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

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PART I

General introduction

Chapter 1

Introduction

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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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