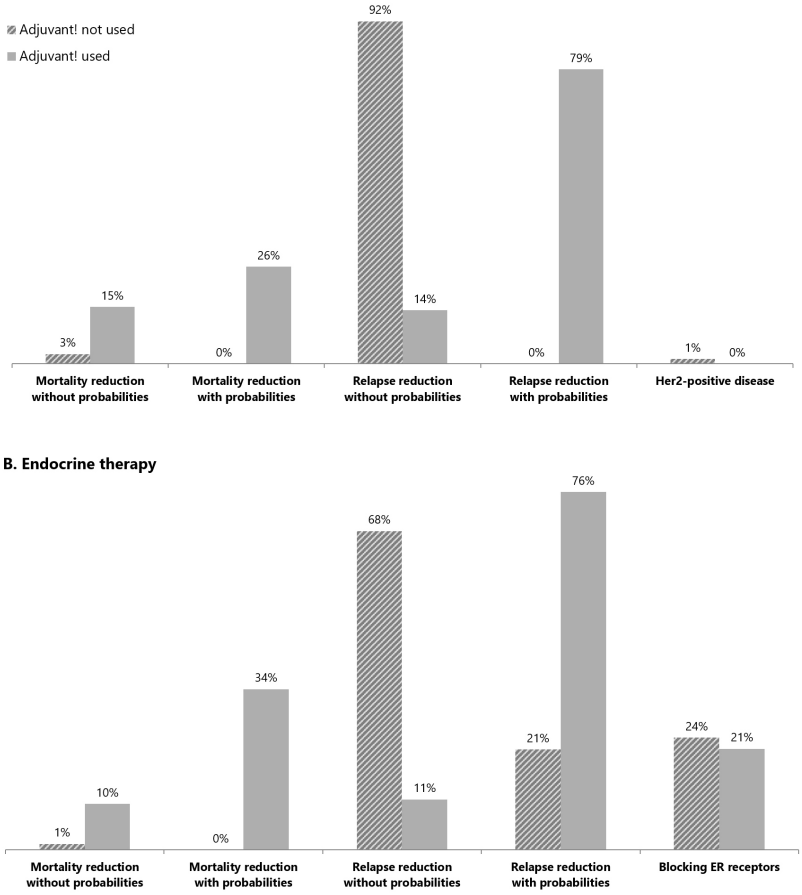
In 173 of the 183 (95%) endocrine therapy consultations, the treatment benefit was discussed. In the remaining 5% patients could only assume a treatment benefit. In 92% of consultations in which endocrine therapy was discussed, relapse reduction was mentioned, and in 26% mortality reduction was (also) mentioned. Mortality reduction was also discussed more often if Adjuvant! was used than if not (P<0.001).

Probabilities regarding benefits were discussed in 189/191 (99%) consultations in which Adjuvant! was used and in 25/92 (27%) consultations in which Adjuvant! was not used. In two consultations Adjuvant! was only used as a '*visual aid*' to indicate that relapse-free or breast cancer-specific survival improved with treatment. On average 4.6 (range: 0-12) probabilities were discussed when Adjuvant! was used, compared to 0.6 (range: 0-5) when Adjuvant! was not used. In 18% (39/214) of all consultations in

which probabilities were discussed (irrespective of Adjuvant! use) we were unable to classify the probabilities communicated. The oncologists' explanation –or lack thereof– made it impossible to determine whether the probabilities mentioned were survival or disease-free survival estimates.

Communication about treatment side-effects

Overall, 59 different chemotherapy and 43 different endocrine therapy side-effects were communicated during the consultations. Of these side-effects 66% (chemotherapy) and 79% (endocrine therapy) respectively were mentioned in fewer than five consultations. In Figures 3 and 4 we provide an overview of the side-effects that were communicated in at least ten consultations. There was no difference in the overall number of side-effects communicated by Adjuvant! use (Adjuvant! used, Md=6.0 (range: 1-13) vs. Adjuvant! not used, Md=6.5 (range: 1-15); P= 0.76). The overall number of side-effects communicated depended mostly on which treatment was discussed. If only chemotherapy was discussed, a median of 7 (range: 1-13) side-effects were mentioned, if only endocrine therapy was discussed a median of 4 (range: 0-9) side-effects were mentioned. If both treatments were discussed, a median of 6 (range: 1-12) chemotherapy and 1 (range: 0-9) endocrine therapy side-effects were discussed.

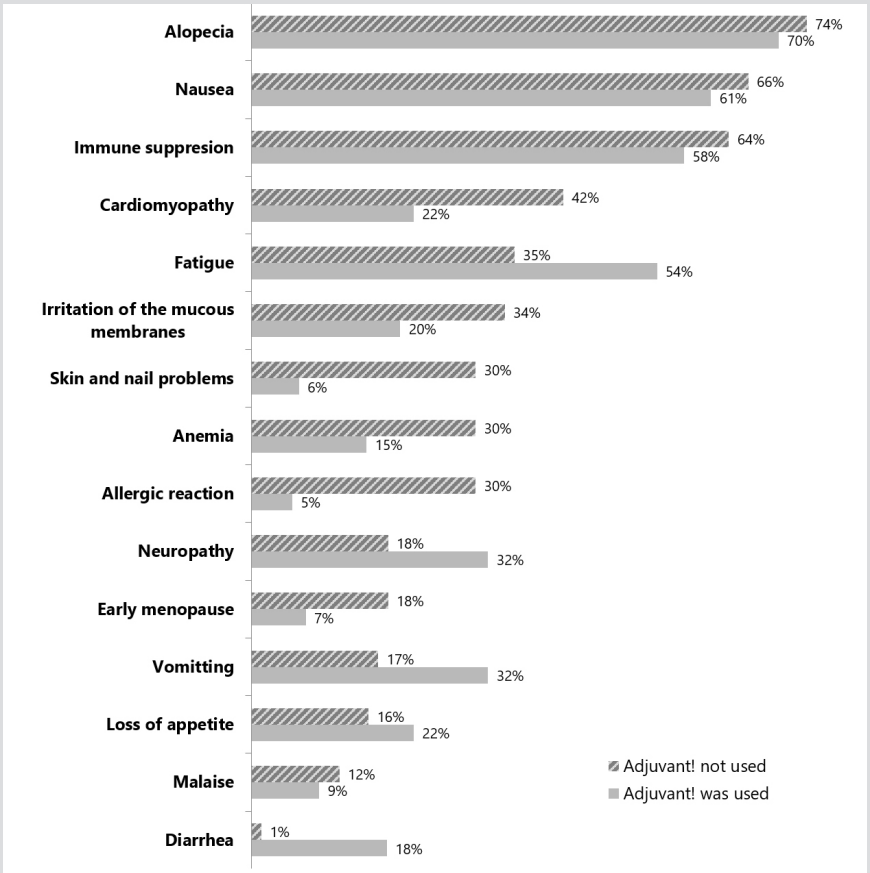


Percentages if Adjuvant! was notused are based on N= 77 chemotherapy and N= 80 endocrine therapy consultations.
Percentages if Adjuvant! was used are based on N= 111 chemotherapy and N= 103 endocrine therapy consultations.

Figure 2 Frequency with which the various treatment benefits are discussed by Adjuvant! use

There also was a wide variation within and between oncologists in the number of side-effects they communicated (Figure 5). The frequency with which specific side-effects were communicated differed by Adjuvant! use (Figures 3 and 4). There was no discernable pattern to the difference in which side-effects were communicated by Adjuvant! use. The comprehensiveness of the description of chemotherapy and endocrine therapy side-effects was basic in the majority of consultations, irrespective

of Adjuvant! use, and consisted only of mentioning the side effect. The probability of developing a side-effect was rarely discussed.



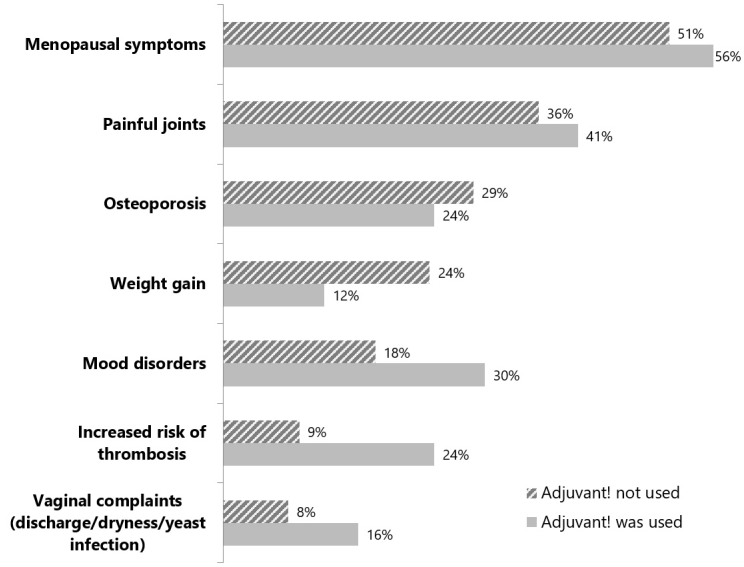
Percentages based on N=77 consultations without Adjuvant! and N=111 consultations with Adjuvant!.
Only side-effects communicated in ≥10 consultations were incorporated in the figure.

Figure 3 Overview of chemotherapy side-effects communicated by Adjuvant! use

RQ4: Association between use of Adjuvant! and decision-making

A decision was made for all treatments discussed in 162 out of 211 (77%) consultations, the decision was postponed in 21 (10%) consultations, and in 26 (12%) consultations a decision was made concerning only one of the treatment options discussed. For two consultations, it was unclear whether or not a decision had been made.

When Adjuvant! was used, decisions were postponed more often (36/118 (31%); Adjuvant! not used= 11/91 (12%); P= 0.005). For chemotherapy, overall the decision was postponed in 39/187 (21%) consultations, and in 30 out of those 39 (70%) consultations, Adjuvant! had been used (P<0.001). Also, in 48/187 (26%) consultations the decision was made to forego chemotherapy, and in 34 (71%) of those 48 consultations Adjuvant! had been used. For endocrine therapy, overall the decision was postponed in 21/178 (12%) consultations, and in 17 (81%) of those 21 consultations Adjuvant! had been used (P= 0.01). Also, in 6/178 (3%) consultations the decision was made to forego endocrine therapy, and in 5 of those 6 consultations Adjuvant! was used.



Percentages based on N=80 consultations without Adjuvant! and N=103 consultations with Adjuvant!.
Only side-effects communicated in ≥10 consultations were incorporated in the figure.

Figure 4 Overview of endocrine therapy side-effects communicated by Adjuvant! use

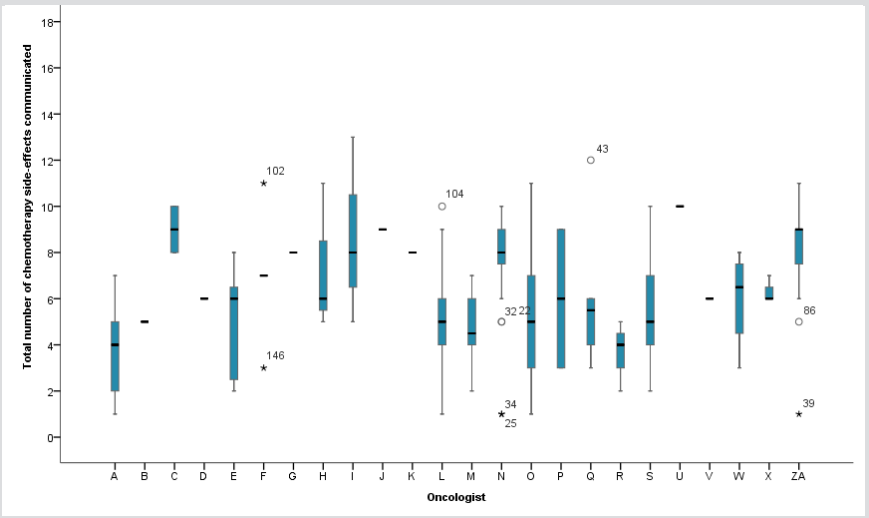
Discussion

In the current study we evaluated the frequency and determinants of use of Adjuvant!. We also assessed information provision about the benefits and side-effects of adjuvant systemic treatment, and whether information provision and the likelihood of reaching a decision during the consultation differed by the use of Adjuvant!.

The oncologists in the current study consulted Adjuvant! prior to 7 out of 10 consultations, and Adjuvant!'s estimates were discussed during 2 out of 3 consultations. This is in line with findings from surveys amongst oncologists about how often they use Adjuvant! (8), and suggests that communicating survival probabilities during consultations with patients is becoming the norm. Less experienced oncologists were more likely to use Adjuvant! both prior to and during consultations. This is likely a generation effect, with younger oncologists being more computer-savvy, but also more open to discussing prognosis than older oncologists. Not surprisingly, the higher the disease stage, the less likely it was that Adjuvant! would be used during the consultation. Oncologists might be hesitant to cause anxiety in patients, to demotivate them for treatment, or cause them to lose hope by communicating modest survival probabilities. Communicating good survival, on the other hand, might be seen by oncologists as a way to comfort and reassure their patients that no matter what they choose to do, their prospects are good. In a recent survey, three out of four oncologists indicated that they used Adjuvant! to convince patients that chemotherapy is not necessary (8), especially so for patients with stage I disease. This could also partly explain why Adjuvant! is used more often when prognosis is better. We found that chemotherapy was waived more often than endocrine therapy, especially if Adjuvant! had been used.

Interestingly, we found that regardless of Adjuvant! use, the reduction in relapse probability was the treatment benefit that oncologists most often discussed (>90%); mortality probabilities were rarely discussed (<5%), although more so if Adjuvant! was used during the consultation. The high frequency of discussing reduction in relapse probability contradicts the findings of an earlier study showing that oncologists valued Adjuvant!'s mortality probabilities more, because they had concerns about the robustness of the relapse estimates (8). Indeed, Adjuvant!'s relapse estimates have been shown to be less sound than its mortality estimates (20-22). Perhaps our oncologists were not aware of this limitation of Adjuvant!, but it seems more likely that they chose to discuss the relapse probabilities because the effect of treatment on relapse is larger than that on mortality. If treatment is an obvious 'best' choice from a medical perspective, such implicit persuasion need not be harmful. However, given that for the majority (>90%) of patients in this study there is no 'best' option, such steering could have unwanted effects (17). Remarkable was that in about one in five consultations we were unable to determine whether the probabilities communicated were overall or disease-free sur-

vival probabilities. Unclear risk communication undermines oncologists' intent to help patients to better understand their prognosis (8). These are disconcerting findings that require further in-depth investigation. If confirmed, it underlines the need for increased attention for risk communication in pre- and post-graduate curricula to provide clinicians with the tools to better convey prognosis to their patients.



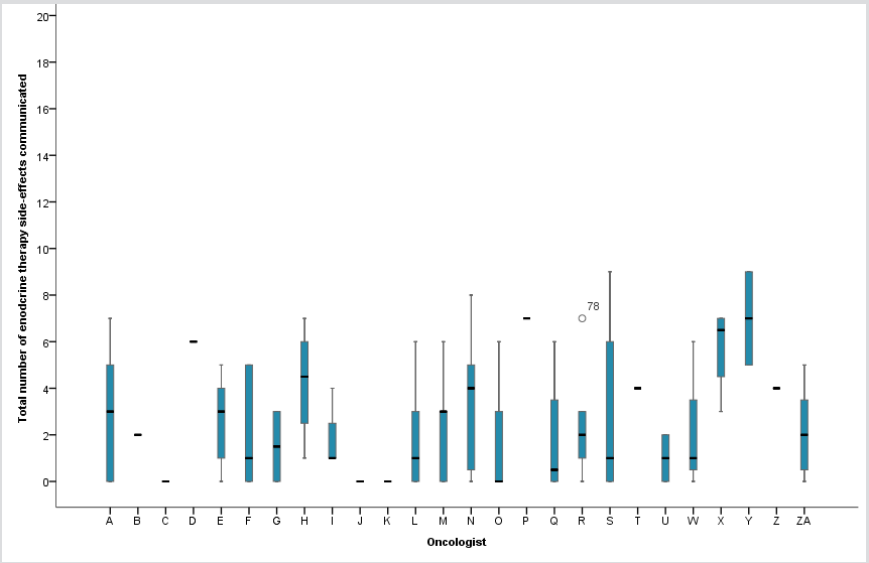


Figure 5 Frequency with which the various treatment benefits are discussed by Adjuvant! use

The use of Adjuvant! does not seem to drive the overall number of side-effects communicated during consultations, but we did find that the specific side-effects communicated varied by Adjuvant! use. One could perhaps think that if Adjuvant! is used to convince patients not to undergo chemotherapy, oncologists might be more inclined to communicate the more severe treatment side-effects, and if the aim is to convince patients about the merits of treatment the more severe side-effects would be omitted. However, such pattern was not identified. No single side-effect of either chemotherapy or endocrine therapy was communicated in all consultations. Apparently, there is no consensus with regards to which side-effects minimally need to be communicated to patients. Indeed, current clinical guidelines do not provide guidance about which side-effects must be communicated (5-7). Moreover, oncologists mostly only *mentioned* the side-effect, without further information on the probability of experiencing the side-effect, its implications for daily life, or its course over time. These findings are worrying, as patients also need to be appropriately informed about what the side-effects of treatment entail to be able to decide whether or not the benefits outweigh the side-effects. In our sample, oncologists regularly indicated that the breast cancer nurse or nurse practitioner would elaborate further on the side-effects (data not shown). This is not a mitigating factor, since in three out of four consultations the treatment decision was made during the consultation. Patients should be informed at that point in time about both the benefits and the side-effects of treatment. Remarkably, in five chemotherapy and nine endocrine therapy consultations, no treatment benefit was explicitly communicated, it had to be inferred. Nonetheless, in all but two of these 14 consultations, it was decided to initiate therapy. If patients are ill-informed about the potential benefits and side-effects their expectations might be unrealistic, which can lead to decisional regret and greater treatment discontinuation rates. For endocrine therapy, high discontinuation rates have been reported (23). Also, patients may receive treatment they might not have chosen had they been able to appropriately weigh side-effects and benefits, in a process of shared decision making.

Interestingly, decision-making was postponed more often when Adjuvant! was used, particularly in patients with stage I disease (data not shown). Perhaps hearing the survival probabilities from Adjuvant! makes patients realize that the treatment benefits are only modest. Patients might therefore need more time to consider whether they feel the benefits outweigh the side-effects.

A limitation of our study is its descriptive nature. Oncologists were not randomized to the use of Adjuvant! and therefore results may have been confounded by specifics of the oncologists or the particular patient. It is important to keep in mind that although we explicitly instructed oncologists to conduct their consultations as they normally would, the study might have influenced their use of Adjuvant!. We therefore asked oncologists in the post-study survey whether their use of Adjuvant! had changed during

the study period. Only two oncologists indicated to have used Adjuvant! more often than before our study.

This is the first study to assess the use of Adjuvant! during real-time patient consultations, its influence on information provision about the benefits and side-effects of treatment, and decision-making. Although Adjuvant! is currently offline due to updates and it is unclear when it will become available again, this study serves as a model for clinical usage of other prediction tools in oncology (e.g., PREDICT(24) or CancerMath(25)). Our findings underscore the importance of obtaining more insights into the use of these tools in clinical practice. Their use during consultations seems to have become commonplace, yet, there is limited knowledge of how well their estimates are communicated, whether patients understand this information, and whether this type of information influences decision-making (26). The findings from this study suggest that there is room for improvement in how probabilities are communicated, as well as in which information about the side-effects of treatment are communicated and how. Adequate information provision is key if oncologists want to enable their patients to participate in decision-making.

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Chapter 7

Disclosing the uncertainty associated with prognostic estimates in breast cancer: *current practices and patients' perceptions of uncertainty*

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Abstract

Background

Treatment decision-making is often guided by evidence-based probabilities, which may be presented to patients during consultations. These probabilities are intrinsically imperfect, and embody two types of uncertainties: aleatory uncertainty arising from the unpredictability of future events, and epistemic uncertainty arising from limitations in the reliability and accuracy of probability estimates. Risk communication experts have recommended disclosing uncertainty. We examined whether uncertainty was discussed during cancer consultations, and whether and how patients perceived uncertainty.

Methods

Consecutive patient consultations with medical oncologists discussing adjuvant treatment in early-stage breast cancer were audiotaped, transcribed, and coded. Patients were interviewed after the consultation to gain insight into their perceptions of uncertainty.

Results

In total 198 patients were included by 27 oncologists. Uncertainty was disclosed in 49% (97/197) of consultations. In those 97 consultations, 23 allusions to epistemic uncertainty were made and 84 allusions to aleatory uncertainty. Overall, the allusions to the precision of the probabilities were somewhat ambiguous. Interviewed patients mainly referred to aleatory uncertainty if not prompted about epistemic uncertainty. Even when specifically asked about epistemic uncertainty, one in four utterances referred to aleatory uncertainty. When talking about epistemic uncertainty many patients contradicted themselves. In addition, one in ten patients seemed not to realize that the probabilities communicated during the consultation are imperfect.

Conclusions

Uncertainty is conveyed in only half of patient consultations. When uncertainty is communicated, oncologists mainly refer to aleatory uncertainty. This is also the type of uncertainty that most patients perceive and seem comfortable discussing. Given that it is increasingly common for clinicians to discuss outcome probabilities with their patients, guidance on whether and how to best communicate uncertainty is urgently needed.

Introduction

Medical decision-making, whether relating to diagnostic procedures or treatment, should ideally be guided by evidence-based probabilities. Numerous prediction models have been developed to promote this goal. The individualized prognostic estimates these models provide facilitate better conceptualization of the trade-offs between benefit and harm of different treatment options. However, even evidence-based probability estimates are intrinsically imperfect. They are based on past observations and unavoidably limited evidence, resulting in two major types of uncertainty. First-order, or *aleatory uncertainty,* arises from the unpredictability of single events arising from the fundamental indeterminacy or randomness of future outcomes. Aleatory uncertainty is inherent to the *concept* of probability (we seldom speak of a probability of 1 or of 0). Second-order, or *epistemic uncertainty*, arises from deficits in knowledge, due to limitations in a) the precision of the risk estimates or b) their applicability to a specific patient (1, 2).

Risk communication experts have argued, mainly from an ethical perspective, that patients should be fully informed, and thus also be informed about these uncertainties (3). Failure to explicitly address epistemic and aleatory uncertainties may create misconceptions about the level of precision and individualization of probabilities presented during consultations. In the absence of adequate communication of such uncertainty, patients may have excessive confidence in probabilities, thus (potentially) resulting in pseudo-certainty.

Currently, no literature is available on the extent to which physicians communicate the epistemic uncertainty of prognostic estimates and the inability to predict individual disease outcomes. In addition, it is unknown to which extent patients understand these uncertainties and how these uncertainties are best communicated (3, 4). Clinicians may be hesitant to communicate uncertainty, fearing that such communication would make the information (even) more difficult for patients to comprehend, for we know that most people struggle to understand probabilities, irrespective of their education level (1, 5). For clinicians it is a challenge to find a balance between ´fully´ informing their patient, whilst not overwhelming them by providing too much information.

In the current study, we investigated the communication of uncertainty in the context of decision-making about adjuvant systemic treatment for early-stage breast cancer. Stage I-III breast cancer patients undergoing adjuvant systemic treatment may experience improvement in both disease-free and cancer-specific survival (6-10). Using known clinical prognosticators (e.g., tumor size, nodal status and differentiation grade) and/or bio-molecular profiles, the likelihood of beneficial treatment outcomes can be

calculated, for instance using the Adjuvant! prediction model (11). The likelihoods from Adjuvant! are frequently discussed during consultations in the adjuvant setting (12, 13). In combination with estimates of treatment effect, these likelihoods improve insight on the balance between the potential benefits and side-effects of treatment (10, 14, 15). We assessed a) *whether* and *which type* of uncertainty oncologists disclosed: i.e., the limitations in the precision of risk estimates/their applicability to an individual patient and/or unpredictability of single events, and b) patients' perceptions of the uncertainty associated with probabilities discussed during the consultation.

Methods

Design

Patient sample

The current study was nested in a large multicenter observational study with a participation rate of 358/500 (72%), which assessed the communication of survival probability estimates calculated by the Adjuvant! prediction model (11) during consultations of stage I-III invasive breast cancer patients by medical oncologists. Consecutive outpatient female breast cancer patients, eligible to receive chemotherapy and/or endocrine therapy, who were fluent in the Dutch language, were invited to participate in the current study. We included patients if survival probabilities from the Adjuvant! prediction model had been discussed during the consultation (Figure 1). This was determined following analysis of the content of the consultations. The medical ethics boards of the participating hospitals approved the study.

Adjuvant! prediction model

Adjuvant! (11) is a freely available online prognostication tool that provides estimates of 10-year a) overall, b) breast cancer-specific, and c) disease-free mortality and d) benefit of adjuvant systemic treatment. The information is presented as bar charts. Adjuvant!'s prognostic estimates are based on patient and tumor characteristics (i.e., age, patient's general health, tumor size, nodal status, estrogen receptor status and histological tumor grade) and type of systemic treatment. Oncologists may print the page to hand to the patient, or show the results on a computer screen.

Procedures

Consultations

Prior to their consultation, patients were informed that the study aimed to investigate information provision during consultations concerning adjuvant systemic therapy. The concept of uncertainty was not introduced. Oncologists were instructed to conduct their consultation as usual. Consultations were audiotaped after patients had given written informed consent.

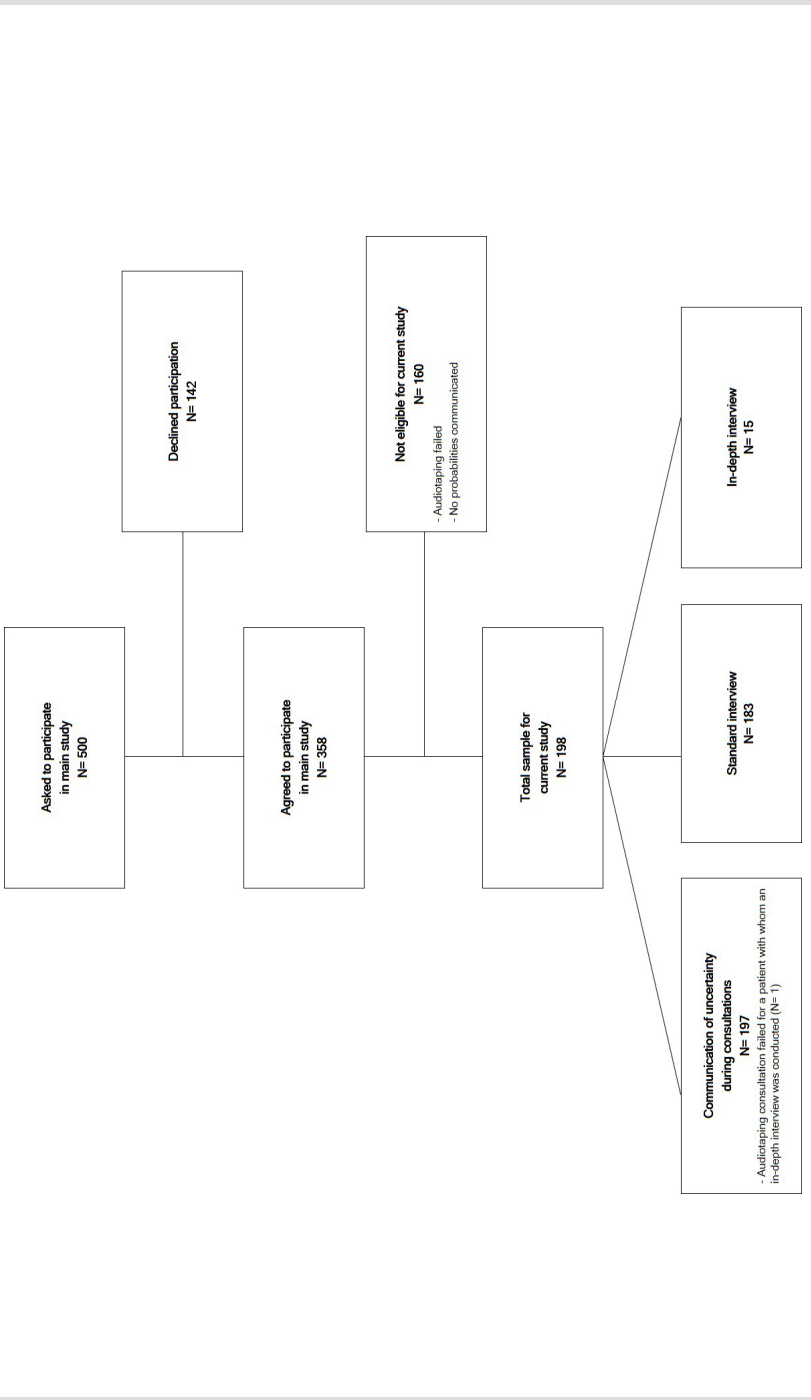

Figure 1 Flow chart of patient recruitment.

Patient interviews

Uncertainty was addressed in two types of interviews, 1) 'Standard' and 2) 'In-depth' interviews. The standard interview was a component of the main study. Patients were interviewed by telephone within seven days of their consultation (mean=3.4 days). The interviewer had no knowledge of what had been discussed during the consultation prior to this interview. Given the extensive character of the interview of the main study, we chose to only probe about epistemic uncertainty, since this is particularly relevant in the context of risk communication using probabilities from prediction models. To begin with, we asked patients whether the oncologist had discussed probabilities during the consultation. If patients indicated that this was the case, we asked them to list the probabilities discussed. Next, we posed two probes on uncertainty. First, we posed an 'Open probe': "*What do the probabilities [repeat probabilities the patient has already mentioned] mean to you?*". Second, we posed a 'Precision probe': "*In your opinion, are the probabilities you were provided with during the consultation [repeat probabilities the patient has already mentioned] exact survival probabilities… [pause] or could they be higher or lower for example*".

As probing turned out to be a challenge, not only practically but also ethically, with limited time, we could not elaborate on uncertainty during the standard interviews. Therefore, we decided to conduct additional in-depth interviews solely dedicated to uncertainty in a subset of patients not previously interviewed. Thus, we hoped to achieve a more comprehensive exploration of the patients' awareness of and views on epistemic uncertainty (consisting of the imprecision of risk estimates and their applicability to an individual patient), and the unpredictability of single events (i.e. aleatory uncertainty). We extended the inclusion period of the main study to recruit patients for these latter interviews. Expecting to need at least 15 interviews to reach saturation, we approached 15 consecutive patients not previously interviewed with whom probabilities had been discussed during the consultation. We conducted the in-depth interview only if patients indicated that probabilities had been discussed, irrespective of whether this had indeed been the case (according to the audiotapes). After 12 in-depth interviews, no new themes had emerged. Consequently, we ended inclusion and completed three already scheduled interviews.

On average, in-depth interviews took place within four days of the consultation (range: 0-12 days), either in person (N=10) or, by telephone if preferred (N=5). We recruited and informed patients in the same way about the study as the patients of the standard interviews. First, we used an '*Open probe*' not introducing the concept of uncertainty, to assess whether patients spontaneously referred to the uncertainty associated with the probabilities. Thereafter, we probed patients' perception of the uncertainty associated with the survival probabilities discussed during the consultation. We also asked patients whether - to the best of their recollection - uncertainty had been discussed

during the consultation and whether they thought it important to hear about such uncertainty during the consultation (see Appendix A for the probes on uncertainty used in the in-depth interviews).

Table 1 Patients and consultation characteristics (N (%))

	Overall N=198	Standard interview sample N=183	In-depth interview sample* N=15
Mean age in years (range)	59 (32-90)	59 (32-90)	54 (37-73)
Recruited at			
Academic medical center	52 (26)	47 (26)	5
General teaching hospital	146 (74)	136 (74)	10
Education			
Low	30 (19)	27 (19)	3
Intermediate	82 (52)	78 (54)	4
High	45 (29)	40 (28)	5
Missing	41	38	3
Numeracy			
Low	33 (21)	31 (21)	2
Intermediate	42 (26)	39 (27)	3
High	84 (53)	77 (52)	7
Missing	39	36	3
Median duration of consultation in minutes (range)	28 (5-80)	28 (5-80)	27 (17-62)
Treatment discussed			
Chemotherapy	21 (11)	19 (10)	2
Endocrine therapy	21 (11)	20 (11)	1
Both	156 (79)	144 (79)	12

* For one patient with whom we conducted an in-depth interview, audiotaping of the consultation failed.

Patient and oncologist questionnaire

Patients completed a written survey after having been interviewed assessing age and education level (defined using the highest level of schooling/vocational training completed) as well as objective numeracy, i.e., their ability to understand and use numbers. We used the seven expanded numeracy items proposed by Lipkus *et al.* (5). Scores (range: 0-7) were divided into three categories (low numeracy= 0-2; intermediate numeracy= 3-5; high numeracy= 6-7).

After patient recruitment was closed, we asked oncologists to fill out a survey to obtain their age, gender, and number of years of experience with the systemic treatment of breast cancer. They were also asked to indicate their reluctance to disclose uncertainty

to patients on the relevant subscale of the Physicians' Reactions to Uncertainty Scale (example of items: "*When physicians are uncertain of a diagnosis, they should share this information with their patients*", and "*If I shared all of my uncertainties with my patients, they would lose confidence in me*") (16) (scored on a six-point Likert scale, range between 5-30, with higher scores indicating greater reluctance towards disclosure). Finally, we asked oncologists to indicate the frequency with which during consultations they discussed epistemic and aleatory uncertainty with patients on five-point Likert scales (categories: never, seldom, sometimes, often, and always).

Coding and analyses

Consultations

Two trained researchers analyzed the content of the consultations to ascertain which treatment had been discussed (chemotherapy, endocrine therapy or both) and identify references to epistemic (yes/no) and aleatory uncertainty (yes/no).

Due to time constraints, it proved impossible to transcribe all consultations. Therefore, consultations were analyzed either directly from a verbatim transcription (N=94/197 (48%)) or from audio (N=103/197 (52%)). The coders first coded ten transcripts independently. Inter-rater agreement was 100%. To also ensure the reliability of coding directly from audio, each coder coded a sample of consultations (N=13-16) that had already been coded from transcript minimally three months after the original coding. The agreement between coding from audio and transcripts was again high (81% and 83%, respectively). As the agreement between coders was good, one researcher performed final coding.

Patient interviews

Patients' answers to the uncertainty probes in the Standard Interviews were transcribed. To categorize emerging themes, the research team developed an initial codebook based on the literature and open coding by two researchers of a subset of five consultations, thereafter it was refined and applied. This process was repeated several times, and the categories in the codebook are based on the coding of a subset of 30 interviews. The content of all standard interviews was double-coded by two trained researchers independently, and discrepancies were resolved in consensus meetings.

All 15 in-depth interviews were transcribed verbatim and coded independently by the two trained researchers, using the same categories used to code the standard interviews as a starting point. New categories were added as encountered. Discrepancies were resolved in consensus meetings.

Table 2 Oncologist characteristics (N=18)	
	N (%)
Median age in years (range)	42 (30-66)
Missing	7
Gender (male)	12 (44)
Experience with breast cancer systemic treatment (in years)	
≤ 5	9 (45)
6-10	2 (10)
>10	9 (45)
Missing	7
Oncologists' reluctance to disclose uncertainty to patients (median (range))*	13 (5-17)
Missing	7
Self-reported frequency of disclosure of uncertainty (% often and always)	15 (79)
Aleatory uncertainty (i.e., the unpredictability of single events)	
Epistemic uncertainty, specifically:	
precision of prognostic estimates	9 (47)
applicability to an individual	8 (42)
Missing	8

* Five-item reluctance to disclose uncertainty to patients subscale of the Physicians' Reactions to Uncertainty Scale (16), scored on a six-point Likert scale; the higher the score, the greater the reluctance towards disclosing uncertainty to patients (score range: 5-30).

Finally, the two coders independently grouped the 40 categories (i.e., themes) identified during the coding of both the standard and in-depth interviews into overarching domains for presentation purposes. The definitive grouping was established through further discussion and consensus among members of the research team (see Table 3 for the Standard Interview themes and Figure 2 for the In-depth Interview domains).

Results

We included 198 patients (Mdn age =59 years; range: 32-90). Overall, 74% of patients were recruited at general teaching hospitals, 29% were highly educated, and 53% were highly numerate (Table 1). The median duration of the consultations was 28 minutes (range: 5-80). Audiotaping of the consultation was successful for all patients except one. In 79% of consultations Adjuvant!'s prognostic estimates were presented orally and its output was displayed visually on the computer screen and/or on a printout of the output. The standard interview was conducted with 170 of the 198 patients, the in-depth interview was conducted with 15 patients, and no interview was conducted with 13 patients (nine patients could not be reached by telephone within 1 week after the consultation, and four declined to be interviewed).

Twenty-seven medical oncologists (Mdn age = 42 years; range: 30-66) recruited patients (Mdn=7 patients per oncologist; range: 1-33) (Table 2). Twenty oncologists (partially) completed the survey (74%), of whom 12 had more than 10 years of experience in this setting. Oncologists showed low to moderate reluctance towards disclosing uncertainty to patients (Mdn=12 out of a maximum of 30 points; range: 5-17). Nine of the 19 oncologists said they often or always discuss epistemic uncertainty (i.e. the imprecision of risk estimates and/or their applicability to a specific patient) during consultations, and 15/19 said they often or always discuss the unpredictability of single events.

Consultations

Disclosure of uncertainty during consultations

In about half (N=97/197 (49%)) of the consultations some type of uncertainty was disclosed. During these consultations, 107 references to uncertainty were made, of which 84 (79%) allusions to the unpredictability of single events (aleatory uncertainty). For example, one oncologist said: *"… [there are] no guarantees. It remains … I always say that in reality if you look at an individual it is 100% or 0%. So you either get the disease back or you don't, right. But if you have 100 women, then you have 30 women in whom during the course of 10 years, metastases will manifest... And I can't tell just by looking at you whether you are one of the 70 lucky ones or one of the 30 unlucky ones".* The remaining 23 (21%) references to uncertainty were allusions to the imprecision of the risk estimates and/or their applicability to a specific patient (epistemic uncertainty). Allusions to the imprecision of the risk estimates were generally somewhat vague, for example: *"Of course there always is a margin associated with such statistics"*. Utterances about the applicability of the probabilities to specific (subgroups of) patients were more tangible, for example: "*… look these are averages … yes. It's a large database, and we can't comment on the individual ... the only thing we can do is look at averages. And of course, there are always exceptions on both sides*", or "*… these probabilities will be somewhat different for you … your relapse risk will be higher, because the model*

[Adjuvant!] does not take the Her2 [Her2neu receptor status] into account".

Standard interviews

Patients' perception of the various types of uncertainty

One hundred forty-four (85%) patients indicated that probabilities had been discussed during the consultation. We posed the open probe to them. Of those 144 patients, 97 (67%) did not make a reference to uncertainty and 47 did. The response to the open probe of 12 of these 47 patients contained allusions to more than one aspect of uncertainty, resulting in 62 allusions. Overall, 37/62 allusions were about the unpredictability of single events, and 10/62 allusions were about the imprecision of the risk estimates or their applicability to a specific patient. The remaining 15/62 allusions were general statements without further clarification as to what the patient was aiming at (e.g., "*It's just statistics …*" or "*… it's statistically a substantial reduction of my recurrence risk*") or statements about the patients' struggle to cope with uncertainty. Table 3 presents patients' utterances about uncertainty during the standard interview.

Understanding of imprecision

The imprecision probe was posed to 80% (115/144) of patients who indicated probabilities had been communicated. This probe was not posed to 29 patients as the interviewer felt they were too emotional and/or had too limited understanding of the probabilities to allow probing. We found that patients generally seemed to struggle with what we were asking them. Patients seemed to think that we were asking them whether the probabilities they had heard during the consultation were correct, e.g., "*I think they calculated that [the probabilities] correctly. Yes, I'm confident about that*". Fifteen out of the 115 patients (13%) indicated they were unable to provide an answer. The 100 patients that did provide an answer made 178 allusions to uncertainty (Table 3). We were asking patients about the imprecision of the risk estimates, yet only 35% (63/178) of utterances referred to imprecision.

One out of three patients who alluded to imprecision (20/63) indicated that the probabilities were exact, i.e., they reported no uncertainty about the probability. About one out of four (41/178) utterances were an allusion to the inapplicability of probabilities to an individual, and 23% (41/178) of utterances were an allusion to the unpredictability of single events. The remaining 26 of the 178 (15%) remarks were statements about patients' struggle to cope with uncertainty or vague allusions to uncertainty (e.g., "*… it's just statistics*").

In-depth interviews

Figure 1 provides an overview of the themes identified in the 15 in-depth interviews (see Table 1 for patients' socio-demographic characteristics). When we posed the open probe, 26 unique references to uncertainty were made, whereas 66 unique references

were made after we posed the probes about the unpredictability of single events (aleatory uncertainty), and the imprecision of the risk estimates, their applicability to a specific patient (epistemic uncertainty). Fourteen of the 26 references to uncertainty following the open probe alluded to the unpredictability of single events, four alluded to the imprecision of the risk estimates, one alluded to the applicability of the probabilities to a specific patient, and seven were vague allusions to uncertainty or patients' struggle to cope with uncertainty.

Again patients seemed to have difficulty understanding what we were asking them when we probed specific elements of uncertainty. Patients mainly struggled with probes about the imprecision of the risk estimates and their applicability to a specific patient. Box 1 provides excerpts from an interview as an illustration of the struggle to formulate answers and inconsistencies between a patient's utterances. Of the six patients who indicated that there was no uncertainty with regard to the precision of prognostic estimates, four were highly numerate. Utterances about the imprecision of the risk estimates and their applicability to a specific patient frequently contained (logical) inconsistencies. An overview of inconsistent utterances within patients is provided in appendix Table 1 (enclosed in boxes).

Table 3 The frequency with which patients alluded to aleatory and epistemic uncertainty during the Standard Interview

	Open probe [a, b] N=62 allusions N (col%)	*Imprecision probe* [a, c] N=178 allusions N (col%)	*Example quotes*
Allusions to epistemic uncertainty			
Precision of the estimates			
Probabilities are exact/ no uncertainty about precision	0	20 (11)	"If they tell me it's 6%, then I think that's pretty definite. They wouldn't just say that." "Exact numbers, because his [oncologist] computer program is based on facts."
Probabilities are not fixed	1 (2)	38 (21)	"It's just statistics, not a fixed number." "The number doesn't really say much, it's just a probability of course. It gives an indication and not much more." "It [the survival probability] could definitely just as well be 16% or 18% …."
There is a margin around the probabilities	0	2 (1)	"I know there is a margin. They [the survival probabilities] are research figures."
Uncertainty associated with the model used to calculate probabilities	0	1 (<1)	"The program [Adjuvant! prediction model for breast cancer] is not precise."
Precision depends on sample size	0	2 (1)	"Depends on how many people took part. Difficult to estimate." "Statistics are not always reliable; you have to investigate a really large group… they're [the survival probabilities] just numbers. Not really exact."

[a]= Rows do not add up to the number of patients to whom we posed the probe, because some patients' answers contained multiple aspects. The percentages reflect how many patients said something about each specific element.
[b]= Open probe was: "*What do the probabilities [repeat probabilities the patient has already mentioned] mean to you?*"
[c]= Imprecision probe was: "*In your opinion, are the probabilities you were provided with during the consultation [repeat probabilities the patient has already mentioned] the exact survival probabilities… [pause] or could they be higher or lower for example?*"

Table 3 continued The frequency with which patients' alluded to aleatory and epistemic uncertainty during the Standard Interview (N (col%))			
	Open probe [a, b] **N=62 allusions** N (col%)	*Imprecision probe* [a, c] **N=178 allusions** N (col%)	*Example quotes*
Applicability of the estimates to individuals			
No uncertainty about the applicability to an individual	0	4 (2)	"Yes, very specifically with my characteristics and then a calculation was made on that [estimates by the Adjuvant! prediction model for breast cancer]."
The probabilities are averages	1 (2)	14 (8)	"I daren't say [whether the survival probabilities are precise]. Average numbers are different per person. That 20% [probability disclosed during the consultation] is an average I think, for one patient a little greater and for the other somewhat less."
Probabilities only apply at group level	8 (13)	30 (17)	"No, no, it doesn't mean anything… or no, it does mean something [the survival probabilities]. I think it's different for everybody. It just depends on whether it works or not." "It's [the survival probabilities] a theoretical given. Every person is different. It's [survival probabilities] a guideline."

[a]= Rows do not add up to the number of patients to whom we posed the probe, because some patient's answers contained multiple elements. The percentages reflect how many patients said something about each specific element.
[b]= Open probe was: "*What do the probabilities [repeat probabilities the patient has already mentioned] mean to you?*"
[c]= Imprecision probe was: "*In your opinion, are the probabilities you were provided with during the consultation [repeat probabilities the patient has already mentioned] the exact survival probabilities… [pause] or could they be higher or lower for example?*"

Table 3 continued The frequency with which patients' alluded to aleatory and epistemic uncertainty during the Standard Interview (N (col%))

	Open probe [a, b] N=62 allusions N (col%)	*Imprecision probe* [a, c] N=178 allusions N (col%)	*Example quotes*
Allusions to aleatory uncertainty			
Inability to predict single events	15 (24)	15 (8)	"It's just statistics, so you could also be one of the 7 in 100 that does get sick again." "If I don't do the endocrine therapy I have a greater chance that it [the cancer] will come back. But just the same, it might also never come back." "It could definitely just as well be 16% or 18% [the survival probabilities]. He can't categorically say that I am completely clean after the chemotherapy"
It's all or nothing	0	3 (2)	"I think I have two probabilities, either it comes back or it doesn't. The chance for either outcome is shown with percentages and those percentages are all averages, and not about me as an individual. They [the survival probabilities] might be true statistically, but as an individual you either get sick or you don't…"
There are no guarantees in life	22 (35)	22 (12)	"One could undergo everything [surgery and all adjuvant treatments] and it [the cancer] could still come back. They really stress that. There never are any guarantees…"
It's a lottery	0	1 (<1)	"…You never know, life's like a big slot machine… it remains a lottery."
General remarks on uncertainty	15 (24)	26 (15)	"*… It's just statistics*"

[a]= Rows do not add up to the number of patients to whom we posed the probe, because some patient's answers contained multiple elements. The percentages reflect how many patients said something about each specific element.
[b] = Open probe was: "*What do the probabilities [repeat probabilities the patient has already mentioned] mean to you?*"
[c] = Imprecision probe was: "*In your opinion, are the probabilities you were provided with during the consultation [repeat probabilities the patient has already mentioned] the exact survival probabilities… [pause] or could they be higher or lower for example?*"

Discussion

We investigated whether and which type of uncertainty oncologists disclose during consultations and explored patients' perceptions of the uncertainty associated with the probabilities discussed during their consultation. Additionally, we queried oncologists about their willingness to discuss uncertainty, and their practice in this regard. We found that communication of uncertainty is limited. First, oncologists talked about uncertainty in only half of the consultations. Second, if they did discuss uncertainty, oncologists infrequently discussed the imprecision of the risk estimates (epistemic or 2nd-order uncertainty), despite its potential relevance in the context of risk estimates produced by prediction models. Furthermore, the discussions that did occur most often consisted of vague allusions to imprecision. If oncologists referred to uncertainty, it was mostly (4 out of 5) an allusion to the unpredictability of single events (aleatory or 1st-order uncertainty).

The focus on disclosure of the unpredictability of single events may not be surprising as this type of uncertainty ('aleatory uncertainty') is relatively straightforward to discuss and comprehend. People are generally aware of the unpredictability of future events. Conversely, comprehending epistemic uncertainty (i.e. uncertainty about the precision of the risk estimates and their applicability to a specific patient) requires insight into the nature of probability and the origin of probability estimates. Clinicians may be hesitant to further complicate matters by bringing up a complex construct such as epistemic uncertainty bearing in mind that many people, even those highly educated, struggle to understand probabilistic information (1, 5). Moreover, the goal of discussing survival probabilities during consultations is to inform patients about their prognosis with and without adjuvant systemic treatment, and ultimately to help patients pass judgment about whether or not undergoing treatment is worthwhile (13). Clinicians may not want to undermine patients' confidence in probabilities by highlighting the limitations in their reliability or accuracy. Additionally, even if oncologists wish to discuss the imprecision of probabilities, this intent might be subverted by the fact that Adjuvant!, like other prediction models, does not provide such information. Perhaps due to the absence of information about precision, allusions to (im)precision were often somewhat vague.

Our study also shows that eliciting patients' perceptions of uncertainty is methodologically difficult. This may be due to the abstract nature of uncertainty. In addition, people may generally not give much thought to such uncertainty, possibly also for reasons of coping. As we interviewed patients shortly (within one week) after the consultation with their medical oncologist, it may have been difficult for them to delve too deeply into this topic. At the time of the consultation, they were still recuperating from surgery or undergoing radiotherapy. They may not have had the time to process all that happened to them recently and put it into perspective. Our questions may also have

caused anxiety by making patients aware of the fallibility of the probabilities guiding their treatment decisions. This posed a moral dilemma for the interviewers; they found themselves trying to find a balance between obtaining an answer to the research question and not distressing patients.

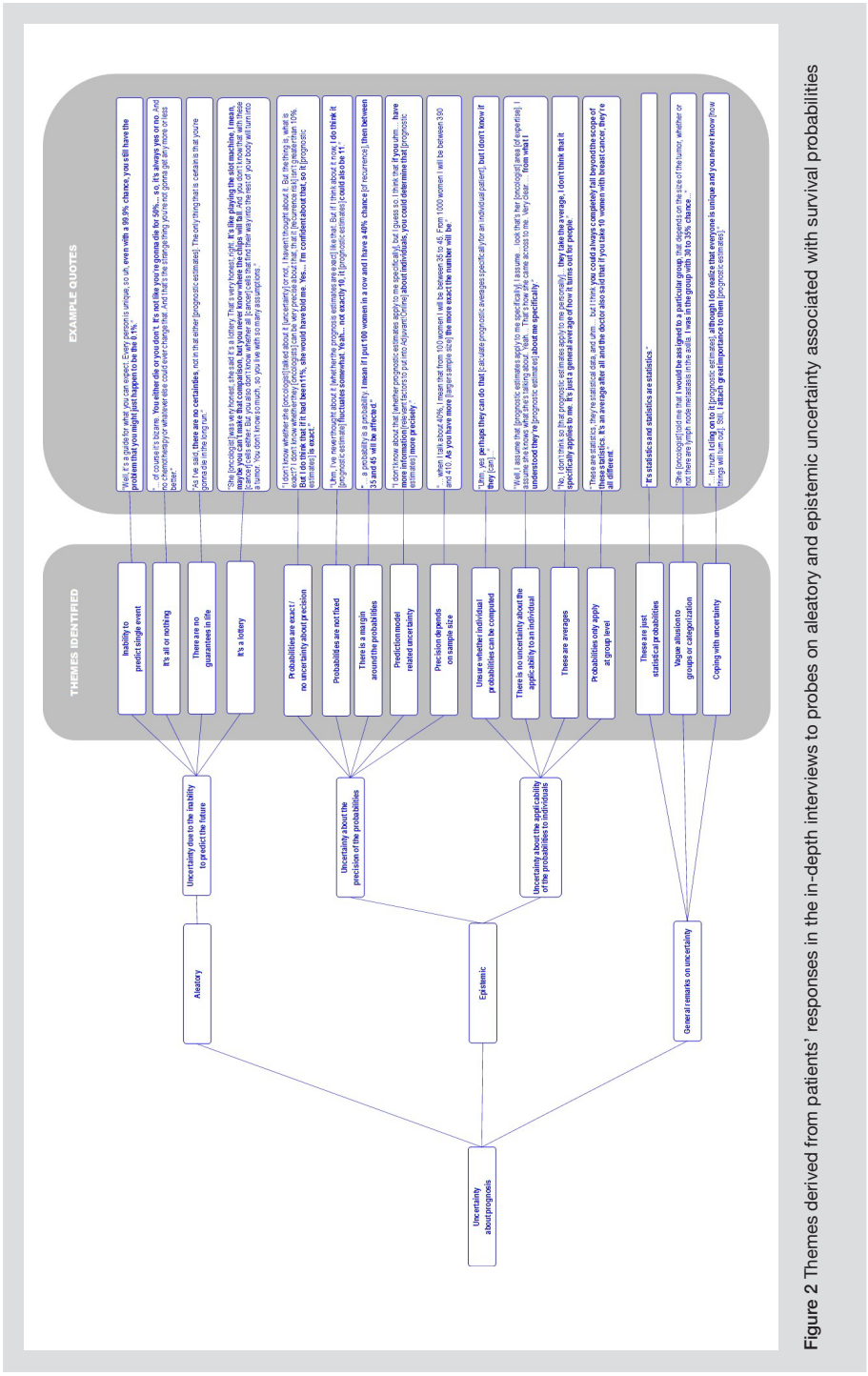

Figure 2 Themes derived from patients' responses in the in-depth interviews to probes on aleatory and epistemic uncertainty associated with survival probabilities

They dealt with this problem by dropping the probe if they perceived signs of apprehension in patients and then did not push the subject any further, even without having gotten a clear answer. This strategy limited the amount of information gained from the standard interviews and the potential inferences we can draw about patients' understanding of uncertainty. A deeper understanding requires probing much further in spite of patients' (perceived) apprehension. The face-to-face in-depth interviews were easier in this respect, but in those, we still ran into substantial incomprehension, perhaps mixed in with some apprehension and/or denial.

Patient A (61 years, highly numerate with stage II disease), her views on:

- **the certainty of the survival probabilities:**
"I cling to it [survival probability], whilst I secretly think, everyone is unique, so you never know. Yet, I still put a lot of… have a lot of faith in them [probabilities]"

- **the precision of the survival probabilities:**
"… uhm I've never thought about it [precision of probabilities]. But now I do think about it, I think it [the probability] does fluctuate a little. Yes, so not exactly 10, it could also be 11."

"… but I think it's more… what is precise? I don't know whether they [oncologists] can say it [survival probability] so precisely, that it's [survival probability] not greater than 10%. But I do think that if it had been 11% she would've told me. Yes… I'm confident about that, so it [survival probability] is exact."

"… on average it [survival probability] could also be higher. If you are in a group [with specific prognostic characteristics], you're in that group… and if you say that on average you have 10% chance of getting it [cancer] again… I'm not so good at this.... I don't think in terms of averages, because then it [10-year recurrence risk] could also be 5 or 15. I want to think about the 10% [recurrence risk after adjuvant treatment discussed during the consultation]."

- **whether her oncologist can predict her prognosis and to what extent available survival probabilities apply her personally:**
"I think so [it is possible to predict prognosis for an individual], but she [the oncologist] did not do it. She explained that I was in a certain group, but not everyone in that group is exactly the same… but an individual risk [estimate] might be possible. No no no, she based it [probabilities] on the group…"

"I do think she could have been more specific, but whether that would've been useful, a single percent [higher or lower on an individual level]. If you got your own percentage [survival probability] it could deviate from 10… a little bit. It wouldn't be far off."

Box 1 Example of answers during an in-depth interview

Patients seemed to struggle with information about uncertainty. This was most true for the imprecision in probability estimates (epistemic uncertainty), and least with the fundamental inability to predict individual futures (aleatory uncertainty). We observed many logical contradictions in patients' answers. In addition, if not specifically asked

about uncertainty, only about one in four referred to uncertainty, and three out of five of those utterances were allusions to the unpredictability of single events. Even when we specifically asked about the imprecision of risk estimates and their applicability to a specific patient, almost one in four utterances were allusions to the unpredictability of single events. It is unclear whether patients do not perceive epistemic uncertainty, or whether they did not understand what we were asking them. For example, when asked about imprecision, patients seemed to think that we were asking whether the probabilities were true – i.e., whether their oncologist had got them right or whether he/she had been truthful with them. They seemed unable to reconcile the thought that a probability can be correct and at the same time not be exact. These seemingly incompatible realities may account for some of the inconsistencies in patients' perceptions of uncertainty. Previous reviews have also identified a struggle to reconcile seemingly incompatible realities; in those cases, patients tried to reconcile the need to be fully informed about prognosis with not being overwhelmed with complex medical information (17, 18). Patients seem to use 'positive thinking', or even an element of denial in their recall of prognostic information (19, 20). Perhaps such coping strategies also play a role here, which may at least partly explain the logical inconsistencies we observed.

Most patients seem to realize that the unpredictability of single events is inherent to probabilities, but across education and numeracy levels they do place value on probability information. These probabilities seem to satisfy patients' need to have some sense of certainty to cling to (e.g., "*I attach a lot of value [to the probabilities] ... in truth, I cling to them [probabilities], even though I think to myself, everyone is unique…*"). Patients seem to perceive the unpredictability of single events as an inevitable part of life (e.g., "*…there are no guarantees in life, not with this [cancer]… not with anything.*"), but uncertainty about the precision of the risk estimates and their applicability may be more challenging to cope with. Acknowledging this type of uncertainty may undermine the sense of security some patients seem to derive from the probabilities communicated during the consultation (e.g., "*I don't think in terms of averages, because then it [10-year recurrence risk] could also be 5 or 15. I want to think about the 10% recurrence risk after adjuvant treatment discussed during the consultation*"). Conversely, it has been suggested that if explicit prognostic information, including its associated uncertainty, is coupled with appropriate emotional support it could be a way of decreasing anxiety, generating greater self-efficacy and ultimately achieving a better quality of life (21). Research is needed to investigate whether this approach is effective in the curative setting.

This is the first study to investigate disclosure of uncertainty during real-time consultations, and to explore perceptions of uncertainty in a large sample of patients. Currently, it is increasingly common for clinicians to discuss probabilities during consultations with patients. Whether disclosure of uncertainty should be part of risk communication or

not, however, is a matter of debate. This debate has so far been based on ethical and/or practical concerns. The available evidence is limited and most work in this area has been experimental or focused on healthy subjects' perceptions of uncertainty (e.g., (2)). Therefore, although informative, the currently available evidence might not be the best indication of how actual patients, especially those facing a potentially life-threatening illness, perceive and understand information about uncertainty.

We did not assess whether uncertainty was communicated during consultations in which prognostic estimates were not communicated. The current debate revolves around whether the uncertainty surrounding risk estimates (e.g., survival estimates) should be communicated whenever these risk estimates are communicated to patients. Therefore, we opted to focus on consultations in which prognostic estimates had been discussed. Further, in the consultations in which no prognostic estimates were discussed, oncologists can only have discussed aleatory uncertainty.

Our study showed that there is wide variability in the communication of uncertainty, and that clarity is often lacking. Oncologists infrequently fully inform their patients about uncertainty around the probabilities given. This is especially true for the uncertainty concerning precision and applicability to individuals. When communicated, such information turns out to be difficult to understand. If clinicians wish patients to become aware of this type of uncertainty, its inherent complexity makes it imperative that such information be presented in a clear manner. Otherwise, the meaning behind clinicians' statements is likely to be lost on most patients. Witteman *et al.* developed pictographs with animated random dispersal of risk events, and the effect of such pictographs has been evaluated in healthy subjects (22, 23). Such visual display formats could facilitate communication about uncertainty, and increase patient awareness of the random nature of probabilities. However, no clear guidance exists today on how best to inform patients about uncertainty, more research is needed. In the meantime, it is clear that it is important to raise awareness in communication skills training about the importance of clearly formulating information about uncertainty if oncologists choose to discuss it with patients. For now it seems that patients can grasp aleatory uncertainty, but have difficulty with epistemic uncertainty.

It was not our aim to assess whether or not there is a discrepancy between oncologists' perception about the frequency with which they disclose uncertainty and their actual disclosure. To answer this question, oncologists should be asked after each consultation whether or not they communicated uncertainty. Such a question could have predisposed oncologists to discuss uncertainty more often than they normally would have, hindering our aim, i.e., to observe what currently happened in clinical practice. It may be of value for future research to explore whether or not oncologists' perception about how often they disclose uncertainty is congruent with observed disclosure during consultations.

Oncologists might feel they communicated uncertainty, but for example the way they formulate this information is not clear or explicit enough. Indeed in the current study we found that especially communication about epistemic uncertainty was somewhat vague. Results of such studies may help shape communication training.

Interestingly, the moral dilemma we encountered while probing patients during the interviews is comparable to the difficulty oncologists face, trying to balance complete information provision and not causing unnecessary confusion and/or distress in patients, and not overwhelming them with too much information. If the problems we encountered during the interviews mainly arise from a lack of understanding, the focus of future research should be on how clinicians can best inform their patients about uncertainty. Alternatively, perhaps the most urgent question currently is whether uncertainty should be communicated at all. If indeed not paying attention to uncertainty may help patients to better cope with their disease, the imperative of autonomy and full disclosure may contradict that of well-being (24, 25). Our findings suggest that the question how to communicate the uncertainty of risk estimates may be secondary to the question whether patients benefit from such information. This dilemma deserves careful consideration in future research.

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Appendix A Interview protocol to explore patient awareness and perceptions about uncertainty

1. Open probe assessing patients' awareness of the uncertain nature of the prognostics estimates discussed if this is not brought up by the interviewer (= *open probe without priming*):
Open probe assessing patients' awareness of uncertainty associated with the survival estimates, without introducing the concept of uncertainty: What did you think about when you first heard these probabilities?

Then the interviewer explicitly stated that some of the questions that would next be posed might be a bit abstract and difficult. We made clear that we were in no way implying that she did not understand the information correctly or that her oncologist withheld information or provided her with incorrect information. We explained that we only wanted to know if she has ever thought about the following concepts and what her views are.

2. Probes for specific elements of uncertainty:

a. Open probe assessing patients' views on the certainty of the survival estimates, after introducing the concept of uncertainty (= certainty probe): We have just talked about the probabilities from ...[name source].. you had talked about with dr…. In your opinion, how certain are the risk estimates your doctor gave you? How much confidence or faith do you have in those probabilities?

b. Probe assessing patients' views on the precision of the risk estimates (= precision probe): How precise or exact do your risk estimates seem? [pause, allowing the patient room to respond] For example, do you think it's possible that your actual risk is higher or lower?

c. Probe assessing patients' views on their oncologist's ability to predict single events (= predicting future/applicability to individual probe):
- In your opinion, to what extent do you think your oncologist is able to predict your prognosis, for you as an individual?
- To what extent do you feel the risk estimates you discussed with your oncologist apply to you personally?

3. Probe to assess whether patients felt they had been informed about uncertainty:

a. We have talked at length about your views on how exact the probabilities you discussed with dr. … are and whether you think they apply to you personally. We were

keen to find out whether you had ever given it any thought and what your thoughts are on this subject. We would also like to know, did you discuss any of these issues with your oncologist?
b. If patient answers *yes*:
What did dr. … say about this?

Appendix Table 1 Overview of patients' characteristics, probes posed and themes discussed in the In-depth interviews																
Participant ID	**P11**	**P12**	**P13**	**P14**	**P15**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P31**	**P32**	**N**
Overview of probes that the interviewer posed[a]																
Open probes																
Without priming	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	15
With priming				x			x	x	x	x		x	x	x	x	9
Epistemic uncertainty																
Precision of the estimates	x	x			x		x	x	x	x		x	x	x	x	11
Applicability to individual probe	x			x			x	x	x		x	x	x	x	x	10
Aleatory uncertainty																
Predicting future events probe	x			x			x	x	x		x	x	x	x	x	10
Patient perception whether oncologist discussed uncertainty	x				x			x	x				x	x	x	7
Patient utterances about uncertainty made after the interviewer posed the *Open Probe*																
No utterances about uncertainty					x			x				x				3
Allusions to aleatory uncertainty																
Inability to predict single events	x			x			x		x		x			x		6
It's all or nothing		x												x		2
There are no guarantees in life			x				x			x				x	x	5

Abbreviations: N= number; X= yes
a= see Appendix 2 for the interview protocol

Appendix Table 1 continued Overview of patients' characteristics, probes posed and themes discussed in the In-depth interviews																
Participant ID	**P11**	**P12**	**P13**	**P14**	**P15**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P31**	**P32**	**N**
Patient utterances about uncertainty made after the interviewer posed the *Open Probe*																
It's a lottery				x												1
Allusions to epistemic uncertainty																
A. Precision of the estimates																
Estimates are exact – no uncertainty about precision						x										1
Estimates are not fixed																0
There is a margin around the estimates		x													x	2
Uncertainty associated with the model used to calculate probabilities																0
Precision depends on sample size															x	1
B. Applicability of the estimates to individuals																
Unsure whether individual probabilities can be computed																0
No uncertainty about the applicability to an individual																0
The probabilities are averages																0
Probabilities only apply at group level															x	1
Abbreviations: N= number; X= yes a= see Appendix 2 for the interview protocol																

Appendix Table 1 continued Overview of patients' characteristics, probes posed and themes discussed in the in-depth interviews																
Participant ID	**P11**	**P12**	**P13**	**P14**	**P15**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P31**	**P32**	**N**
Patients' utterances about uncertainty made after the interviewer posed the *Open Probe*																
General remarks about uncertainty																
These are just statistical probabilities	x	x							x				x			4
Vague allusion to group size or categorization													x			1
Coping with uncertainty				x										x		2
Patients' utterances about uncertainty made after the interviewer posed probes for specific elements of uncertainty																
Allusions to aleatory uncertainty																
Inability to predict single events	x	x		x			x	x	x				x		x	8
It's all or nothing		x														1
There are no guarantees in life				x			x	x		x			x			5
It's a lottery	x			x												2
Allusions to epistemic uncertainty																
A. Precision of the estimates																
Probabilities are exact - no uncertainty about precision							x	x	x			x	x	x		6
Estimates are not fixed	x	x						x					x		x	5
There is a margin around the estimates	x								x				x			4
Abbreviations: N= number; X= yes a= see Appendix 2 for the interview protocol																

Appendix Table 1 continued Overview of patients' characteristics, probes posed and themes discussed in the in-depth interviews																
Participant ID	**P11**	**P12**	**P13**	**P14**	**P15**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P31**	**P32**	**N**
Uncertainty associated with the model used				x										x		2
Precision depends on sample size															x	1
B. Applicability of the estimates to individuals																
Unsure whether individual probabilities can be computed				x												1
No uncertainty about the applicability to an individual				x			x		x			x	x	x		6
The estimates are averages	x			x					x		x	x	x			6
Estimates only apply at group level	x			x	x			x	x	x	x		x		x	9
Patients' utterances about uncertainty made after the interviewer posed probes for specific elements of uncertainty																
General remarks about uncertainty																
These are just statistical estimates	x		x	x			x	x	x							6
Vague allusion to group size or categorization	x						x	x								3
Coping with uncertainty			x													1
Patient indicated that uncertainty had been discussed by oncologist		x														1

Abbreviations: N= number; X= yes
a= see Appendix 2 for the interview protocol

Chapter 8

Use of implicit persuasion in decision-making about adjuvant cancer treatment: a potential barrier to shared decision-making

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Abstract

Background

Shared decision-making (SDM) is widely advocated, especially for preference-sensitive decisions like those on adjuvant treatment for early-stage cancer. Here decision-making involves a subjective trade-off between benefits and side-effects, and therefore patients' informed preferences should be taken into account. If clinicians consciously or unconsciously steer patients towards the option they think is in their patients' best interest (i.e., implicit persuasion), they may be unwittingly subverting their own efforts to implement SDM. We assessed the frequency of use of implicit persuasion during consultations, and whether the use of implicit persuasion was associated with expected treatment benefit, and/or decision-making.

Methods

Observational study design in which consecutive consultations about adjuvant systemic therapy with stage I-II breast cancer patients treated at oncology outpatient clinics of general teaching hospitals and university medical centers were audiotaped, transcribed and coded by two researchers independently.

Results

In total 105 patients (median age=59; range: 35-87 years) were included. A median of five (range: 2-10) implicitly persuasive behaviors were employed per consultation. The number of behaviors used did not differ by disease stage (P=0.07), but did differ by treatment option presented (P=0.002) and nodal status (P=0.01). About 50% of patients with stage I or node-negative disease were steered towards undergoing chemotherapy, whereas 96% of patients were steered towards undergoing endocrine therapy, irrespective of expected treatment benefit. Decisions were less often postponed if more implicit persuasion was used (P=0.03).

Interpretation

Oncologists frequently use implicit persuasion, steering patients towards the treatment option that they think is in their patients' best interest. Expected treatment benefit does not always seem to be the driving force behind implicit persuasion. Awareness of one's use of these steering behaviors during decision-making is a first step to help overcome the performance gap between advocating and implementing SDM.

Introduction

Shared decision-making (SDM) is broadly advocated as an ideal for clinical practice. It is especially relevant for so-called preference-sensitive decisions (1), for which there is no obvious 'best' treatment. Treatment choice then depends on a necessarily subjective trade-off between the benefits and side-effects of treatment alternatives. Therefore, patients' *informed* values and preferences should drive decision-making. The SDM process can be disrupted if the presentation of treatment options contains implicit value judgments, driven by clinicians' own assessment of whether the benefits outweigh the side-effects. When the presentation of evidence implicitly steers patients towards a particular choice, patients may get the erroneous impression that this is the only or 'best' option (i.e. implicit persuasion). Ziebland *et al.* showed such behaviors to be barriers to SDM, albeit without framing them as such (2). Karnieli-Miller and Eisikovits are, to the best of our knowledge, the only researchers who systematically analyzed the use of implicitly persuasive behaviors (3).

The current study describes a systematic assessment of the use of implicit persuasion in adjuvant systemic treatment in oncology. Chemotherapy and endocrine therapy for stage I-II breast cancer reduce the probability of disease recurrence, but the size of the benefit varies widely (generally between ˷3-10% benefit in terms of 10-year survival), depending on patient and tumor characteristics (e.g., tumor size, nodal status and Her2neu status). Yet, these treatments are associated with important short- and long-term side-effects, making the decision preference-sensitive (4-7). As it is impossible to predict which patients will benefit from undergoing treatment, international guidelines suggest to discuss adjuvant systemic treatment with patients if treatment minimally yields 3-5% absolute benefit in terms of overall mortality (8-12). This however also implies 95-97% overtreatment.

We investigated 1) whether and which implicitly persuasive behaviors oncologists use when discussing adjuvant systemic treatment for breast cancer overall and by treatment, 2) whether the frequency and/or direction of implicit steering is associated with expected treatment benefit, and 3) whether the use of implicitly persuasive behaviors is associated with reaching a decision and with the decision made.

Methods

Patient selection

The current study was embedded in a larger multicenter observational study assessing communication about adjuvant treatment. Consecutive female patients with stage I-III breast cancer, eligible to receive chemotherapy and/or endocrine therapy and fluent in Dutch, were invited to participate (72% response). All oncologists treating breast cancer patients at four participating general teaching and academic hospitals consented to participate in the main study.

For the current study, we selected a random sample of 105 consultations with stage I-II breast cancer patients available by February 2014. The study protocol was approved by the medical ethics boards of the participating hospitals.

Procedures and measures

After patients had provided written informed consent, the first consultation with their medical oncologist, in which chemotherapy and/or endocrine therapy was discussed, was audiotaped. All consultations were transcribed verbatim. Next, a coding scheme to code the use and direction of implicit steering was developed using the behaviors described by Karnieli-Miller and Eisikovits (3) as a starting point. All consultations were independently coded by two coders (EGE and AvdH), and discrepancies resolved through consensus (Appendix A describes the development of the coding scheme and coding procedures). We classified the implicitly persuasive behaviors into four overarching themes, namely, 1) *unbalanced presentation of benefits and side-effects*, 2) *presenting treatment recommendations as authorized decisions*, 3) *creating the illusion of decisional control*, and 4) *persuading patients using (clinical) experience* (Appendix Table 1 describes the behaviors coded).

Information on patients' education level and oncologists' age were collected using self-report questionnaires. Information on consultation characteristics were extracted from the transcripts of the consultations, namely: a) adjuvant treatment discussed, b) number of side-effects communicated, c) timing of decision-making (prior to, during the consultation, or postponed) and d) treatment choice. If the treatment decision was postponed, medical charts were consulted to determine treatment choice. Tumor characteristics (size, histological grade, nodal status, estrogen and Her2neu receptor status) were collected from medical records. Stage (based on Tumor Node Metastasis (TNM)) was based on the American Joint Committee on Cancer definition, 7th edition (13).

Statistical analysis

Descriptive analyses were performed. We report the frequency of use of the behaviors

per theme, overall and for chemotherapy and endocrine therapy separately. Fisher's Exact Tests for categorical variables were used to compare: a) the use of each implicitly persuasive behavior by treatment discussed, and b) the direction of the implicit steering by patient and tumor characteristics. When appropriate, Mann-Whitney and Kruskal-Wallis tests were used to make comparisons between the frequency with which implicitly persuasive behaviors were exhibited and a) TNM stage, b) nodal status and c) whether or not a decision was reached during the consultation. The congruence between the direction of implicit steering by oncologists (forego or undergo (neutral category excluded)) and treatment choice (forego or undergo) was computed for chemotherapy and endocrine therapy separately using Cohen's kappa (κ). Significance testing was done two-sided at $\alpha=0.05$. Analyses were performed in SPSS 20.

Results

Eighteen oncologists (56% male; mean age 51 years (range:34-66)) included 105 patients (see Table 1). Patients were on average 59 years (range:35-87) and 53% had stage I disease. In 71% of the consultations, both chemotherapy and endocrine therapy were discussed.

RQ1: use of specific implicitly persuasive behaviors, overall and by treatment
Overall, a median of five (range:2-10) implicitly persuasive behaviors were observed, and the number of behaviors used greatly varied between and within oncologists (Figure 1). More implicitly persuasive behaviors were used in consultations in which both chemotherapy and endocrine therapy (Md.=6.0) were discussed than in those where chemotherapy (Md.=4.0) or endocrine therapy (Md.=4.0) alone were discussed (P=0.001). There was variation in the overall use of implicitly persuasive behaviors as well as in which specific behaviors were used by the treatment under discussion (see Table 2). Below we report the frequency of use of the implicitly persuasive behaviors by theme, overall and for chemotherapy and endocrine therapy separately.

Theme 1: Unbalanced presentation of benefits and side-effects
In 81% (85/105) of consultations side-effects were underreported (fewer than five, see Appendix A for coding) (see Table 2). This was significantly more often the case for endocrine therapy (65/90 (72%)) than chemotherapy (47/90 (52%)) (P=0.009), irrespective of whether only endocrine therapy or endocrine therapy alongside chemotherapy was discussed (P=0.75). On average 2.6 (range: 0-9) endocrine therapy side-effects and 4.2 (range:0-13) chemotherapy side-effects were communicated.

Overall, side-effects were presented after the treatment decision was made in 67% (70/105) of consultations, more often in the case of endocrine therapy (59/90 (66%)) than in that of chemotherapy (32/90 (36% P<0.001). In the consultations where side-effects were communicated after the decision was made, decisions seemed to have been made prior to the consultation by the oncologist (and/or the multidisciplinary team) (chemotherapy=59% (19/32) and endocrine therapy=81% (48/59)), or the decision was made during the consultation after only discussing the expected benefits (chemotherapy=41% (13/32) and endocrine therapy=19% (11/59)).

In 51% (53/105) of consultations, oncologists emphasized patients' ability to minimize discomfort caused by the side-effects, especially for chemotherapy-related side-effects. The improvements in the ability to prevent/control chemotherapy-induced nausea were particularly stressed, as was the reversibility of severe side-effects (e.g., trastuzumab-induced cardiac failure, or chemotherapy-associated peripheral neuropathy).

Table 1 Patient, disease, oncologist and consultation characteristics	
	N (%)
Patient' characteristics (N=105)	
Mean age in years (range)	59 (35-87)
Education	
Low	11 (13)
Intermediate	49 (56)
High	28 (32)
Unknown	17
Oncologists' characteristics (N=18)	
Mean age in years (range)	51 (34-66)
Median number of patients included (range)	6 (1-18)
Male	10 (56)
Hospital	
General teaching	10 (56)
University medical center	8 (44)
Disease characteristic	
TNM Disease stage	
Stage I	55 (53)
Stage II	48 (47)
Unknown	2
Consultation characteristics	
Mean duration of consultations in minutes (range)	26 (9-64)
Which treatments discussed	
Chemotherapy only	15 (14)
Endocrine therapy only	15 (14)
Both	75 (71)
Decision made during consultation	
Decision postponed	12 (11)
Decision partly madea	10 (10)
Decision made	83 (79)
[a] When both chemotherapy and endocrine therapy had been discussed, a decision was made for only one of them; TNM= Tumor size – Nodal status – (presence of distant) Metastasis.	

Additionally, in 43% (45/105) of consultations the impact of treatment on patients' quality of life was minimized – more often for endocrine therapy (38 of 90 (42%)) than chemotherapy (8 of 90 (9%)) (P<0.001). Phrases used when talking about endocrine therapy were, e.g., "*It's just a little pill a day*" or "*Well, aspirin has side-effects too"*. Oncologists also emphasized how innocuous endocrine therapy is compared to chemotherapy.

Table 2 Overview of the use of the various implicit persuasion behaviors by treatment discussed (N (col%))

			If behavior was used, it alluded to b:		
		Overall N= 105	Chemotherapy a N= 90	Endocrine therapy N= 90	P*
Unbalanced presentation of benefits and side-effects	Minimal number of side-effects presented+	85 (81)	47 (52)	65 (72)	0.009
	Presenting the side-effects after the final treatment decision had been made+	70 (67)	32 (36)	59 (66)	<0.001
	Emphasizing the ability to control the side -effects of the treatment	53 (51)	45 (50)	9 (10)	<0.001
	Minimizing the treatment's impact+	45 (43)	8 (9)	38 (42)	<0.001
	Emphasizing the benefits or side-effects of treatment	41 (39)	30 (33)	28 (31)	0.873
Present treatment recommendations as authorized decisions	Presenting treatment as an authorized 'we' decision	87 (83)	59 (66)	51 (57)	0.284
	Presenting treatment as an authorized decision based on 'the guideline'	35 (33)	27 (30)	19 (21)	0.231
Creating the illusion of decisional control	The illusory power to decide	52 (50)	15 (17)	44 (49)	<0.001
	Having one treatment implicitly tag along with another+	28 (27)	0	28 (31)	<0.001
	From mild to serious treatment - a gradual decision	19 (18)	11 (12)	11 (12)	1
Persuading patients using (clinical) experience	Deterring vs. encouraging: using others as examples	10 (10)	9 (10)	1 (1)	0.018
	Giving the impression that undergoing or foregoing treatment is quite unusual+	10 (10)	7 (8)	3 (3)	0.330
	Making assertions about the patient's personality+	9 (9)	5 (6)	5 (6)	1
	Frightening patients about non-compliance	3 (3)	1 (1)	1 (1)	1
	Dramatizing the evil	1 (1)	1 (1)	0	1

col%= column percentage; + Persuasive behaviors added to the list originally coined by Karnieli-Miller *et al.* (3); [a]Treatment with trastuzumab was discussed in a small number of consultations, therefore implicit persuasion behaviors that alluded to treatment with trastuzumab, have been grouped under chemotherapy; [b] Numbers do not add up as some behaviors used in a consultation could allude to both chemotherapy and endocrine therapy or made in general (i.e. not specifically relating to either chemotherapy or endocrine therapy, but about treatment in general); * P-values for Fisher's exact test.

In 39% (41/105) of consultations either the benefits or harms of treatment were emphasized irrespective of which treatment was discussed, by repeatedly making statements such as: "*The benefits are truly substantial*", "*You cannot say that with treatment the disease will not return, but the probability it will, gets much, much smaller*" or "*Undergoing chemotherapy is serious overkill for such small benefits"* or "*Luckily you don't need chemotherapy, that's the good news… only endocrine therapy suffices*".

Theme 2: Presenting treatment recommendations as authorized decisions
In 83% (87/105) of consultations oncologists presented treatment as an authorized '*we*' decision, common wordings being: "*You would not be here, if we as a professional group, did not think that it* [the treatment] *is at least worth considering…*", "*In the Netherlands, we* [medical oncologists] *agree that…*". Overall, 35 explicit references to the guideline were made. No differences were seen between endocrine treatment and chemotherapy.

Theme 3: Creating the illusion of decisional control
The most important decision that needs to be made during these consultations is whether or not to start treatment. Yet in 50% (52/105) of consultations, the oncologist and/or the multidisciplinary team seemed to have unilaterally made the main treatment decision.

Patients were given the power to decide about secondary decisions, namely *when* to start or *whether or not to (dis)continue* endocrine therapy (49% (44/90) or chemotherapy (17% (15/90); (P<0.001)). For example: "*About the hormone tablets we often say to patients, just try it. The side-effects are really not so severe that you cannot handle them. And if you find that the hot flashes are really awful… then you can always stop and they will go away…"*. Overall, in 33% (30/90) of chemotherapy and 57% (51/90) of endocrine therapy consultations, decision-making seemed to have taken place prior to the consultation, and the aim of the consultation seemed to be to notify the patient of the treatment plan and not to decide about treatment, e.g.: "*You are here to talk about whether or not it is worthwhile to undergo chemotherapy, endocrine treatment we'll do anyway* ".

Table 3 Direction of implicit steering per treatment discussed by patient and tumor characteristics

	Chemotherapy direction of steering:				Endocrine therapy direction of steering:			
	Forego N_{col} = 19	Neutral# N_{col} = 15	Undergo N_{col} = 56	P*	Forego N_{col} = 0	Neutral# N_{col} = 4	Undergo N_{col} = 86	P*
Patient and tumor characteristics (N(row%))								
Age in years								
Younger than 50	1 (5)	2 (10)	17 (85)	0.048	0	1 (5)	19 (95)	1
Between 50 to 70	15 (24)	11 (18)	37 (59)		0	3 (5)	55 (95)	
Older than 70	3 (43)	2 (29)	2 (29)		0	0	12 (100)	
Stage								
Stage I	13 (28)	11 (23)	23 (49)	0.037	0	2 (4)	43 (96)	1
Stage II	6 (15)	4 (10)	31 (76)		0	2 (5)	41 (95)	
Missing	0	0	2		0	0	2	
Nodal status								
Node-negative	16 (27)	14 (23)	30 (50)	0.003	0	3 (5)	59 (95)	1
Node-positive	3 (10)	1 (3)	25 (86)		0	1 (4)	26 (96)	
Missing	0	0	1		0	0	1	
Tumor grade								
Grade 1	2 (20)	1 (10)	7 (70)	0.005	0	0	12 (100)	1
Grade 2	15 (33)	9 (20)	21 (47)		0	3 (6)	51 (94)	
Grade 3	1 (3)	5 (15)	27 (82)		0	1 (4)	22 (96)	
Missing	1	0	1		0	0	1	
Estrogen receptor status								
ER negative	2 (12)	0	14 (88)	0.050	0	0	0	1
ER positive	17 (23)	15 (20)	42 (57)		0	4 (4)	86 (96)	
Her2neu receptor status								
Negative	19 (24)	14 (18)	45 (58)	0.076	0	4 (5)	76 (95)	1
Positive	0	1 (8)	11 (92)		0	0	10 (100)	

Ncol= total number of patients in the column.; row%= row percentage; Missing category was excluded from pertinent analysis; Stage= TNM stage (13); Grade = Bloom-Richardson grading system; # Neutral means that if a technique was used, it did not clearly steer either towards foregoing or undergoing treatment (e.g., a consultation in which only a reference to the guideline was made); * P-values for Fisher's exact test.

In 31% (28/90) of consultations endocrine therapy implicitly tagged along with chemotherapy, with patients agreeing to both treatments while only chemotherapy had been discussed. Also, in 18% of consultations (19/105) it was emphasized that the proposed treatment is milder than the 'standard' treatment. For example, "*…given that you are older, we would not go for the toughest regimen, the six courses. We would give you four courses* [of chemotherapy] *instead…"*.

Theme 4: Persuading patients using (clinical) experience

Behaviors in this category were observed in ≤10% of consultations. The most frequently

observed behaviors were a) deterring vs. encouraging: using others as examples (10/105 (10%)) (e.g., "*In my experience most patients get through the chemotherapy quite well nowadays, it's not like shown in movies, people spending the whole day hunched over the toilet*…"), and b) giving the impression that undergoing or foregoing treatment is quite unusual (e.g., "*It's unheard for patients with these disease characteristics to forego treatment*…").

RQ2: association of frequency and direction of implicit persuasion with expected treatment benefit

We did not find a significant difference in the number of of implicitly persuasive behaviors used between patients with stage I (Md.=5.0; range: 2-10) vs. those with stage II disease (Md.=5.5; range: 2-10) (P=0.07). Nodal status was significantly associated with the number of implicitly persuasive behaviors observed (N+ Md.=6.0 (range: 2-10) vs. N0 Md.=5.0 (range: 2-10); P=0.01).

For chemotherapy more patients with stage II (76% (31/41)) or node-positive (86% (25/29)) disease were steered towards undergoing treatment than those with stage I (49% (23/47)) or node-negative (50% (30/60)) disease (Table 3). For endocrine therapy, 96% (86/90) of patients were steered towards undergoing treatment, irrespective of prognostic factors.

RQ3: association of implicit persuasion with decision-making

More implicitly persuasive behaviors were observed if the treatment decision was made (Md.=5.0; range: 2-10) or partly made (Md.=6.5; range: 3-10), than if the decision was postponed (Md.=3.5; range: 2-9) (P=0.03). There was congruence between the direction of implicit steering and the final treatment choice (chemotherapy κ=0.7 (95%-CI: 0.5-0.9) and endocrine therapy κ=0.8 (95%-CI: 0.7-0.9)). Overall, 89% (50/56) of patients steered towards undergoing chemotherapy consented to undergoing chemotherapy, and, 84% (16/19) of patients who were steered towards foregoing chemotherapy, consented to foregoing treatment. Similarly, 95% (82/86) of patients steered towards undergoing endocrine therapy, consented to undergoing treatment.

Discussion

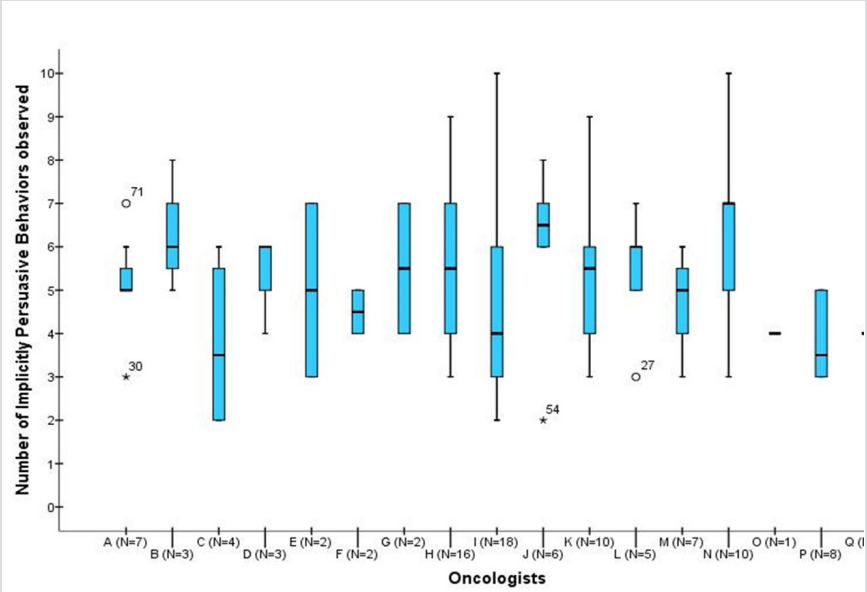
We investigated *whether* and *how often* oncologists exhibit implicitly persuasive behaviors overall and by treatment discussed, and whether the use of these behaviors was associated with expected treatment benefit, and reaching a decision during the consultation. Oncologists exhibited implicitly persuasive behaviors in all 105 consultations analyzed. These behaviors seemed aimed at steering patients towards the treatment option the clinician favored. This is noteworthy, as we focused on decisions where there is no clear-cut 'best' option, thus decision-making should be guided by the patient's *informed* preferences. Yet, for patients to develop *informed* preferences, the presentation of the treatment options has to be free of implicit value judgments.

How many and which behaviors are used depended on the treatment discussed. Behaviors used when discussing chemotherapy entailed an unbalance presentation of benefits and side-effects. Chemotherapy is well-known to patients and its impact is generally feared. The tendency to stress the benefits and/or emphasize that patients are well-capable of controlling the side-effects may be an understandable attempt to correct potential misconceptions and balance patients' perceptions about treatment. However, if overdone this may cause patients to make a decision based on unrealistic expectations, or it may create the erroneous perception of a 'best' or only choice.

Endocrine therapy was consistently presented as a *standard* treatment for hormone-sensitive tumors, implying that there is no choice. However, given that 53% of the patients in this population had stage I disease and 69% had node-negative disease, foregoing treatment would often have been a viable option to present. Endocrine therapy was also consistently framed as a 'walk in the park', especially compared to chemotherapy. In four out of ten consultations the impact of endocrine therapy was minimized, potentially causing patients to underestimate the impact of treatment. Consequently, patients might opt to discontinue treatment sooner if the side-effects are more severe than they expected. Although endocrine therapy side-effects may be relatively mild, a substantial number of women find them burdensome.(14) Coping with those 'mild' side-effects may constitute an unsustainable long-term burden. Indeed, ~40-50% discontinuation rates of endocrine therapy are reported (15-18). The reported discontinuation rates for chemotherapy are lower (~12%) (19).

A worrisome finding is that in two-thirds of all consultations, a treatment decision was made before the patient received information on the side-effects, thus without the patient being afforded the opportunity to weigh the benefits against the side-effects. It appears that the final decision was driven mainly, if not solely, by the expected benefits of treatment. Hence, in a large proportion of consultations an essential premise of SDM was not met. Interestingly, a large proportion of treatment decisions seemed to have

been made unilaterally by clinicians *prior* to the consultation. This is a puzzling observation, given that three out of four patients wanted to be involved in decision-making and seven out of ten oncologists indicated that they favored involving their patients in decision-making (data not shown). Perhaps SDM took place during the post-operative consultation with the surgeon. However, this seems unlikely, as adjuvant systemic treatment decisions are the domain of medical oncologists. From our own and others' research we know that in the field of surgery, little patient involvement is seen (20, 21). More likely, the *recommendation* of the multidisciplinary team meeting was presented to the patient as a *decision* (22).



Bars show the range of implicitly persuasive behaviors used by individual oncologists, and the median number of implicitly persuasive behaviors used is indicated.
Between brackets on the x-axis the number of patients each oncologist contributed to these analysis is indicated.

Figure 1 Use of implicit persuasion behaviors within and between oncologists

We did not find a strong association between expected benefit and the use of implicitly persuasive behaviors. For chemotherapy there was more steering towards undergoing treatment in patients with a worse prognosis, but still half of the stage I and node-negative patients were steered towards undergoing treatment. For endocrine therapy steering was always towards undergoing treatment. These findings are surprising, as

in a survey Dutch medical oncologists indicated that between 6-10% absolute survival gain is the minimal percentage benefit that offsets the potential side-effects of systemic therapy (23). Yet, oncologists still steered patients for whom the potential absolute survival gain was <6% towards undergoing treatment.

More implicitly persuasive behaviors were observed in consultations were a decision was made, than in those in which decision-making was postponed. The direction of steering was also congruent with the treatment decision in over 80% of consultations. It can be argued that implicit persuasion need not impede patients' choosing the option that best suits them, however, this argument relies on the assumption that patients' preferences are known. Yet, oncologists' only explored patients' endocrine therapy preferences in a quarter of consultations, and chemotherapy preferences were explored with four in ten patients considering treatment (data not shown). Similar findings have been reported in the literature (21, 24).

This study is the first to systematically investigate the use of implicit persuasion during consultations about adjuvant systemic treatment in cancer. In a similar vein in pancreatic cancer, oncologists impeded patients from foregoing treatment by presenting investigations into the feasibility of surgery as an assessment of whether patients '*qualified* for surgery', instead of presenting surgery as an option to be considered (2). Patients who 'qualified' for surgery subsequently failed to realize that they had a choice, as surgery was presented as 'a win' (2). Note that our study has some limitations. We audiotaped the consultations, and therefore, could not explore non-verbal cues. Also, in some subgroups the number of patients was small.

It is perhaps not surprising, that implicitly persuasive behaviors are frequently exhibited during consultations in the current setting, given that these decisions involve a difficult trade-off between the chances of preventing metastasis and death and those of side-effects associated with treatment. Adding to the difficulty is the timing. Patients barely have had time to process the diagnosis and recuperate from surgery, when they have to decide about the next step in the treatment process. It is thus understandable that some patients feel overwhelmed and incapable of making a treatment decision. Oncologists' desire to help their patients by consciously or unconsciously steering them towards the option they believe is in their patients' best interest is understandable and even commendable. Indeed, the utterances made by oncologists were often attempts to comfort and reassure patients or assuage any perceived decisional conflict. However, if oncologists wish to stimulate patient participation in decision-making and decisions to be the result of a shared process, employing these behaviors undermines this intent. In order to truly make strides in the implementation of SDM in clinical practice, the regular use of implicit persuasion deserves careful consideration in further research. Additionally, clinical education programs (at both pre- and postgraduate level) need

to address this issue to create awareness, and provide clinicians with tools to help patients share in the decision-making process.

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Appendix A Additional information on the methods applied

Development of coding scheme

For the current study we used the list of implicitly persuasive behaviors coined by Karnieli-Miller and Eisikovits(3) as a starting point. As Karnieli-Miller and Eisikovits had analyzed diagnostic disclosure consultations by pediatric gastroenterologists, we used our first 35 consultations to translate the original behaviors to the oncological setting and to identify additional behaviors. We (EGE, AvdH, AHP and AMS) identified new implicitly persuasive behaviors, namely: 1) selectively presenting the side-effects of treatment, 2) giving the impression that undergoing or refusing treatment is quite unusual, 3) having one treatment implicitly tag along with another, 4) presenting the side effects after the final treatment decision had been made, 5) minimizing the treatment's impact, 6) making assertions about the patients' personality, and 7) presenting treatment as an authorized decision based on 'the guideline'. Additionally, we adapted one of the behaviors described by Karnieli-Miller and Eisikovits. We felt that 'emphasizing the benefits of treatment and frightening patients about non-compliance' were two separate behaviors and thus coded them separately. We also extended 'emphasizing the benefits of treatment' to incorporate steering by placing emphasis on the side-effects of treatment. One behavior described by Karnieli-Miller and Eisikovits was not coded, namely 'Trying to avoid offering other treatment alternatives'. This could have been relevant for elderly (70 years and older) patients, for whom chemotherapy (in a lighter form, 4 instead of 6 courses for example) may be a realistic alternative to 5-years of endocrine treatment, if the patient is physically able to cope with the chemotherapy. However, this option was never discussed with patients unless endocrine treatment was not an option (ER-negative disease), which is in line with current guidelines.

Descriptions of the 15 behaviors included in the final coding scheme can be found in Appendix Table 1.

Coding procedures

Coding implicitly steering behaviors

Two coders independently coded transcripts of all included consultations. If after coding we found discrepancies in coding, the coders reviewed the transcript together and resolved the discrepancies through consensus. After coding the first 35 consultations, the agreement between coders varied for the various behaviors between 43-97%, with the most disagreements about the behavior *emphasizing the benefits or side-effects of treatment* (43% agreement). For all other behaviors agreement was more than 70%. After coding the first 35 consultations we did not identify new implicitly persuasive behaviors. However, we did encounter new examples of behaviors already included in the coding scheme. After consensus we included these examples into our definition and all the consultations that had been coded up to that point were analyzed again

to see if we previously had not missed the newly identified example of a behavior in the coding scheme.

Categorization of implicitly persuasive behaviors

After all the consultations had been coded (as at that point no new behaviors could be identified) the implicitly persuasive behaviors were grouped into categories for presentation purposes, namely: a) unbalanced presentation of benefits and side-effects, b) presenting treatment recommendations as authorized decisions, c) creating the illusion of decisional control and d) persuading patients using (clinical) experience. As both chemotherapy and endocrine therapy have numerous side-effects that can significantly impact patients' quality of life, we chose an arbitrary cut-off of five side-effects as a proxy for balanced communication about side-effects. Two coders independently devised categories to divide the 15 behaviors in the final coding scheme into. Afterwards they compared the categories they had created and decided on the final categorization through consensus.

Coding direction of steering

We also assessed the direction of the steering observed during consultations, i.e., whether the oncologist was steering the patient towards *undergoing* or *foregoing* treatment. We coded this after we had achieved consensus about which implicitly steering behavior had been used and had finalized the coding of these behaviors. Coding of the direction of steering is based on the coders' impression after analyzing the consultations for use of implicit steering. We coded the direction of steering as 'neutral' when the technique(s) used did not clearly steer either towards foregoing or undergoing treatment (e.g., a consultation in which only a reference to the guideline was made). Two coders coded the direction of steering for 20/105 consultations, afterwards the congruence in coding between the coders was computed for chemotherapy and endocrine therapy decisions separately, using Cohen's kappa (κ). This resulted for chemotherapy decision in $\kappa=0.80$ and for endocrine therapy decisions in $\kappa=0.85$. As congruence was good, from that point on one coder coded the direction of steering. If the coder was in doubt about the direction of steering, she asked the other coder to independently review the transcript and direction of steering was determined through consensus.

Appendix Table 1 Coding scheme implicit persuasion behaviors

Category	Behaviors	Description	Behavior used?
Unbalanced presentation of benefits and side-effects	Minimal number of side-effects presented+	Fewer than five side-effects were communicated about chemotherapy and endocrine therapy respectively. Often if the oncologist only focuses on the most common and least threatening side-effects.	□ No □Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	Emphasizing the benefits or side-effects of treatment+	The oncologist either emphasizes the magnitude of the treatment effect and minimizes the side-effects or vice versa.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	Minimizing the treatment's impact+	The oncologist downplays the impact of treatment, for example: "*Endocrine therapy is a relatively innocuous treatment, you just have to take a little tablet everyday… besides even aspirin has side-effects*".	□ No □ Yes, and alluded to: □ Chemotherapy □ Herceptin □ Endocrine therapy
	Emphasizing the ability to control the side-effects of the treatment	The oncologist emphasizes that he/she and/or the patient is able to control and oversee the side-effects of treatment. In order to combat chemotherapy-induced nausea, for example all the patient needs to do is ask and the dosage of anti-emetics can be increased or other anti-emetics could be tried.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	Presenting the side-effects after the final treatment decision has been made+	The oncologist presents the side-effects of treatment after a decision on whether to start treatment or not was made.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
Presenting treatment recommendations as authorized decisions	Presenting treatment as an authorized decision based on 'the guideline'	The oncologist presents the treatment as an authorized decision based on guideline recommendation for patients with her personal (e.g., age) and/or disease characteristics (e.g. tumor size or nodal status).	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	Presenting treatment as an authorized 'we' decision	The oncologist presents the treatment as an authorized decision based on consensus amongst experts, "*We are in favor of…*".	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy □ Treatment in general

+ Persuasive behavior adapted from or added to the list originally coined by Karnieli-Miller *et al.* (3)

Appendix Table 1 continued Coding scheme implicit persuasion behaviors

Category	Behaviors	Description	Behavior used?
Creating the illusion of decisional control	From mild to serious treatment - a gradual decision+	The oncologist presents the various treatment strategies in such a way that the proposed course of treatment seems to be the least aggressive or invasive and consequently more appealing. For example: "*In your case we propose a four-course chemotherapy regime instead of the standard six-course regime, which only yields slightly less disease-free survival gain but is easier pull through*".	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	Having one treatment implicitly tag along with another+	The oncologist presents the combination of chemotherapy and endocrine therapy as a "package deal". He/she focusses on chemotherapy during the consultation and implicitly assumes that by agreeing to start chemotherapy, the patient is agreeing to undergo the whole treatment package, although endocrine therapy was not (extensively) discussed.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	The illusory power to decide	The oncologist for example decides that endocrine therapy will be started, which is the main treatment decision that needed to be made. However, the patient is told that she could always decide to terminate treatment if the side-effects become too much to bare. Thus the actual decision – *to start treatment or not* – is made by the oncologist, and by leaving the decision on when and whether or not to terminate treatment in the patients' hands, the illusion is created that treatment decision-making was shared or even patient-driven.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
Persuading patients using (clinical) experience	Dramatizing the evil	The oncologist emphasizes the seriousness of the diagnosis and the potential negative implications of the disease, especially if the patient foregoes adjuvant treatment, before presenting the treatment options.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy □ Treatment in general
	Frightening patients about non-compliance+	The oncologist stresses what could go wrong if the patient does not comply with the recommended course of treatment, i.e. foregoes treatment against medical advice or does not take the treatment in the dosage and intervals prescribed.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	Making assertions about the patients' personality+	The oncologist makes assertions about what the patient could or could not handle, her ability to persevere and priorities in life, to steer her towards undergoing or foregoing treatment.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	Deterring vs. encouraging: using others as examples	The oncologist uses other patients' frightening or hopeful stories as examples to convince patients to choose the course of treatment favored by the oncologist.	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy
	Giving the impression that undergoing or foregoing treatment is quite unusual+	The oncologist emphasizes that it is very unusual for patients like yourself to undergo or forego treatment, e.g.: "*It is unheard of for patients with HER2-positive disease like you to forego chemotherapy and trastuzumab*"	□ No □ Yes, and alluded to: □ Chemotherapy □ Endocrine therapy

+ Persuasive behavior adapted from or added to the list originally coined by Karnieli-Miller *et al.* (3)

Part V

General discussion

Summary and discussion

This thesis contains studies that provide new insights in how breast cancer patients are informed about the benefits and side-effects of adjuvant systemic treatment, with a particular emphasis on the use of prediction tools in the information provision process. Of available prediction tools, Adjuvant! is arguably the best known worldwide. Its use is recommended by several (inter)national guidelines (e.g., British NICE (1), American National Comprehensive Cancer Network (2) and the Dutch national treatment guidelines (3)). Therefore, in this project Adjuvant! (4) is the common thread between the various studies.

From the work contained in this thesis, seven key findings can be distilled, namely:

I.	Many prediction tools are available to aid adjuvant systemic treatment decision-making, however, they require either further calibration and/or broad validation	(Chapter 2 and 3)
II.	Medical oncologists set higher thresholds for considering adjuvant systemic treatment worthwhile compared to the thresholds used in clinical guidelines	(Chapter 4)
III.	Adjuvant! is regularly used by medical oncologists to inform patients about their prognosis and the potential treatment benefit	(Chapter 5 and 6)
IV.	In spite of reservations about the robustness of Adjuvant!'s relapse estimates, medical oncologists usually only communicate the relapse probabilities to patients	(Chapter 6)
V.	The uncertainty associated with Adjuvant!'s estimates is not always communicated, and patients struggle with the concept of epistemic uncertainty	(Chapter 5 and 7)
VI.	The suboptimal information provision about treatment side-effects during consultations suggests that adjuvant systemic treatment decisions are mainly driven by the potential treatment benefits	(Chapter 6)

VII. In spite of the lack of a 'best' treatment option, medical oncologists use implicit persuasion to steer patients towards the treatment option they deem in their patients' best interest (Chapter 8)

Below these seven key findings are discussed. The buildup of the discussion for each key finding is as follows: first, the key finding is described; thereafter follows a reflection on the significance of our finding in the context of available literature and/or clinical practice and our thoughts on future directions.

I. Many prediction tools are available to aid adjuvant systemic treatment decision-making; however, they require either further calibration and/or broad validation (Chapter 2 and 3)

Summary
We conducted a systematic review of published prediction tools to help decision-making about adjuvant systemic treatment for early-stage breast cancer (Chapter 2). We identified 20 prediction tools developed to primarily aid medical oncologists' clinical decision-making. Even though the development study of many of these tools reported that their discriminatory accuracy was good, many have not undergone broad external validations and recalibration if needed, or widespread implementation in clinical practice. Exceptions are Adjuvant! (4), PREDICT (5), Nottingham Prognostic Index (6), and tools based on bio-molecular profiles, most notably Oncotype Dx (7) and MammaPrint (8). Our review suggests that Oncotype Dx and MammaPrint are able to accurately discriminate between patients with high vs. low risk of recurrences. Generally, in validation studies, Adjuvant!'s estimates seem reasonably sound in the whole study population. However, review of the studies reporting validations of Adjuvant! shows that its relapse probabilities are less reliable than its mortality estimates, and shortcomings in the model's discriminative ability and calibration in young (<40 years) and elderly patients (>70 years) were reported.

Further, Adjuvant! and MammaPrint can be used all over the world, but they have mainly been validated in North American and European patient populations (Chapter 2). The validation studies we reviewed in Chapter 2 suggest that Adjuvant!'s estimates and MammaPrint's classification of patients into risk categories might be less accurate in Asian populations. Evidence on the performance of other tools in non-western populations is limited.

Also, none of the tools we identified in Chapter 2 provide insights in both the benefits and harms of treatment. All of them solely focused on disease-free, all-cause and/or breast cancer specific survival. We also assessed the readability of the output of

available prediction tools (Chapter 2). We found that the output regularly contained complex bio-medical jargon that was not explained in laymen terms.

In Chapter 3 we assessed the discriminative ability and calibration of Adjuvant! and PREDICT's all-cause mortality estimates for patients younger than 50 years at diagnosis. We found that the discriminatory accuracy of both tools was poor to moderate, and calibration was poor in the extremes (i.e., for patients with the best and those with the poorest prognosis). The magnitude of Adjuvant!'s and PREDICT's underestimations of all-cause mortality was smaller than what had been reported in previous studies (differences of up to 35% between observed and predicted mortality), but both tools tended to underestimate all-cause mortality for patients younger than 40 years (range underestimation: 6.0 to 6.6%).

In conclusion, many prediction tools have been developed to predict survival with/without adjuvant systemic therapy for early-stage breast cancer. However, most have not undergone broad validation. Those for which there is more evidence on their performance, need to be recalibrated to improve their performance in multiple populations, e.g., patients younger than 50 years and those older than 70 years at diagnosis, and patients in Asian populations.

Reflections and Future Directions

Numerous prediction tools are available to aid decision-making about adjuvant systemic therapy for breast cancer. These tools only focus on one side of the trade-off between benefits and harms involved in decision-making about adjuvant systemic therapy, namely survival probabilities. Thus, if medical oncologists do not provide patients with balanced information about the side-effects, decision-making will be mainly driven by the treatment benefits.

An important element that is often missing, even for tools that have been validated more extensively and have seemingly found their way into clinical practice, is an impact analysis. As described by Reilly *et al.* (9), an impact analysis consists of four assessments, namely: 1) did the decision rule lead to the intended effect on patient care (e.g., reduce chemotherapy uptake); 2) was the observed impact greater or less than the expected impact; 3) was the accuracy of the tool preserved; and 4) did modification of the tool itself or its target population impact its accuracy (9). Adopting these steps could elevate the development of prediction tools to more than merely scientific endeavors. Recently published prospective studies (i.e., TAILORx (10) and MINDACT (11)) reported that for specific patient populations Oncotype Dx and MammaPrint can be used to safely select patients that can forego adjuvant chemotherapy. Prospective studies are rare, as they are difficult to carry out in clinical practice. Additionally, Oncotype Dx and MammaPrint provide a clear advice – i.e., low risk means chemotherapy can be fore-

gone. However, for tools such as Adjuvant! and PREDICT it is difficult to provide such advice. Additionally, they arguably do not aim to provide strong directives on whether or not to undergo treatment, but to inform clinicians and patients, and thereby help them decide whether they feel the treatment benefits are worthwhile. A randomized controlled trial showed that patients receiving Adjuvant! estimates did decide to forego treatment more often than those who did not (12). Such work suggests that Adjuvant! does influence the treatment preferences and final treatment decisions.

When we zoomed in on Adjuvant!'s calibration and discriminative ability, we found that Adjuvant!'s relapse probabilities are less accurate than its mortality estimates (as discussed in Chapter 2) (13,14). This can in part be attributed to the fact that the model does not distinguish between loco-regional and distant metastases. Until these estimates are updated and there is evidence that they are accurate, clinicians need to be careful if they decide to use them. A factor complicating clinicians' ability to somewhat gauge the precision of these estimates is Adjuvant! (like many other prediction tools) does not provide the confidence interval around its estimates. Given the limitations identified, it could be argued that perhaps clinicians should refrain from communicating the relapse probabilities to patients, in any case to the subgroups of patients where the largest over- and/or underestimations have been reported (e.g., patients < 50 years and those > 70 years at diagnosis). Further, Adjuvant! and PREDICT's breast cancer specific and/or all-cause mortality estimates are not optimally accurate in young patients (as discussed in Chapter 2 and 3, and reported in recent studies such as Maishman *et al*. (15) and Lambertini *et al*. (14)). Adjuvant! also does not perform well in elderly patients (aged 70 years and older) (as discussed in Chapter 2). Prediction tools to help medical oncologists and patients better weigh the pros and cons of options are particularly useful in this patient population, as there is a fine line between "doing too little" and "doing too much" (16,17). A validation study in a large population of elderly patients found that Adjuvant!'s discriminatory accuracy was moderate for mortality, but poor for recurrence (13). Calibration was poor for both Adjuvant!'s mortality and recurrence estimates. An analysis of PREDICT's estimates showed that its 5-year overall survival estimates were reliable for elderly patients, whilst its 10-year overall survival estimates were not (18). Currently, both Adjuvant! and PREDICT are undergoing extensive updating, which could improve their performance in young and elderly patients, but this needs to be assessed when the new versions become available.

One characteristic of Adjuvant! that is deemed as an advantage (e.g., in the Dutch national breast cancer guidelines (3)) over other tools, is the fact that it is the only tool that takes comorbidity into account. This is especially relevant when predicting (disease-free) survival for elderly patients as there is large heterogeneity in terms of comorbidity in this patient subgroup, i.e., potentially competing causes of death. The variable that Adjuvant! uses is classified into categories namely: *perfect health*, *average for age*,

minor problems, *major problem +10*, *major problem +20*, and *major problem +30*. However, the categories used to define patients' general health have not been clearly defined by Adjuvant!'s developers. Thus, how medical oncologists classify patients is subject to interpretation and not likely to be uniform. For example, if a patient has well-managed diabetes, is that a minor problem or is it a major problem? There is no average diabetic. This disease can have a varying level of impact on patients' health, and its impact on patients' life expectancy may also vary. Therefore, it is understandable that providing standard classification rules for this general health variable is a challenge. However, the validation study by de Glas *et al*. suggests that the choice of general health category does significantly influence the prognostic estimates generated by Adjuvant!. If patients' general health was classified systematically (using a system based on consensus among experts), Adjuvant!'s estimates of recurrence were significantly more accurate, but it overestimated overall survival (13). If the general health variable was set to 'average for age', Adjuvant! tended to overestimate both the recurrence and overall survival estimates (13). In sum, it seems that some more thought needs to be given to Adjuvant!'s general health variable, and it most definitely needs to be better defined in order for it to be of added value.

Currently, validation studies mainly focus on assessment of the discriminatory accuracy and calibration of available prediction tools. However, applying methods such as net benefit modelling (19,20) could improve insights in the added value of prediction tools for decision-making. The net benefit method provides information on whether using a prediction tool leads to better decisions being made or not, i.e., is it safe to use a specific prediction tool to select patients that can forego chemotherapy for example. Additionally, comparison of the performance of a prediction tool across validation populations (e.g., different countries and in different clinical settings), could provide further insights in the strengths and weaknesses of the tool.

Finally, it remains imperative for medical oncologists to exercise caution if they choose to use prediction tools. Such tools can be useful, and our work as well as that of others shows that in selected populations their estimates are accurate. However, such tools are inherently imperfect, and should serve as guidance, clinical judgment and deliberation between medical oncologists and patients remain important.

II. Medical oncologists set higher thresholds for considering adjuvant systemic treatment worthwhile compared to the thresholds used in clinical guidelines (Chapter 4)

Summary

Clinical guideline developers provide a recommendation about when treatment benefit outweighs the side-effects, in order to formulate guidance on eligibility for treatment. Currently, guidelines (1-3) endorse discussing adjuvant systemic therapy if the expected

absolute treatment benefit in terms of 10-year survival is ≥ 3-5%. Thus, of 100 patients who meet the minimum required survival benefit for treatment, three will benefit from treatment and 97 will only experience the side-effects of treatment and no benefit. The difficulty lies in the fact that it is not possible to know a priori which patients will be amongst the 3% that will benefit from systemic treatment, and which patients are amongst the 97% that either do not require adjuvant treatment or will develop a disease recurrence in spite of treatment.

A survey by Stiggelbout *et al.* (21) conducted among medical oncologists in the year 2000 showed that they felt that chemotherapy needs to yield between 6 to10% absolute 10-year survival benefit to be worthwhile. We replicated this study among 42 medical oncologists and found that medical oncologists agreed that adjuvant systemic therapy is worthwhile if the expected 10-year survival gain is 10% or more, but not if the expected gain is less than 10% (Chapter 4). Medical oncologists' minimally desired chemotherapy benefit was the same in our sample (Chapter 4) as in the sample Stiggelbout *et al.* surveyed over a decade ago (21). New compared to Stiggelbout *et al*. (21) was that we also assessed the minimally desired benefit to make endocrine therapy worthwhile. For endocrine therapy the minimal absolute 10-year survival benefit that made treatment worthwhile tended to be higher for medical oncologists (6 to 10%) compared to surgical medical oncologists (1 to 5%), but 50% of respondents felt that 1 to 5% survival benefit was sufficient to make treatment worthwhile (Chapter 4).

To conclude, oncologists set higher thresholds for considering adjuvant systemic treatment worthwhile compared to the thresholds used in clinical guidelines, and set the thresholds higher for chemotherapy than for endocrine therapy.

Reflections and Future Directions

Over the past decades, the eligibility criteria for chemotherapy have become broader. This especially occurred following the publication of the early breast cancer trialists collaborative group's (EBCTCG) meta-analyses of adjuvant systemic treatment effect (22,23). However, surgical and medical oncologists' minimally desired chemotherapy benefit has not decreased. Our findings also suggest that medical oncologists deem the impact of endocrine therapy to be less serious than the impact of chemotherapy. Even though the side-effects of endocrine therapy might be relatively innocuous from a medical perspective, they can prove to be a heavy burden for patients during the 5 years (or possibly even 10 years) treatment period, as may be the resulting constant reminder of the illness (24-26). Finally, our findings might denote a sense amongst medical oncologists that by having such broad guidelines, too many patients undergo treatment needlessly. This could influence oncologists not to adhere to the recommendation in the guideline if they personally feel that the benefits do not outweigh the side-effects – i.e., undergoing treatment is not in their patients' best interest. Even if

they do not explicitly communicate this to patients, the choices oncologists make in terms of what they disclose to patients and how they formulate this information, could imply their personal preference. The findings of the study we report in Chapter 8 support this hypothesis (this study is discussed under key finding VII).

III. Adjuvant! is regularly used by medical oncologists to inform patients about their prognosis and the potential treatment benefit (Chapter 5 and 6)

Summary

In Chapter 5 we assessed surgical and medical oncologists' frequency of use and motivation for employing prediction tools using an online survey (N= 51). The best known (95%) and most frequently used (96%) prediction tool was Adjuvant!. Our respondents indicated they regularly used it to inform their own treatment advice (86%), to inform patients about their prognosis (>80%), and to convince patients either to forego or undergo treatment, particularly chemotherapy (74%). Three quarters of respondents felt that using Adjuvant! during the consultation helped patients to better understand their prognosis.

As Adjuvant! was the most frequently used prediction tool, in Chapter 6 we focused on how often Adjuvant! was actually used prior to and during consultations with patients, and which factors were associated with its use. To this end, we used 287 audiotaped consultations. We found that medical oncologists consulted Adjuvant! prior to 70% of consultations to inform themselves, and it was used during two thirds of consultations. Adjuvant! was used less frequently during consultations with patients with TNM stage II/III than with stage I. Adjuvant! use was also associated with medical oncologists' age, with the older medical oncologists using Adjuvant! less often, both *prior to* and *during* consultations, than their younger counterparts.

In sum, medical oncologists frequently use Adjuvant! both prior to and during patient consultations to inform patients about their prognosis, convince them about their proposed treatment plan. A majority of surgical and medical oncologists believe that using Adjuvant! helps their patients to better understand their prognosis. Use of Adjuvant! was less frequent in older oncologists and during consultations with patients with stage II/III disease.

Reflections and Future Directions

The higher the disease stage, the poorer the prognosis, and medical oncologists might be hesitant to communicate such probabilities. Receiving explicit information about poor prognosis might prove difficult for patients to come to terms with, cause them anxiety, and/or demotivate them. Also, medical oncologists might be more inclined to discuss the prognostic probabilities when treatment benefit is limited, in order to convince patients that undergoing treatment is not worthwhile. Indeed in our survey

(Chapter 5), a large proportion of medical oncologists listed this as a reason to use Adjuvant!. Further, it is perhaps not surprising that older medical oncologists use Adjuvant! less often, as they were trained at the time before the use of prediction tools became commonplace. Older medical oncologists are also more experienced, and might feel that using prediction tools has little or no added value to their preparation for the consultation or information provision to patients. Our finding that younger medical oncologists also more often consulted Adjuvant! prior to the consultation to inform their own treatment advice is in line with this hypothesis.

It is interesting that medical oncologists use Adjuvant! frequently during consultations, as it would be reasonable to fear that conveying risk estimates from prediction tools might cost more time than what is allotted for consultations. Yet, additional analyses of the data used in Chapter 6, suggested that on average the use of Adjuvant! did not significantly increase the duration of consultations (on average 1.5 minutes longer if Adjuvant! was used, P= 0.69 (data not shown)). Even though a definitive answer would have required an RCT, this finding suggests that a lack of time should not be a reason to forego the communication of probabilities. It remains a question whether probabilities can be adequately explained without increasing the length of the consultation. We did not aim to explore this in-depth in Chapter 6, but we did observe two tendencies in how probabilities were communicated during patient consultations. First, of all the probabilities communicated, 93% were presented as percentages and 41% were (also) presented as proportions (e.g., 3 out of 100) (data not shown). This finding was irrespective of the use of Adjuvant!. Communicating probabilities only using percentages is not advised, as a significant proportion of people struggle to understand percentages (27,28). It is helpful to (also) present the survival estimates as frequencies (e.g., 1 out of 4), but this was done in less than half of the consultations in which probabilities were discussed (data not shown). Second, in about one in five consultations the coders of the audiotaped consultations were unable to determine whether the probabilities communicated were for example overall or disease-free survival probabilities. Unclear risk communication undermines medical oncologists' intent to help patients to better understand their prognosis. These are disconcerting findings that require replication. If confirmed, these findings suggest that adequately communicating probabilities may require more time, and they underline the need for increased attention for training in risk communication in pre- and post-graduate curricula.

IV. In spite of reservations about the robustness of Adjuvant!'s relapse estimates, medical oncologists usually only communicate the relapse probabilities to patients (Chapter 6)

Summary

Analyses of the 287 audiotaped consultations indicated that the medical oncologists communicated Adjuvant!'s relapse probabilities in more than 90% of patient consulta-

tions, whereas the mortality estimates were only communicated in a quarter of those consultations (Chapter 6). Thus, in most consultations only the relapse probabilities were communicated.

Reflections and Future Directions

These findings contradict the findings of our survey (described in Chapter 5), in which medical oncologists indicated they seldom only communicated relapse probabilities. The frequent communication of relapse probabilities we observed in clinical practice, is also surprising given the available evidence that Adjuvant!'s relapse probabilities are significantly less accurate than its mortality estimates (as described in Chapter 2), and the concern medical oncologists expressed about the accuracy of Adjuvant!'s relapse estimates in our survey (as described in Chapter 5). Perhaps medical oncologists prefer to communicate the relapse probabilities in spite of their reservations because relapse is the nearest endpoint. Moreover, given the efficacy of currently available treatment, death due to cancer can often be postponed for a significant period of time even after patients develop a relapse. Additionally, it might be easier to discuss the possibility of relapse than to discuss the probability of dying due to the disease. Nevertheless, given the limitations in Adjuvant!'s relapse probability estimates, medical oncologists need to exercise caution when communicating these probabilities to patients.

V. The uncertainty associated with Adjuvant!'s estimates is not always communicated, and patients struggle with the concept of epistemic uncertainty (Chapter 5 and 7)

Summary

Probabilities from prediction tools are intrinsically imperfect and embody two types of uncertainties: aleatory uncertainty arising from the unpredictability of future events, and epistemic uncertainty arising from limitations in the reliability and accuracy of probability estimates (29). Communication about the uncertainty surrounding the estimates of prediction models is a controversial topic. Risk communication experts argue that uncertainty also needs to be communicated to patients if medical oncologists discuss the prognostic estimates with them (30). However, given that even highly educated people struggle to understand probabilistic information (28), this raises the question whether also communicating uncertainty is of added value to patients, or will only serve to increase their anxiety, unnecessarily making it more difficult for them to understand their survival probabilities.

In our survey amongst medical oncologists we assessed whether they wanted to know the uncertainty surrounding the probability estimates, and their views on communicating this uncertainty to patients (Chapter 5). Interestingly, only half of them wanted to know the width of the confidence interval around Adjuvant!'s prognostic estimates, and a third felt that this information was of no added value to them. However, more than 90% of respondents said that they currently communicate with their patients about

the uncertainty associated with Adjuvant!'s survival estimates.

In Chapter 7 we investigated how often and which type of uncertainty was communicated during 198 audiotaped patient consultations in which Adjuvant! had been used (same sample as Chapter 6). In our consecutive sample of patients, medical oncologists communicated some form of uncertainty in about half of the consultations. If medical oncologists referred to uncertainty, it was mostly (4 out of 5 times) an allusion to aleatory uncertainty. When medical oncologists did discuss epistemic uncertainty, they were somewhat vague (e.g., "*these are averages*" or "*of course there always is a margin associated with such statistics*").

We also conducted interviews with patients in the week after the consultation with the medical oncologist, to gain insights in patients' perceptions of uncertainty. In these interviews, the patients mainly made references to aleatory uncertainty. Further, the patients made more references to aleatory than to epistemic uncertainty, even when we specifically asked them about epistemic uncertainty (Chapter 7). One in 10 patients indicated that the probabilities were exact; they perceived no uncertainty associated with the survival estimates. Further, during interviews patients seemed to struggle with our questions about epistemic uncertainty. On the one hand, they seemed to think we were asking them whether the medical oncologists had been truthful with them or if their medical oncologists had gotten the probabilities correct. They seemed unable to reconcile the fact that probabilities can be both *true* and *imprecise*. Patients often contradicted themselves when talking about epistemic uncertainty. They indicated that the probabilities gave them a sense of security amongst all the uncertainty. Thus, thinking about the limitation of the estimates was difficult. The interviewers struggled to find a balance between obtaining answers to the research questions, and not unnecessarily upsetting patients by pushing the subject too hard.

In conclusion, we found that medical oncologists discussed uncertainty in less than half of the consultations, and if they discussed it, they more frequently communicated about aleatory uncertainty, Patients seem aware and comfortable talking about aleatory uncertainty, but they struggle with epistemic uncertainty.

Reflections and Future Directions

We found that in about half of the consultations medical oncologists talked about some form of uncertainty during the consultation, and most often aleatory uncertainty. A previous study, by Politi and colleagues, found that breast cancer surgeons talked about the margin around estimates in 48% of consultations, and in 28% of consultations they discussed the uncertainty about the strength of the evidence in the literature (31). These findings are not in line with ours, as epistemic uncertainty was discussed only in 1 in 5 consultations in our sample. However, the surgeons in the study by Politi and

colleagues knew that the study intended to assess communication of uncertainty and decision satisfaction. Therefore, they might have communicated uncertainty more often that they usually would have. Our study was observational for one, and the question about uncertainty was not the primary focus. Thus, in comparison our study would not have stimulated the participating medical oncologists to discuss uncertainty more often than they normally would have. Our findings might be a better reflection of clinical practice, but on the other hand the context of the studies is somewhat different, and might therefore not be comparable.

Perhaps the fact that aleatory uncertainty is communicated more often and patients struggle least with it, might be because it is more intuitive and does not *require* understanding of the nature of probabilistic information, compared to epistemic uncertainty. People are generally aware that it is impossible to predict the future, therefore, it might also be easier to accept aleatory uncertainty. Further, the fact that Adjuvant!, like many other prediction tools, does not provide information about the width of the confidence interval around its estimates, might make it more difficult for medical oncologists to be more specific about epistemic uncertainty. This could explain the vagueness of medical oncologists' utterances about uncertainty. Also, it is remarkable that half of the surgical and medical oncologists in our survey (Chapter 5) felt that knowing the width of the confidence interval was of no added value to them. This type of information could help clinicians gauge the precision of the estimates, and help them decide whether or not to disclose this to patients. Survival probabilities can strongly influence patients' treatment preference and their decision-making, it is therefore, important that this information is as reliable is possible. Clinicians have the duty to ensure the reliability of the information they provide patients with.

That uncertainty was discussed in only half of the consultations might be partly explained by the fact that medical oncologists indicated they communicate probabilities to inform patients about their prognosis, and also to convince them about the merits of their proposed treatment plan (Chapter 5). Therefore, they might be hesitant to discuss the limitations of the probabilities as this could undermine the patients' ability to 'trust' the estimates and use them in decision-making. Indeed, during our interview with patients, they indicated that they derive a sense of security from the probabilities. Also, one study reported that communicating scientific uncertainty was associated with decreased decision satisfaction among women facing cancer treatment decisions (31). However, there is no *hard* evidence to either support or refute this hypothesis. Most work in this area of risk communication has been conducted in healthy volunteers (e.g., (29)), and it is unclear to what extent it applies to patients facing real treatment decisions.

Further, the difficulty we encountered in talking about uncertainty with patients meant that we cannot make strong statements about patients' understanding of uncertainty.

We can only describe to what extent they perceive uncertainty, i.e., whether they are aware that there is uncertainty and how they viewed this uncertainty. Research is needed to get insights in patients' understanding of uncertainty. Finally, the difficulty we experienced during the interviews also seems to be congruent with medical oncologists' struggle with regard to communicating uncertainty. Whilst most efforts in this area of risk communication center around building an evidence base on how to best communicate uncertainty, our study raises the question whether uncertainty, especially epistemic uncertainty, *should* be communicated to patients. This also deserves careful consideration in further research.

VI. The suboptimal information provision about treatment side-effects during consultations suggests that adjuvant systemic treatment decisions are mainly driven by the potential treatment benefits (Chapter 6)

Summary

The use of Adjuvant! did not influence *how many* side-effects were communicated during audiotaped patient consultations (Chapter 6). Overall, fewer side-effects of endocrine therapy than of chemotherapy were communicated. Whether or not chemotherapy was discussed alongside endocrine therapy did not influence the number of side-effects of endocrine therapy discussed during consultations. Medical oncologists' choices with regard to which side-effects he/she felt was *necessary* to communicate to patients also seem to be a driving force behind which side-effects are communicated. There was great variation within and between medical oncologists with regard to how many side-effects were communicated during the consultation (in Chapter 6). Medical oncologists seem to have delegated the task of informing patients about side-effects to breast cancer nurses or the nurse practitioner as they regularly told patients that the nurse would discuss the side-effects with them.

In sum, we observed a great variation within and between oncologists in terms of which side-effects they communicated, and not one side-effect of either chemotherapy or endocrine therapy was communicated in all consultations.

Reflections and Future Directions

The variation we found in the communication of side-effects illustrates a lack of consensus amongst medical oncologists on a core set of adjuvant systemic therapy side-effects that need to be communicated to patients. This finding is in line with a study in the UK (32). Some side-effects might be less relevant for some patients. However, as the majority of side-effects apply to all patients, the variation in side-effects communicated can hardly be explained by tailoring of side-effects to the patients' situation. Currently, no guidance is provided in clinical guidelines on which side-effects minimally need to be communicated in order to enable patients to weigh the benefits and harms of treatment and develop informed treatment preferences. We conducted a pilot study, in which we

asked a panel of five experienced medical oncologists to create a list of side-effects of taxane-based chemotherapy (the most frequently prescribed chemotherapy regimen in our cohort) that patients minimally need to know in order to be able to weigh the treatment benefits against the harms. We considered that participants had reached consensus if 80% agreed on whether a side-effect should *always* be communicated to patients. Reaching consensus proved a difficult task. After three rounds, for a number of side-effects still no consensus could be reached. We applied the minimum list of side-effects on which the experts could reach a consensus (see Box 1) to a set of 70 consultations (sample of the cohort used in Chapter 6). We found that in none of the consultations all the items on the minimum list had been communicated to patients (data not shown). These findings further underscore a need for guidance. Guideline developers need to take steps towards developing a core set of adjuvant systemic therapy side-effects (e.g., like described by Kunneman and colleagues (33)).

Neuropathy	Cardiomyopathy
Alopecia	Allergic reaction
Immune suppression	Thrombocytopenia
Nausea	Altered defecation pattern
Malaise	Fatigue

Box 1 Taxane-based chemotherapy side-effects that *always* need to be communicated

Further, fortunately, nurses provide patients with more extensive information about the side-effects than medical oncologists do during the consultation (Chapter 6). However, given that treatment decisions are made during the consultation with the medical oncologist, it is disconcerting that information provision about side-effects is limited during that consultation itself. Patients are essentially only basing their treatment decision on the benefits of treatment. This hampers a proper weighing of the expected benefits against the side-effects. If information provision is limited, patients might have erroneous expectations of treatment impact, which can lead to early treatment cessation if the treatment burden is greater than expected. Indeed, early discontinuation rates of up to 50% have been reported for endocrine therapy (24,34).

Finally, thorough information provision is not only relevant from an ethical or legal viewpoint. Studies have also suggested that feeling (fully) informed could improve patients' mental health and wellbeing. It might give them a sense of being in control and being taken seriously, and thereby helping them cope with their new situation (35,36). Comprehensive information provision is a key premise of involving patients in the decision-making process, and perceived involvement in decision making can lead to

more satisfaction with the treatment decision, better compliance, and less anxiety (37).

VII. In spite of the lack of a 'best' treatment option, medical oncologists use implicit persuasion to steer patients towards the treatment option they deem in their patients' best interest (Chapter 8)

Summary

Medical oncologists are tasked with providing patients with information about the benefits and harms of relevant treatment options, in order to enable patients to weigh the pros and cons of these options and develop informed treatment preferences. Patient participation in decision-making about adjuvant systemic treatment is key, given that there often is no one best option from a medical perspective, and decision-making thus needs to be guided by patients' preferences. In such preference-sensitive decisions, shared decision-making is especially relevant. A key premise of shared decision-making is that information provision is balanced. Ideally, it should be free from implicit value judgments, and thus not driven by clinicians' own assessment of whether the benefits outweigh the side-effects. When the presentation of evidence implicitly steers patients towards a particular choice, patients may get the erroneous impression that a specific option is the only or 'best' one (i.e., implicit persuasion).

In Chapter 8 we evaluated medical oncologists' use of implicit persuasion during patient consultations using a self-developed coding scheme. Some form of implicit persuasion was used in all the 105 audiotaped consultations we analyzed. Medical oncologists' use of implicit persuasion was not primarily driven by the magnitude of the expected treatment benefit. Significantly more implicitly persuasive behaviors were observed when endocrine therapy was discussed as compared to chemotherapy. Moreover, the direction of steering (i.e., either towards or away from a treatment option) was not always congruent with the expected treatment benefit. About half of the patients with stage I or lymph node negative disease were steered towards undergoing treatment. For endocrine therapy, if implicit persuasion was used, it was *always* to steer patients towards undergoing treatment. Endocrine therapy was generally presented as 'standard' treatment for patients with hormone receptor positive disease, not as an *option* that could to be considered. Decisions were significantly less often postponed if more implicit persuasion was used during the consultation.

In conclusion, medical oncologists regularly used implicitly persuasive behaviors during patient consultations, even though there is no best treatment option in this patient population. Their use of implicit persuasion nor the direction in which patient were steered was congruent with the expected treatment benefit. Use of implicit persuasion was associated with less decisions being postponed.

Reflections and Future Directions

Our study is the first to systematically investigate the use of implicit persuasion in oncology. Karnieli-Miller and Eisikovits were the first to systematically assess the use of such behaviors by pediatric gastroenterologists (38). Undoubtedly, many studies have also described implicitly persuasive behaviors, but without naming them as such. For example, Ziebland *et al*. observed that surgeon did not present surgery for pancreatic cancer as a viable treatment option that could be considered, they presented the feasibility of a surgical procedure for pancreatic cancer as a 'win' – patients were lucky that they could be operated on (39). Our findings suggest that the provision of balanced information about treatment, a key premise of shared decision-making, is often not met in clinical practice. This is especially worrying as there is no best option medically speaking: essentially adjuvant systemic treatment is targeted at reducing the probability of a negative outcome, and not detectable disease. Whether or not it is worthwhile to undergo treatment, depends on a subjective trade-off that patients can only make on the basis of balanced information. That decision-making was significantly less often postponed if more implicit persuasion was used, suggests that steering is important in influencing the decision-making process.

Noteworthy is that the implicitly persuasive behaviors medical oncologists used during the consultation were often attempts to comfort and reassure patients or assuage any perceived decisional conflict. However, if medical oncologists wish to stimulate patient participation in decision-making, and for decisions to be the result of a shared process, employing these behaviors undermines this intent. Especially, as medical oncologists generally do not tend to explicitly communicate that the purpose of the consultation is to discuss treatment options and make a decision whether or not undergoing treatment is worthwhile (40). In only 3 out of the 100 consultations analyzed by Kunneman *et al.*, medical oncologists explicitly stated that the purpose of the consultation was to make a treatment decision (40). This lack of explicit disclosure that there is a choice was more manifest in the endocrine therapy than in the chemotherapy consultations we analyzed in Chapter 8. This suggests that oncologists think that the benefits of endocrine therapy generally outweigh its side-effects.

The lack of explicit disclosure that there is a choice, is compounded by the fact that medical oncologists infrequently explored patients' preferences during consultations (as discussed in Chapter 8). This is in line with available literature (41). It is likely that patients could consent to a treatment that does not match their preferences and goals, and is based on the medical oncologists' nudges. Additionally, if the implicitly persuasive behavior used involves downplaying for example the impact of treatment on patients' quality of life, this might cause patients to underestimate the impact of treatment. Decision-making about long-term treatment modalities is not solidified in a single moment, it is an organic process that develops over a long period of time (42).

Realization over time that treatment does not meet the patients' expectations – based on incomplete information – can lead to a change in resolve, and early discontinuation of treatment. To ensure that patients make decisions that best match their preferences and goals, medical oncologists need to be aware of their own preferences and carefully consider the implications of their potentially steering behavior towards patients. Preferably, implicit persuasion is addressed in medical teaching curricula to increase awareness amongst clinicians about the potential impact of such behaviors.

Concluding remarks

Relevance and limitations of our work

The work presented in this thesis focuses on current practice with regard to communication about the benefits and side-effects of adjuvant systemic therapy for early-stage breast cancer, particularly the use of prediction tools to communicate prognosis during patient consultations. The common thread running through most of the work presented in this thesis is Adjuvant!. We focus on this specific tool (offline as of November 2015, due to updating), but the work on information provision presented in this thesis can serve as a template for other prediction tools.

Our findings suggest that prediction tools are becoming commonplace in clinical practice. Therefore, it is also becoming increasingly important that the influence of using such tools in clinical practice is investigated. Given the lack of information about the prevalence of use of prediction tools in clinical practice and current practices with regard to information provision about treatment, we opted for an observational design. We set out to explore current practices, and identify potential targets for research and education. Strength of our observational study is the fact that we approached consecutive patients and a large number of them participated (72% participation rate). The use of audio recordings of consultations is also a strength, as we did not need to solely rely on the recollections of patients and oncologists, and thereby avoided the associated potential for recall bias. However, the observational design of our study also has drawbacks. For one, it does not allow us to make causal inferences. Another limitation is that our study was not randomized, and therefore results on the use of Adjuvant! might have been confounded by specifics of the oncologists or the patient. Although we had a relatively large sample (N=287), the distribution of patients within medical oncologists, was not ideal. More than a third of the participating medical oncologists contributed fewer than five patients to the study. This limited our ability to perform meaningful analyses (e.g., multilevel analyses) to explore relationships between multiple variables and our outcomes of interest. Further, we were not able to assess non-verbal communication as we only had audiotaped consultations. Also, we mainly included patients treated at hospitals in Leiden, The Hague, and Delft. There might be differences in practice in other regions of the Netherlands. Thus, we do not know to what extent our findings are generalizable to the whole Dutch context, or clinical

practice outside the Netherlands. It is also important to keep in mind that although we explicitly instructed oncologists to conduct their consultations as they normally would, participating in this study might have influenced their use of Adjuvant!. In a survey participating medical oncologists completed after patient recruitment closed, we asked them whether their use of Adjuvant! had changed during the study period. Only two oncologists indicated to have used Adjuvant! more often than before our study.

Implications for research
The insights that we have gained from this work raises important questions that need to be addressed in future research.

As prediction tools are frequently used to communicate prognosis to patients, it is important that the presentation of the survival estimates is clear. This holds for both the graphical presentation of the estimates by the tool itself, as well as how the clinician presents this information. Worrisome findings were that probabilities were not always communicated in a clear manner and they were usually only presented as percentages. It begs the question whether patients understand the probabilities from prediction tools communicated during the consultation. This needs to be investigated, especially since oncologists use prediction tools to inform patients about their prognosis in the belief that it helps them to better understand their prognosis.

Further, there is no evidence about how patients experience the use of prediction tools during consultations, and the role the information from such tools play in their decision-making. This also needs to be explored in future research.

Our exploration of communication of uncertainty suggests that further evaluation of patients' understanding of uncertainty is necessary, as well as whether communicating uncertainty is of added value at all to patients. Even though it is unclear whether or not communicating uncertainty to patients is beneficial to them or necessary for them to be able to better gauge probabilistic information, it remains important to develop guidelines on how best to communicate this type of information, if clinicians choose to do so. To that end, there is a need for more studies evaluating which presentation format best facilitates understanding of uncertainty, and how clinicians can best talk about uncertainty to patients.

A recurrent theme in many of our analyses of current information provision practices is that the impact of endocrine therapy on quality of life appears to be underestimated by oncologists. Moreover, endocrine therapy was presented as *standard* treatment; the decision to undergo treatment often seemed a foregone conclusion. However, endocrine therapy starts after chemotherapy is completed. Perhaps the endocrine therapy decision is revisited during a consultation after completion of chemotherapy, and more

extensive information on especially the side-effects is provided by medical oncologists at that time. Logistically it was not possible for us to also audiotape the consultation after completion of chemotherapy to assess this. In our sample, the extensiveness of information provision about endocrine therapy does not differ depending on whether chemotherapy was discussed alongside endocrine therapy or not, but the number of only endocrine therapy consultations we analyzed was small and predominantly conducted in patients over 70 years. Therefore, to confirm or refute our findings for endocrine therapy, future studies need to assess information provision in both the first consultation on adjuvant systemic therapy and the consultation after completion of chemotherapy.

There is no consensus on which side-effects patients minimally need to be made aware. A core list of side-effects for the various chemotherapy and endocrine therapy regimes needs to be developed and incorporated in clinical guidelines. In the development of such core lists both patients and clinicians need to be consulted.

Finally, some general points are a) our work needs to be replicated, when possible, using a randomized design, and b) more work is needed to elucidate the underlying mechanisms of the associations we have found.

Practice implications

Our work has raised more questions for future research than it has provided answers for current practice. We have identified subjects that need to be incorporated in clinical guidelines and addressed in pre- and post-graduate medical curricula. Specific areas requiring attention in medical curricula are: a) which elements need to be addressed during consultations to help patients develop an informed treatment preference (e.g., using the principles of shared decision making), b) how to best communicate probabilities, and c) how to best frame information in order not to unintendedly steer patients towards a specific treatment option. Clinical guidelines need to include guidance on which side-effects minimally need to be communicated to patients facing adjuvant systemic treatment decisions.

Take home message

Even if, as researchers, we focus on methodology and statistics, the most important thing is to use the knowledge that our work generates to improve the care for patients, and provide them with the support they need to make it through a difficult period in their life.

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Part VI

Appendices

Nederlandse samenvatting

Dit proefschrift bevat studies die nieuwe inzichten geven in de manier waarop borstkankerpatiënten worden geïnformeerd over de voordelen en de bijwerkingen van aanvullende behandelingen (c.q. adjuvante systemische therapie), namelijk chemotherapie en hormonale therapie. Er wordt ook specifiek gekeken naar het gebruik van predictiemodellen om patiënten te informeren over hun prognose. Het predictiemodel Adjuvant!, is wereldwijd misschien wel de beste predictietool. In ons onderzoek hebben wij ons vooral gericht op Adjuvant!, omdat dit het bekendste predictiemodel is wereldwijd en ook aanbevolen wordt in (inter)nationale klinische richtlijnen. De lessen die getrokken kunnen worden uit ons onderzoek naar het gebruik van Adjuvant!, kunnen mogelijk ook inzichten bieden bij het gebruik van andere predictiemodellen.
Uit het werk in dit proefschrift kunnen zeven kernbevindingen worden gedistilleerd, namelijk:

I	Er zijn veel predictiemodellen beschikbaar om de besluitvorming rondom adjuvante therapie te ondersteunen, maar ze moeten nader gevalideerd worden	(Hoofdstuk 2 en 3)
II	Adjuvante therapie wordt in richtlijnen aanbevolen voor een minimale baat die lager is dan de baat waarvoor oncologen aangeven de therapie de moeite waard te vinden	(Hoofdstuk 4)
III	Oncologen gebruiken Adjuvant! regelmatig om patiënten over hun prognose en de mogelijke baat van de behandeling te informeren	(Hoofdstuk 5 en 6)
IV	Ondanks beperkingen m.b.t. de betrouwbaarheid van schattingen van de kans op recidief communiceren oncologen meestal alleen de recidiefkansen aan de patiënt	(Hoofdstuk 6)
V	De onzekerheden rondom schattingen van Adjuvant! worden niet altijd besproken en patiënten worstelen met het begrip epistemische onzekerheid	(Hoofdstuk 5 en 7)
VI	De suboptimale informatieverschaffing over bijwerkingen suggereert dat beslissingen over adjuvante therapie vooral genomen worden op basis van de baten van de behandeling	(Hoofdstuk 6)

VII Ondanks het ontbreken van een “beste” behandeloptie, gebruiken oncologen impliciet sturende mechanismen die de patiënt in de richting van de therapie kan sturen die de oncoloog het beste voor de patiënt vindt (Hoofdstuk 8).

I. Er zijn veel predictiemodellen beschikbaar om de besluitvorming rondom adjuvante systemische therapie te ondersteunen, maar ze moeten nader gevalideerd worden
We hebben een systematisch literatuuroverzicht uitgevoerd naar gepubliceerde risico predictiemodellen voor de besluitvorming rondom adjuvante therapie bij vroeg-stadium borstkanker (Hoofdstuk 2). We vonden dat de meeste predictiemodellen geen uitgebreide externe validatie ondergaan hebben, niet doorontwikkeld zijn en niet wijdverbreid zijn geïmplementeerd. Een uitzondering is Adjuvant! en ook tools die op bio-moleculaire profielen gebaseerd zijn, zoals Oncotype Dx en MammaPrint. Onze review suggereert dat Oncotype Dx en MammaPrint accuraat patiënten met hoog risico van die met laag risico op recidief kunnen onderscheiden (Hoofdstuk 2). Ofschoon over het geheel genomen de schattingen van Adjuvant! accuraat lijken, vonden de studies die wij hebben beoordeeld ook beperkingen in het onderscheidingsvermogen en de kalibratie ervan. In een volgende studie hebben we het onderscheidend vermogen en de kalibratie van Adjuvant! en PREDICT bepaald voor de overall sterfte van vrouwen onder de 50 jaar op het moment van diagnose (Hoofdstuk 3). PREDICT is een predictiemodel dat erg op Adjuvant! lijkt en snel de weg naar de kliniek gevonden heeft. Dit is deels omdat dit tot op heden het enige model is dat automatisch de Her2neu-status en behandeling met trastuzumab (c.q. Herceptin) meeweegt. We vonden dat het onderscheidend vermogen van beide modellen zwak tot matig was en dat de kalibratie slecht was voor de uitersten (d.w.z. patiënten met de beste of juist de slechtste prognose). De grootte van de onderschatting van de overall sterfte door Adjuvant! en PREDICT was kleiner dan gerapporteerd in eerdere studies (namelijk, verschillen van wel 35% tussen geobserveerde en voorspelde sterfte). Desalniettemin onderschatten beide modellen de sterfte voor patiënten van 36-40 jaar (met 6.0 tot 6.6%).

II. Adjuvante therapie wordt in richtlijnen aanbevolen voor een minimale baat die lager is dan de baat waarvoor oncologen aangeven de therapie de moeite waard te vinden
Richtlijnontwikkelaars geven aanbevelingen wanneer de verwachte baten van behandelen groter zijn dan de verwachte bijwerkingen. Momenteel adviseren richtlijnen adjuvante therapie te bespreken met patiënten vanaf 3-5% toename in 10-jaars overleving. In een enquête vonden Stiggelbout *et al.*[1] in 2000 dat oncologen dachten dat chemotherapie een absolute 10-jaars overlevingswinst tussen de 6-10% moest bieden om de moeite waard te zijn. We herhaalden deze studie en vonden dat alle oncologen in de studie het eens waren dat adjuvante therapie de moeite waard is bij een absolute 10-jaars

1 Stiggelbout AM, de Haes JC, van de Velde CJ: Adjuvant chemotherapy in node negative breast cancer: patterns of use and oncologists' preferences. Ann Oncol 11:631-3, 2000

overlevingswinst van 10% of meer, maar er was geen consensus tussen oncologen als de overlevingswinst minder dan 10% was (Hoofdstuk 4). In de afgelopen 15 jaar zijn de criteria voor het adviseren van chemotherapie verruimd, maar de vereiste baat die oncologen wenselijk achten is niet gedaald. Voor hormoontherapie is de vereiste baat hoger voor medisch dan voor chirurgisch oncologen (6-10% vs 1-5%). Echter de helft van alle respondenten vond dat 1-5% voldoende winst was om behandeling met hormonale therapie de moeite waard te maken. Het lijkt erop dat men de impact van hormoontherapie minder groot acht dan die van chemotherapie. De bijwerkingen zijn inderdaad meestal milder, maar het kan een zware last voor patiënten zijn om lange periodes (wel 5-10 jaar) deze therapie te moeten ondergaan, ook vanwege het steeds herinnerd worden aan de ziekte.

III. Oncologen gebruiken Adjuvant! regelmatig om patiënten over hun prognose en de mogelijke baat van de behandeling te informeren

We bepaalden hoe vaak chirurgisch en medisch oncologen aangaven predictiemodellen te gebruiken en hun redenen voor het gebruik (Hoofdstuk 5). Het bekendste en meest gebruikte model was Adjuvant!. Oncologen gaven aan het regelmatig te gebruiken om hun eigen advies de onderbouwen, om patiënten te informeren over hun prognose en om patiënten ervan te overtuigen juist wel of niet therapie, met name chemotherapie, te ondergaan. Driekwart van de deelnemers gaf aan dat het gebruik van Adjuvant! in de spreekkamer ertoe leidt dat patiënten hun prognose beter begrijpen. Deze gedachte was voor hen een reden om Adjuvant! te gebruiken tijdens consulten met patiënten.

Aangezien onze enquête aangaf dat Adjuvant! het meest gebruikte model was, richtten we ons onderzoek op het gebruik ervan in de spreekkamer. We bepaalden hoe vaak het vóór en tijdens het consult gebruikt werd en met welke factoren het gebruik ervan samenhing (Hoofdstuk 6). We vonden dat in tweederde van de 287 geanalyseerde consulten Adjuvant! gebruikt werd. Ook raadpleegden clinici het model in 70% van de gevallen vóór het consult. Adjuvant! werd frequenter gebruikt in consulten met patiënten met een lager TNM-stadium (I vs. II/III; m.a.w. patiënten met een lage kans op sterfte (stadium I) t.o.v. patiënten met een hogere kans op sterfte (stadium II/III). Oncologen zijn waarschijnlijk meer geneigd het model te gebruiken als er slechts beperkte baat van behandeling verwacht wordt, om de patiënt ervan te overtuigen dat het ondergaan van adjuvante behandeling geen zin heeft. Het gebruik van Adjuvant!'s hing ook samen met de leeftijd van de oncoloog: oudere oncologen gebruikten het minder vaak dan jongere oncologen. Wellicht komt dit omdat er in het verleden geen predictiemodellen beschikbaar waren en ze gewend zijn hun consulten te voeren zonder het model. Ook hebben zij meer ervaring en ervaren daarom wellicht minder behoefte aan de schattingen.

IV. Ondanks beperkingen m.b.t. de betrouwbaarheid schattingen van de kans op recidief communiceren oncologen meestal alleen de recidiefkansen aan de patiënt

Oncologen bespraken de recidiefkansen uit Adjuvant! in meer dan 90% van de consulten, terwijl de sterftekansen slechts in een kwart van de consulten verteld werden (Hoofdstuk 6). Dit ondanks het feit dat men in onze enquête (Hoofdstuk 5) aangaf zelden alleen recidiefkansen te bespreken, dat de literatuur aangeeft dat de recidiefkansen minder accuraat zijn dan de sterftekansen, en dat artsen hier ook van op de hoogte waren. Het is waarschijnlijk makkelijker recidiefkansen te bespreken dan de kans te overlijden aan de ziekte.

V. De onzekerheden rondom schattingen van Adjuvant! worden niet altijd besproken en patiënten worstelen met het begrip epistemische onzekerheid

Kansen uit predictiemodellen zijn intrinsiek imperfect en omvatten twee soorten onzekerheid: “aleatoire onzekerheid”, voortkomend uit de onvoorspelbaarheid van toekomstige gebeurtenissen en “epistemische onzekerheid”, voortkomend uit beperkingen in de betrouwbaarheid en accuraatheid van de schattingen. Het bespreken van de onzekerheid rondom de schattingen is een controversieel onderwerp in de literatuur. Risico communicatie experts beargumenteren uit voornamelijk een ethisch perspectief dat als oncologen hun patiënten informeren over de overlevingsschattingen, zij hen ook moeten informeren over de onzekerheid geassocieerd met de overlevingsschattingen. Het is echter nog niet duidelijk hoe je patiënten het beste kunt informeren over onzekerheid. In onze enquête (Hoofdstuk 5) gaf slechts de helft van de oncologen aan zelf het betrouwbaarheidsinterval rondom de schattingen te willen weten en een derde gaf aan dat die informatie voor hem geen toegevoegde waarde had. Echter, meer dan 90% van de deelnemers gaf aan over de onzekerheid van de schattingen van Adjuvant! te spreken met hun patiënten.

We onderzochten hoe vaak onzekerheid werd besproken in de consulten waarin Adjuvant! gebruikt werd en welk type onzekerheid er dan werd besproken. Ook bepaalden we in interviews òf en hoe de betreffende patiënten de besproken onzekerheid waarnamen (Hoofdstuk 7). In totaal includeerden 27 oncologen 198 consulten. Met ongeveer de helft van deze 198 patiënten besprak men enige vorm van onzekerheid. Oncologen bespraken viermaal vaker aleatoire dan epistemische onzekerheid. Als ze deze laatste vorm bespraken, waren ze veelal wat vaag (bijv. “dit zijn gemiddelden” of “natuurlijk zit er altijd een marge aan dergelijke statistieken”). Aleatoire onzekerheid is intuïtiever en daardoor mogelijk eenvoudiger te communiceren en te begrijpen. Men is zich over het algemeen bewust van het feit dat de toekomst niet met zekerheid te voorspellen valt. Tijdens de interviews refereerden patiënten ook vooral naar aleatoire onzekerheid, ook wanneer we hen specifiek naar epistemische onzekerheid vroegen. We merkten dat patiënten worstelden met het begrip epistemische onzekerheid. Zelfs wanneer ze het waarnamen, leken ze zich ongemakkelijk te voelen bij het bespreken ervan. Zij gaven aan dat de kansen hen een stuk zekerheid gaven te midden van alle onzekerheid, iets om zich aan vast te klampen. De moeite die wij hadden om de patiënten ernaar

te vragen, reflecteert waarschijnlijk ook de moeite die oncologen hebben met het bespreken van onzekerheid tijdens consulten. Dit doet de vraag rijzen of en wanneer het met de patiënt besproken zou moeten worden.

VI. De suboptimale informatieverschaffing over bijwerkingen suggereert dat beslissingen over adjuvante therapie vooral genomen worden op basis van de baten van de behandeling

Het gebruik van Adjuvant! beïnvloedde niet het aantal bijwerkingen dat besproken werd (Hoofdstuk 6). Wel was er een grote variatie binnen en tussen oncologen in de bijwerkingen die zij met hun patiënten bespraken. Voor chemotherapie werden meer bijwerkingen besproken dan voor hormonale therapie, dit was ook het geval in consulten waarin alleen hormonale therapie werd besproken. Het lijkt erop dat de oncologen een deel van het bespreken van de bijwerkingen aan de verpleegkundige overlaten. Dit leidt er echter toe dat de beslissing genomen wordt op basis van alleen de baten en niet op basis van een kosten-baten overweging.

VII. Ondanks het ontbreken van een "beste" behandeloptie, gebruiken oncologen impliciet sturende mechanismen die de patiënt in de richting van de therapie kan sturen die de oncoloog het beste voor de patiënt vindt

De beslissing over het wel of niet ondergaan van adjuvante systemische therapie is een voorkeursgevoelige beslissing, omdat er niet één duidelijk beste optie is. Bij voorkeursgevoelige beslissingen is gedeelde besluitvorming (c.q. shared decision making) belangrijk. Een uitgangspunt hierbij is dat de informatieverschaffing neutraal gebeurd. Als de wijze waarop de informatie aan de patiënt wordt gepresenteerd de patiënt impliciet stuurt in de richting van een bepaalde behandeling, kunnen patiënten ten onrechte de indruk krijgen dat die behandeling de enige goede keuze is (impliciete overreding). We bestudeerden in hoeverre oncologen in hun consulten impliciete overreding gebruikten (Hoofdstuk 8). Enige vorm ervan was in alle 105 consulten die we evalueerden aan de orde. Het gebruik van impliciete sturing werd niet gedreven door de grootte van de verwachte baat.

Een factor van belang was de behandeling die besproken werd: er vond meer sturing plaats voor hormoontherapie dan voor chemotherapie. De richting van sturen was niet altijd congruent met de verwachte baat. Meer patiënten met stadium II of lymfklierpositieve ziekte werden weliswaar gestuurd in de richting van behandeling met chemotherapie ondergaan, maar ook bij de helft van de patiënten met stadium I of met lymfklier negatieve ziekte was dit het geval. Voor hormoontherapie werden vrijwel alle patiënten in de richting van behandeling ondergaan gestuurd, onafhankelijk van ziektestadium. Beslissingen werden minder vaak uitgesteld in het geval sprake was van impliciete overreding.

About the author

Ellen was born on Bonaire, where she attended the Scholengemeenschap Bonaire (SGB). After getting her high school diploma (HAVO) in 2003, she moved to The Hague, The Netherlands. She studied nursing at the Leiden University of Applied Sciences, and obtained her Bachelor in Nursing in 2007. After a 1-year pre-master, followed by a 2-year research master, Ellen obtained her master in Health Sciences at the VU university in Amsterdam in 2010. After obtaining her master degree, she stayed on as a research assistant at the Division of Psychosocial Research and Epidemiology of the Netherlands Cancer Institute (NKI), where she had done her master internship. During her time at the NKI, she developed a keen interest in oncology, particularly breast cancer. September 2011, Ellen started as a PhD student at the Department of Medical Decision Making at the Leiden University Medical Center. Her work there gave her the opportunity to develop herself as a researcher, while maintaining a connection to clinical practice. During her time in Leiden, Ellen developed a keen interest in risk communication, the role of prediction tools in decision-making, and shared decision-making in general.

Ellen has given both oral and poster presentations at national and international conferences. In 2014, she won a *Lee B. Lusted Student Prize* in Decision Psychology and Shared Decision Making from the Society for Medical Decision Making. Until May 2017, she was the editor of the digital newsletter of the Dutch Psychosocial Oncology Association. Ellen is currently the deputy editor of the newsletter of the international Society for Medical Decision Making. As of the summer of 2016, she chairs the web editors of the Dutch Epidemiology Association and also is a member of the PR working party. The research presented in Chapter 8 of this thesis has been selected as *co-recipient of the Outstanding Paper by a Young Investigator Award for 2017 from the Society for Medical Decision Making*.

Since February 2016, Ellen works as a researcher at the Department of Epidemiology and Biostatistics of the VU University Medical Center in Amsterdam. Until November 2016, she worked on a project in which she assessed the clinical usefulness of available decision support tools for decision-making about palliative care for incurable colorectal cancer, and invertoried oncologists' unmet decision support needs in that setting. She is now working on a grant proposal to develop a decision support tool for decision-making about extended adjuvant endocrine therapy for breast cancer. Additionally, Ellen coordinates the Methodology research program of the Amsterdam Public Health research institute, which has resulted from collaboration between VU, VUmc, AMC and UVA research programs in the field of Health Sciences and Public Health.

List of publications

1. Engelhardt EG, Révész D, Tamminga JJ, Punt CJA, Koopman M, Onwuteaka-Philipsen BD, Steyerberg EW, Jansma EP, de Vet HCW, Coupé VMH. **Clinical usefulness of tools to support decision-making on palliative treatment for metastatic colorectal cancer: a systematic review. Clinical Colorectal Cancer** [in press]

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1. Van den Boorn H.G., Engelhardt E.G., van Kleef J.J., van Oijen M., Sprangers M., Abu Hanna A., Zwinderman K., Coupe V.M.H., Van Laarhoven H.W.M. **Prediction models for survival, adverse events and health-related quality of life in patients with esophagogastric cancer: A systematic review and meta-analysis.** [in preparation]
2. Engelhardt EG, Pieterse AH, van Duijn-Bakker N, Cluitmans F, Bos MMEM, Maartense E, Weijl NI, Quarles van Ufford-Mannesse P, Sleeboom H, Portielje JEA, van der Hoeven JJM, Woei-a Jin FJ, Kroep JR, Punt CJA, de Haes JCJM, Smets EMA, Stiggelbout AM. **Information provision about the benefits and side-effects of adjuvant systemic therapy for breast cancer in clinical practice: does the use of Adjuvant! facilitate communication?** [submitted]
3. Engelhardt EG, Révész D, Tamminga JJ, Punt CJA, Koopman M, Onwuteaka-Philipsen BD, Steyerberg EW, De Vet HCW, Coupé VMH. **Tools to support decision-making about palliative treatment for metastatic colorectal cancer: are available tools meeting clinical needs?** [submitted]
4. Révész D, Engelhardt EG, Tamminga JJ, de Vet HCW, Coupé VMH, Onwuteaka-Philipsen BD. **Decision support systems to aid palliative care consultants with decision-making about palliative care for cancer patients.** [submitted]
5. Révész D, Engelhardt EG, Tamminga JJ, Schramel FMNH, Onwuteaka-Philipsen BD, van de Garde EMW, Steyerberg EW, de Vet HCW, Coupé VMH. **Current use of decision support systems and unmet needs in the treatment of patients with incurable non-small cell lung cancer.** [submitted]
6. Révész D, Engelhardt EG, Tamminga JJ, Schramel FMNH, Onwuteaka-Philipsen BD, van de Garde EMW, Steyerberg EW, Jansma EP, de Vet HCW, Coupé VMH. **Decision support systems for incurable non-small cell lung cancer: a systematic review**. [submitted]

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