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Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

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Etterlevelse av antihormonell behandling hos pasienter med brystkreft

Fokus på etterlevelse er viktig i alle kliniske spesialiteter. Dersom en pasient ikke tar sin medisin som foreskrevet, enten dette er et bevisst valg eller ikke, er det sannsynlig at utfallet av sykdommen blir påvirket i negativ retning. Økt oppmerksomhet og kunnskap om etterlevelse er viktig både blant helsepersonell og pasienter. God kommunikasjon mellom kliniker og pasient er av stor betydning. Informasjon om hvorfor behandlingen gis, dosering, mulige bivirkninger og forventet effekt er viktige punkter å snakke om. Oppfølging av pasientene er også viktig. Dette er spesielt viktig for antihormonell behandling da bivirkninger er den vanligste årsaken til dårlig etterlevelse. Behandling av plagsomme bivirkninger kan føre til bedre etterlevelse. Det er viktig å skille mellom *primary non-adherence* og *secondary non-adherence*. Dersom man kan forutsi hvilke pasienter som er i risiko for dårlig etterlevelse, kan tiltak settes inn her.

I den første studien viser vi at det er de yngste og de eldste pasientene som har høyest risiko for dårlig etterlevelse av antihormonell behandling. De fleste som avslutter behandlingen for tidlig, gjør dette i den første delen av behandlingsperioden. Det er derfor i denne perioden at oppfølging er viktig med tanke på å forbedre etterlevelse. Pasienter med de mest alvorlige brystkreftdiagnosene, hadde oftere god etterlevelse. I tillegg viser vi at *primary non-adherent* pasienter i denne studien ofte hadde en god prognose sammenlignet med resten av studiepopulasjonen.

I den andre studien, fokuserte vi på hvordan etterlevelse av antihormonell behandling påvirker overlevelse hos brystkreftpasienter. Pasienter med *secondary non-adherence* har dårligst overlevelse sammenlignet med de andre pasientene. *Primary non-adherent* pasienter hadde god overlevelse, dette kan nok i stor grad forklares av deres gode prognose. I fremtiden tror vi at et mer individualisert behandlingsopplegg basert på genekspresjonsanalyser vil bli mer vanlig når man selekterer pasienter for antihormonell behandling.

I den tredje studien, undersøkte vi hvorfor vaktpostdiagnostikk fortsatt blir utført hos eldre brystkreftpasienter med lavgradige svulster på tross av retningslinjer som sier at man trygt kan utelate denne prosedyren hos disse pasientene. Vi mistenker at mulige aksillemetastaser og dårlig etterlevelse er to faktorer som kan forklare klinikernes skepsis til å utelate vaktpostdiagnostikk hos disse pasientene. Vi viser at omtrent en tredjedel av pasientene hadde aksillemetastaser bekreftet på postoperativ histologisk undersøkelse. I tillegg viser vi at omtrent en tredjedel av pasientene hadde dårlig etterlevelse av antihormonell behandling. Vi mener at disse faktorene, til en viss grad, kan forklare hvorfor vaktpostdiagnostikk fortsatt utføres i stor grad i denne pasientgruppen. I fremtiden tror vi avgjørelsen om utelatelse av vaktpostdiagnostikk i økende grad vil bli basert på genekspresjonsanalyser og komorbiditet.

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1 Acknowledgements

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2 List of papers

The following studies are included in this thesis:

Paper 1:

Predictors of adherence and the role of primary non-adherence in antihormonal treatment of breast cancer. Dragvoll I, Bofin AM, Søiland H, Taraldsen G, Engstrøm MJ. BMC Cancer. 2022;22(1):1247.

Paper 2:

Adjuvant antihormonal treatment in breast cancer. A study how adherence behaviours affect survival. Dragvoll I, Bofin AM, Søiland H, Salvesen Ø, Engstrøm MJ.

Paper 3:

How to Optimize Deimplementation of Sentinel Lymph Node Biopsy? Dragvoll I, Bofin AM, Søiland H, Engstrøm MJ. The Breast Journal, vol. 2024, Article ID 7623194, 9pages, 2024. https://doi.org/10.1155/2024/7623194.

3 Abbreviations

AI	Aromatase inhibitors
ALND	Axillary lymph node dissection
ASCO	American Society of Clinical Oncology
BCI	Breast Cancer Index
BCSS	Breast cancer specific survival
CBT	Cognitive behavioural therapy
CRN	The Cancer Registry of Norway
DCIS	Ductal carcinoma in situ
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ERα	Oestrogen receptor alpha
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
LH	Luteinizing hormone
MPR	Medication possession ratio
NEJM	New England Journal of Medicine
NorPD	The Norwegian Prescription Database
PNA	Primary non-adherent
POI	Protein of interest
PROTAC	Proteolysis targeting chimeric molecules
QoL	Quality of life
REK	Regional Committee for Medical and Health Research Ethics
SERD	Selective oestrogen receptor downregulator
SERM	Selective oestrogen receptor modulator
SLNB	Sentinel lymph node biopsy
SNA	Secondary non-adherent
SNRI	Serotonin-norepinephrine reuptake inhibitor

SSRI	Selective serotonin reuptake inhibitor
TB	Tuberculosis
WHO	World Health Organization

4 Summary

Adherence to medical treatment is of relevance in all clinical specialities. If a patient does not take a prescribed medication, whether intentionally or unintentionally, the outcome for that patient is likely to be negatively affected. As clinicians we believe that the medications we prescribe will benefit our patients. More knowledge regarding adherence to medical treatments is needed. To overcome the obstacles of poor adherence, increased awareness both among health care professionals and patients, is important. Good communication is paramount; comprehensible information about why the treatment is given, dosage, possible side effects and expected benefit is necessary. Close follow-up of the patients is also important. This is especially true for antihormonal treatment where side effects are often the reason for non-adherence. Prescribing treatments to overcome bothersome side effects might help improve adherence rates. Differentiating between primary non-adherence and secondary non-adherence is of importance as the former group will largely benefit from good communication and close follow-up. Patients in the latter group have frequently become non-adherent due to troublesome side effects. Being able to predict who will become non-adherent is important.

In the first study, we show that the young and the elderly are at increased risk of non-adherence to antihormonal treatment. As most discontinue the therapy in the initial part of the treatment period, this is the time when close follow-up will be most important. Patients with the most severe breast cancers are more often adherent to antihormonal treatment. We also show that primary non-adherent (PNA) patients tend to have a better prognosis than the rest of the study population.

In the second study, we examine the effect of adherence to adjuvant antihormonal therapy on survival in the same series of breast cancer patients. Secondary non-adherent patients have poorer survival compared to the rest of the study population. The PNA-patients did better than anticipated. This can probably be explained by their favourable prognostic profile. We suggest that in the future, a more individualized antihormonal treatment regimen based on biomarker profiling will become the preferred way of selecting patients for antihormonal treatment.

In the third study, we wanted to investigate why the omission of the sentinel lymph node biopsy (SLNB) procedure in low-risk elderly patients with breast cancer has not been widely implemented despite guidelines stating that it is safe to do so. We suspected that the presence of axillary lymph node metastases and poor adherence would be factors contributing to the reluctance amongst clinicians to omit the SLNB-procedure. We show that about one third of these patients had axillary metastases as confirmed on the postoperative pathology report. Furthermore, we show that about one third of these low-risk, elderly patients are non-adherent to the antihormonal treatment they were prescribed. We suggest that these factors, at least partly, explain the rather unsuccessful implementation of the omission of the SLNB-procedure. In the future, we believe that the selection of patients eligible for the omission of SLNB will be more personalised based on biomarker profiling and assessment of comorbidities.

5 Background

5.1 Introduction

Breast cancer is the world's most prevalent cancer (1, 2). In Norway, 4,076 women and 35 men developed breast cancer in 2023. The incidence of breast cancer is increasing (3). This increase can partly be explained by the introduction of the mammography screening programme, but also by the use of hormone replacement therapy (HRT), lifestyle factors and genetical predisposition. In 2020, there was a decrease in newly diagnosed cases of breast cancer due to the covid-19 pandemic, the numbers increased significantly in 2021 followed by a decrease in 2023. In Norway, the mammography screening program was introduced in 1996 and became nationwide in 2004. Since 1996, there has been a gradual increase in the incidence of breast cancer in Norway (3, 4). Well known risk factors for developing breast cancer include early menarche, late menopause, nulliparity and HRT. These risk factors reflect the stimulating effects of oestrogen. Other, and more modifiable risk factors, include increased body mass index (BMI), sedentary lifestyle, alcohol intake and smoking. Also, the risk of breast cancer increases with age. Lastly, genetic factors play an important role in a patient's lifetime risk of developing breast cancer, the most common mutations being breast cancer gene 1 (BRCA 1) and breast cancer gene 2 (BRCA 2) (5-7). There has been an improvement in the survival of breast cancer over the last decades. Nine out of ten women with breast cancer will now be alive five years after diagnosis. With the introduction of the mammography screening programme and improved treatments, more women are now surviving breast cancer (4-6).

As research leads to new and improved treatment regimens, survival gradually improves. Between 2016-2020, the five-year relative survival for stage 1 breast cancer was 100% (Figure 1). However, with distant metastases at the time of diagnosis, this number was 33.9% (4). One of the most important improvements in breast cancer treatment has been the discovery and introduction of antihormonal treatment.

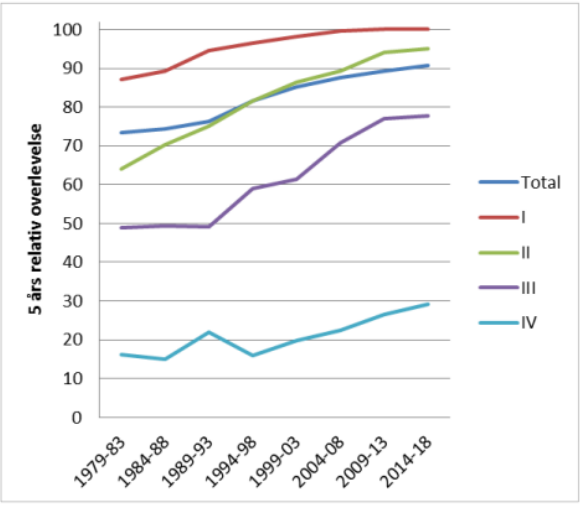

Figure 1: Five-year relative survival of breast cancer according to stage (4).

5.2 Antihormonal treatment

5.2.1 The history of antihormonal treatment

The important role of oestrogen in female physiology has long been known. In the 1800s, German women with menopausal symptoms were effectively treated with injections of bovine ovarian tissue (8). Ovarian ablation was acknowledged early to be an effective treatment for breast cancer. Initially, in the late 1800s, this was done by surgically removing the ovaries. This meant quite extensive surgery with its possible complications and lengthy recovery. During the first decades of the 1900s, as radiation therapy became available, ovarian ablation was achieved by radiation of the ovaries (9, 10). Since the early 1980s the standard way of blocking ovarian function has been with gonadotropin-releasing hormone (GnRH) agonists (11). Several studies have confirmed the effectiveness of ovarian ablation, especially when given in conjunction with antihormonal treatment such as tamoxifen or an aromatase inhibitor (AI) (12, 13).

Surgery

Oophorectomy is the oldest form of antihormonal treatment. While it was suggested by Shinzinger as early as in 1889, he never published his findings (9). In 1896, Beatson published an interesting and detailed case report in the Lancet (14). Here, he describes a 33-year-old woman with a left sided breast tumour that occurred while breast feeding her first child. The tumour increased in size while breast feeding her second child. In January 1895 she underwent surgery in which her left breast was removed in addition to a large area of skin, the pectoral muscle and axillary lymph nodes. She remained in hospital for almost two months. However, it did not take long before the tumour recurred. She presented to Dr Beatson at the Glasgow Cancer Hospital with the following referral letter in May the same year:

> *"37 Apsley Place, 6th May 1895.*
> *DEAR DR BEATSON, -The bearer, Mrs B., is, and has been suffering, I fear, from a malignant breast. She has been in the Royal Infirmary before she came to me. My own opinion is that nothing can be done for her; but as she is a woman of great courage, you might have a look at it for my sake, and perhaps you can order her something in the way of dressing. Even this little will be accepted by her as a great deal. -With kindest regards, yours very truly, James W. Wallace."*

Dr Beatson performed a bilateral oophorectomy. Mrs B. improved after this and survived for nearly four years before she died from recurrent disease. In 1905, Lett reported that 24 out of 99 women with breast cancer experienced marked improvement when treated with bilateral oophorectomy (9).

In 1955, Sir Stanford Cade, a senior surgeon at the Westminster hospital, published an article in the British Medical Journal (BMJ) where he reported that he had performed bilateral

adrenalectomies and oophorectomies on 56 patients with advanced breast cancer. At this stage he had no indication as to which of the patients would benefit from this surgery. He described marked improvement in 13 of these patients. He noted the following effects: relief of pain from skeletal metastases, regression of visible and palpable lesions, re-ossification of skeletal metastases and union of pathological fractures. He also mentioned that 8 patients died during this procedure, a mortality of 13.6% (15).

In 1956, Luft et al who were neurosurgeons in Stockholm, published an article describing the use of hypophysectomy (removal of the pituitary gland) in the treatment of malignant tumours. They did not know exactly why this worked in certain tumours and not in others. They postulated that sex hormones probably play an important role as this procedure only seemed to have an effect in cases such as breast- and prostate cancer and not in others such as malignant melanoma and sarcoma (16).

Radiation therapy

As radiation therapy became more widely available, so did the possibility of blocking the function of the ovaries by radiation. Roar Nissen-Meyer at the Norwegian Radium Hospital in Oslo was one of the first in the late 1950s to study ovarian radiation (9). In 1967 he published an article (17) where he described the beneficial effect of ovarian radiation. Nissen-Meyer also recognized the side effects induced by inhibiting ovarian function. He stated:

> "*It is the duty of the doctor in charge of the patient in each single case to consider the prognosis, the possible effect and the side-effects of a primary ovarian irradiation, and to give his advice if such treatment should be given".*

Gonadotropin-releasing hormone agonist

Oophorectomy and radiation of the ovaries has fallen out of fashion after the introduction of gonadotropin-releasing hormone (GnRH) agonist. Shally and Guillemin discovered GnRH in 1971. They did extensive research on GnRH and other hypothalamic hormones and won the Nobel Prize for Physiology and Medicine for this work in 1977 (18, 19). GnRH analogues came into clinical use in the 1980s. GnRH analogues are used in the treatment of a wide variety of conditions, such as breast cancer, prostate cancer, endometriosis and fertility treatment. Due to this wide variation of use, over 5,000 synthetic analogues of this hormone have been produced between 1972 and 2016 (11, 20).

Tamoxifen

Tamoxifen, initially called ICI46,474, was first developed in 1962 by researchers at Imperial Chemical Industries (ICI, now AstraZeneca) in the UK. Their goal was to develop an emergency contraceptive medication. However, experiments showed that this compound failed as a contraceptive as it stimulated ovulation rather than suppressing it. Imperial Chemical Industries was on the verge of stopping the project. However, the team leader Arthur Walpole had a strong belief that the drug could be beneficial in the treatment of breast

cancer. He threatened to resign if the project was terminated. Walpole collaborated with V. C. Jordan, and in 1973 the drug was licensed in the UK for the treatment of advanced breast cancer (21, 22). Several studies involving tamoxifen were carried out in the 1970s and 1980s. In 1988 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published a meta-analysis in the New England Journal of Medicine (NEJM) supporting the use of tamoxifen, especially in postmenopausal women (23). The EBCTCG has since published several reviews on the use of anti-hormonal treatment. In 1998, they published an article in the Lancet further supporting the use of tamoxifen, also in premenopausal women (24).

Aromatase inhibitors

Parallel to the development of tamoxifen, interest in aromatase inhibition grew. In the early 1980s Santen et al showed that aminoglutethimide could block the peripheral conversion of androgens into oestrogens suggesting that this could affect breast cancer growth. This was a way of inducing a medical adrenalectomy and aminoglutethimide became the first AI in clinical use (25, 26). It was given in conjunction with hydrocortisone to overcome its non-selective effect on the adrenals (27). In 1981, Santen et al published an article in the NEMJ (28) in which they randomized 96 postmenopausal women with metastatic breast cancer to receive either surgical adrenalectomy or aminoglutethimide and hydrocortisone. They concluded that medical treatment could replace surgical treatment. However, aminoglutethimide was subsequently used only as second -and third line-therapy and not as a first-line therapy due to equal efficacy to tamoxifen and its side effect profile (25, 29). Later, third generation AIs (such as anastrozole and letrozole) with a selective effect on the oestrogen synthesis were introduced. These medications achieved an inhibition of oestrogen synthesis of ≥ 98% compared to first -and second generation AIs with around 90% inhibition of oestrogen synthesis (25). After the Anastrazole and Tamoxifen Alone and in Combination trial (ATAC) and The Breast International Group/Femara R-Tamoxifen trial (BIG-FEMTA), AIs were approved in the adjuvant setting (30).

The oestrogen receptor

The oestrogen receptor was first identified by Elwood Jensen, who, did extensive work on this receptor (31, 32). In 1978, George Block and Elwood Jensen were the first to discover the correlation between the oestrogen receptor and antihormonal treatment. They conducted a study (33) where they determined the oestrogen receptor status in 37 women who underwent surgery for primary breast cancer and later developed recurrent disease. They all received antihormonal treatment. Fifteen of these women had tumours with a significant content of oestrogen receptors, and 11 of these benefited from the treatment. They stated that:

> *"If the ER [oestrogen receptor] content of the primary tumor successfully characterizes the hormonal dependency of a given tumor, it is obvious that this would be of immense clinical value".*

Testing for the presence of the oestrogen receptor in a breast tumour has since become routine practice. The presence of the oestrogen receptor is used as a prognostic marker in order to assess who will benefit from antihormonal treatment (34, 35).

5.2.2 Oestrogen and the oestrogen receptor

Oestrogen is essential both for female physiology and reproduction. It is a steroid hormone that also affects many other physiologic functions, mainly the musculoskeletal system, the cardiovascular system and the brain. The effect of oestrogen is mediated when oestrogen binds with high affinity to the oestrogen receptor (36, 37). There are two oestrogen receptor subtypes: oestrogen receptor alpha (Erα) and oestrogen receptor beta (Erβ) (34, 38). In breast cancer, the predominant form of the oestrogen receptor is the Erα subtype (39). The expression of Erα has a clear association to the prognosis and response to antihormonal treatment (34).

In premenopausal women, the granulosa cells of the ovaries convert androgens into oestrogen. This occurs during the follicular phase and under the regulation of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In premenopausal women, most of the oestrogen is produced by the ovaries, however, 10% is produced by aromatization process in peripheral tissues (36, 37). After menopause oestrogen is still present, though in lower quantities. In postmenopausal women oestrogen is produced from androgens by the aromatase enzyme, this occurs in peripheral tissues, mainly in adipose tissue, but also in brain, blood vessels, skin, bone, endometrium and breast tissue (36).

The mechanism by which oestrogen exerts its effect on a breast cancer is not fully understood. Oestrogen may, via the oestrogen receptor, increase proliferation and thereby increase the likelihood of genetic mutations leading to cancer. Evidence also suggests that the metabolites of oestrogen may be genotoxic causing oxidative damage to DNA(5, 27). Regardless of the mechanism by which oestrogen works, it increases the risk of breast cancer and accelerates the development and growth of hormone receptor positive breast cancers.

5.2.3 Mechanism of action

Antihormonal treatment takes advantage of the fact that about 75% of breast tumours express oestrogen receptors. Oestrogen is an important accelerator in the growth of the tumour cells. By blocking the interaction between oestrogen and the receptor on the tumour cells or inhibiting the production of oestrogen, antihormonal treatment can significantly improve the survival of patients with hormone receptor positive breast cancers. An overview of the mechanisms of action of various antihormonal treatments is shown in figure 2.

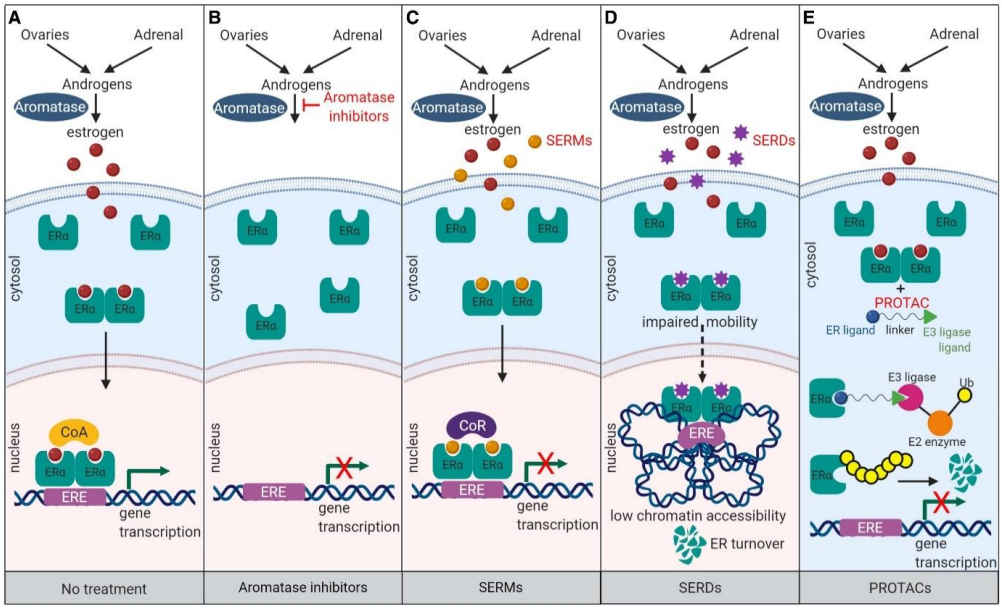

Figure 2: Mechanism of action of antihormonal treatments (40).

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Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs) are competitive inhibitors of oestrogen binding to the oestrogen receptor. Tamoxifen and raloxifene are both SERMs. Tamoxifen has both anti-oestrogenic and oestrogenic properties depending on the target tissue. In breast tissue, its anti-oestrogenic properties are exploited in the treatment of breast cancer. Tamoxifen has an oestrogenic agonist effect on the uterus inducing endometrial hyperplasia and in the vascular system it can induce thromboembolism (36, 41, 42). Tamoxifen has a complex metabolism. It is an inactive prodrug, mainly metabolized by different cytochrome P-450 enzymes and eventually transformed into its active metabolite endoxifen. The CYP2D6-enzyme is the final and rate-limiting step in the synthesis of endoxifen. Both genetic polymorphisms of the CYP2D6-gene and medications that inhibit the CYP2D6-enzyme have been shown to reduce the activity of this enzyme, reducing the endoxifen levels and thereby reducing the efficacy of tamoxifen treatment (43-45).

Aromatase inhibitors

Aromatase inhibitors deplete systemic oestrogen levels. In postmenopausal women, oestrogen production from the ovaries has ceased. However, the ovaries and adrenals still produce androgens. As the aromatase enzyme converts these androgens into oestrogens in peripheral tissues, this becomes the main source of oestrogen production in postmenopausal women. By blocking this enzyme, AIs significantly reduce oestrogen levels in these patients (27, 36, 40). First generation AIs were rather unspecific in their action requiring concomitant corticosteroid replacement therapy. Third generation AIs, such as anastrozole and letrozole,

are more specific and potent in their action and do not interfere with the synthesis of other steroids (27).

Selective oestrogen receptor downregulator

Fulvestrant has high affinity for the ERα and works by blocking the activity of the ERα and by causing degradation of the oestrogen receptor proteins. The "D" in SERD is sometimes referred to as "degrader" (34, 46). Evidence also suggests that that fulvestrant acts by impairing the mobility of the Erα-complex into the nucleus (40). Fulvestrant is often used as a second-line treatment when resistance to tamoxifen or AIs has developed (34, 47). It has recently been approved as first-line treatment for selected hormone receptor positive patients in the metastatic setting (4).

A meta-analysis (48) compared the role of fulvestrant in postmenopausal women with locally advanced or metastatic breast cancer with standard antihormonal treatment regimens. This meta-analysis found that there was no difference between fulvestrant and standard antihormonal therapies in overall survival. There were no significant differences between the groups with regard to side effects including vasomotor symptoms, arthralgia and gynaecological symptoms. The authors conclude that fulvestrant is at least as effective and safe as standard antihormonal treatment regimens, and that there was no advantage in combination therapy.

Clinical limitations of fulvestrant include intramuscular injection and low bioavailability. Ongoing research aims to develop novel oral SERDs with better bioavailability and efficacy (47).

Proteolysis targeting chimeric molecules

Proteolysis targeting chimeric molecules (PROTACs) were first introduced in 2001 by Sakamoto et al. They comprise a group of bifunctional molecules consisting of two distinct ligands that are capable of selectively degrading proteins of interest (POIs) in breast cancer and other types of cancers. In breast cancer, one unit attaches to the endogenous E3 ligase and the other unit attaches to the target protein or POI. This leads to degradation of the POI/cancer-promoting protein. Despite much ongoing research on these molecules; however, they are not in clinical use yet (40, 49, 50).

Gonadotropin-releasing hormone agonist

Gonadotropin-releasing hormone is produced by the hypothalamus, released in a pulsatile fashion, transported in a portal circulation to the anterior pituitary where it binds to its receptor. This stimulates the secretion of LH and FSH which in turn stimulates the ovaries to produce oestrogen (11, 51). GnRH agonists have been used in the treatment for breast cancer for decades, usually in conjunction with chemotherapy and/or other antihormonal treatments (11). Both GnRH agonists and GnRH antagonists supress the production of steroid sex hormones. However, in the agonists group, this suppression is only seen 7-14 days after the onset of treatment, and is preceded by an initial increase or "flare" in steroid sex hormone

production (51). GnRH antagonists act without this initial "flare" of hormone production and could be beneficial in the treatment of breast cancer. However, their clinical use has been restricted by solubility limitations and anaphylactic reactions. GnRH analogues seem to have a dual action on breast cancer. They suppress oestrogen production as described above. Furthermore, GnRH agonists may also exert a direct effect in the GnRH receptor itself leading to concomitant reduction in tumour growth and the prevention of distant metastasis (11). A third favourable effect of GnRH analogues is their ability to induce "ovarian protection". When administered simultaneously to chemotherapy, they reduce chemotherapy-induced ovarian failure and infertility (52).

5.2.4 The efficacy of antihormonal treatment

Since their introduction of tamoxifen and third generation AIs have become widely used in the treatment of hormone receptor positive breast cancer. Initially, tamoxifen was used in postmenopausal women in the metastatic setting for 1-2 years only. As research and large studies have proven the benefit of antihormonal treatment, their use has expanded to also include treatment regimens for up to10 years in the adjuvant, curative setting. Below is a selection of important benchmark studies, these have contributed to the expanded use of antihormonal treatment over the past decades.

Tamoxifen trials

Early Breast Cancer Trialists' Collaborative Group 2005

In 2005 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) presented a meta-analysis showing that five years of tamoxifen reduced annual breast cancer death rate by 31%. It also showed that five years of tamoxifen treatment was significantly more effective than one-two years (53).

Early Breast Cancer Trialists' Collaborative Group 2011

The EBCTCG published in 2011 a comprehensive meta-analysis supporting the use of five years of adjuvant tamoxifen. This was a meta-analysis of 20 trials including 21,457 women comparing five years of adjuvant tamoxifen with no adjuvant tamoxifen. During the initial 15 years, breast cancer mortality was reduced by about a third (54).

Aromatase inhibitor trials

Arimidex, Tamoxifen Alone or in Combination (ATAC)

Anastrozole became available in 1995. In 2002, the first results of the ATAC-trial were published (55). A total of 9,366 postmenopausal women were randomized to receive either

tamoxifen, anastrozole or a combination as adjuvant treatment. This study supported the adjuvant use of anastrozole in postmenopausal women with early breast cancer. The anastrozole-group showed better efficacy compared to the tamoxifen-group with 89.4% as opposed to 87.4% disease-free survival rate at three years. The outcome in the combination-group was equivalent to the tamoxifen-group and significantly worse than when anastrozole was given alone. Anastrozole was associated with a 58% reduction in the incidence of contralateral breast cancer compared to the tamoxifen-group (55). Following these results in favour of anastrozole, NICE (National Institute for Health and Care Excellence) approved anastrozole as an alternative to tamoxifen in the adjuvant setting in 2002, the same year as the ATAC-study was published (56). Interestingly, the combination-group was discontinued as no benefit was demonstrated when compared to tamoxifen alone (57). A 10-year follow-up of the ATAC-trial published in the Lancet in 2010 showed that the anastrozole group had better disease-free survival, time to recurrence and time to distant recurrence (58).

Breast International Group (BIG 1-98)

The BIG 1-98 is a randomized double-blinded trial comparing five-year adjuvant endocrine treatment regimens consisting of four treatment arms; letrozole, tamoxifen, letrozole followed by tamoxifen or tamoxifen followed by letrozole. A total of 8,010 women were included in the study.

The first report from this study was published in 2005 in the NEJM. This study compared letrozole with tamoxifen within the first two years of the BIG 1-98 trial. It showed that both disease-free survival and recurrence at distant sites was significantly better in the letrozole group compared to the tamoxifen group. Also, it suggested that letrozole have a favourable safety profile compared to tamoxifen (59).

Due to the above-mentioned early results after 2 years, 619 (25.2%) of the women in the tamoxifen monotherapy group choose to switch to letrozole treatment. This “selective crossover” led to problems with the statistical analysis thereafter. However, this was overcome with advanced statistical methods. These analyses continued to show a benefit with letrozole compared to tamoxifen in terms of risk of death and risk of recurrent disease. The “switch-regimens” (letrozole followed by tamoxifen and tamoxifen followed by letrozole), did not improve disease-free survival when compared to monotherapy with letrozole (60).

Early Breast Cancer Trialists’ Collaborative Group 2015

A large meta-analysis of 31,920 postmenopausal women published by the EBCTCG in 2015 showed that five years of an AI reduced the rate of breast cancer mortality by 15% when compared with five years of tamoxifen (61).

Early Breast Cancer Trialists’ Collaborative Group 2022

This meta-analysis of four trials included 7,030 women. It concluded that an aromatase inhibitor with ovarian suppression rather than tamoxifen prescribed to premenopausal women

reduced the absolute risk of recurrence by 3% at five and ten years. There was no increase in deaths due to other causes during the ten-year follow-up period (62).

Switch trials

The Intergroup Exemestane Study (IES)

This randomised double-blind study recruited women from 37 countries between 1998-2003. The trial comprised postmenopausal women who have received two-three years of tamoxifen as adjuvant treatment for primary breast cancer. These women were subsequently randomised to receive either continued treatment with tamoxifen or switch to the AI exemestane to complete a total of five years of antihormonal treatment. Results published in the Lancet in 2007 (63), showed that switching to exemestane after two-three years of tamoxifen resulted in improved disease free-survival and also showed early indications of improvement in overall survival. Later results published in 2017 supported these finding concluding that the switch regimen led to sustained improvements in disease recurrence and mortality (64).

In a meta-analysis from 2009, a total of 18,871 women were included comparing trials of adjuvant AIs versus tamoxifen. This showed significant lower recurrence rates with aromatase inhibitors compared with tamoxifen, this was true for both AIsas initial monotherapy and switch therapy after 2-3 years of tamoxifen (65).

Extended therapy trials

National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42

This study (66) published in 2019 included 3,966 postmenopausal women from 158 centres in the USA, Canada and Ireland. Following 5 years of an AI or tamoxifen followed by an AI, these women were randomized to receive either letrozole or placebo for another 5 years. Disease-free survival was the primary endpoint, being defined as the time from randomization to breast cancer recurrence, second primary malignancy or death. This study did not show a significant increase in disease-free survival for those receiving extended letrozole treatment compared to those receiving placebo. This was surprising as these results at first glance were different from those in the MA.17R study (67). However, looking more carefully at how these two studies defined disease-free survival it became clear that the results are concordant. The MA.17R study defined disease-free survival as the time to recurrence of breast cancer or the development of a new breast cancer. The NSABP-B42 defined disease-free survival as the MA.17R study, but also added a second non-breast cancer and death from any cause to this definition. Allowing for this, it became clear that breast cancer-free survival in the NSABP-B42 study is the same as the definition of disease-free survival in the MA.17R study. This means that both the studies show a significant reduction in breast cancer recurrence and development of a new breast cancer for those patients receiving letrozole beyond the initial five years of antihormonal therapy. As for the MA.17R

study, the NSABP-B42 study did not show an improvement in overall survival for those taking letrozole compared to placebo (66, 68).

Adjuvant tamoxifen -To offer more? trial (aTTom)

The aTTom trial included 6,953 women from 1991 to 2005 from 176 centres in the UK. Of these, 2755 were confirmed oestrogen receptor positive and 4198 had unknown oestrogen receptor status (80% of these were estimated to be oestrogen receptor positive). Following five years of adjuvant tamoxifen, the women were randomized to take tamoxifen for another five years or to stop the treatment. The study showed that those who received tamoxifen for ten years had reduced breast cancer recurrence, breast cancer mortality and overall mortality, all these variables were time dependent showing greater benefits with longer treatment duration (69).

Adjuvant Tamoxifen: Longer Against Shorter (ATLAS)

The ATLAS study was a worldwide study including 12,894 women, randomized participants who had been treated with tamoxifen for five years to either continue with tamoxifen to 10 years, or to stop treatment at five years. Like the aTTom-trial, this study also showed a significant reduction in breast cancer recurrence and mortality with 10 years of tamoxifen compared to five years. These benefits were also observed after 10 years when the treatment was stopped (70).

MA.17

In the MA.17 trial (71) a total of 5,187 postmenopausal women were randomized to receive either letrozole or placebo following 5 years of adjuvant tamoxifen treatment. In October 2003, after a median follow-up of 2.4 years, the study was terminated because of the very favourable effects in the letrozole-group. The study showed a significant higher estimated four-year disease-free survival rate in the letrozole-group of 93% compared to 87% in the tamoxifen-group. The study also showed reduced occurrence of distant metastases and reduced death due to breast cancer in the letrozole-group (71). In the MA.17 trial overall survival was not significantly improved, however, letrozole significantly improved overall survival in node-positive tumours. This was the first time an aromatase inhibitor showed improved survival in early breast cancer (72).

DATA

This study from 2017 included 1,912 postmenopausal women from 79 hospitals in the Netherlands. Following 2-3 years of adjuvant tamoxifen treatment, these women were randomized to receive either 3 years of anastrozole or 6 years of anastrozole. The study concluded that extended treatment with anastrozole for 3 years following 5 years of sequential treatment did not significantly increase disease-free survival or overall survival.

However, it suggested that certain high-risk patients might derive benefit from extended therapy (73).

5.2.5 Risk of recurrence

Following primary treatment, the risk of recurrence for hormone receptor positive cancers remains high until at least 15 years after diagnosis. For hormone receptor negative breast cancers, the risk of recurrence is at its highest a few years after diagnosis but declines thereafter (74). The EBCTCG has looked at the risk of recurrence of breast cancer when stopping antihormonal treatment after 5 years. In 2017 they published a meta-analysis (75) of 88 trials including 62,923 women. This showed that breast cancer recurrences continued to occur at a steady rate from 5-20 years. Even in low-grade T1N0-cancers, the risk of recurrence was 10% in the 5-20 years period. There was a strong correlation between nodal status and recurrence (75). The NSABP-B42 trial showed a reduction in the recurrence of breast cancers and new primary breast cancers with the extended treatment with an aromatase inhibitor beyond 5 years of antihormonal treatment. The study did not show an effect on overall survival (66, 67). In 2014, the American Society of Clinical Oncology (ASCO) published guidelines that recommended extending antihormonal treatment to 10 years (76).

5.2.6 Prediction of recurrence and biomarkers

Traditionally, the classical clinicopathological features (stage, histological grade, oestrogen receptor, progesterone receptor, HER-2 status and Ki67-level) have been used to guide treatment choice and to give prognostic information. With ongoing research, gene expression analysis has become available to further aid decision-making. Many of these multi-gene biomarkers are now commercially available, examples include: Oncotype Dx, Prosigna, Breast Cancer Index (BCI), EndoPredict and MammaPrint (77, 78). These biomarkers can help predict who will benefit from adjuvant chemotherapy, but also predict who will benefit from extended adjuvant antihormonal treatment (35). PEPI (Preoperative Endocrine Prognostic Index) is a biomarker specifically designed for neoadjuvant endocrine treatment. It stratifies patients into three risk groups based on post-treatment oestrogen receptor expression, Ki67, histological grade, tumour size, nodal status and treatment response. The score can assist in decisions regarding other adjuvant treatments (74, 78).

The efficacy of extending adjuvant antihormonal treatment to 10 years has been well documented (67, 69-71). The need to further stratify and select those patients who will benefit from this treatment regimen is important. It is important to spare patients from unnecessary side effects of antihormonal treatment beyond 5 years if this is deemed safe. This is especially of interest as personalised treatment is an important focus-point in cancer therapy.

A retrospective study (77) compared 6 multigene biomarkers, these were: Oncotype Dx, Prosigna, BCI, EndoPredict, CTS (Clinical Treatment Score) and IHC4 (a four-marker immunohistochemical score). The study compared these biomarkers in 774 postmenopausal women (derived from the ATAC-trial) who had oestrogen receptor positive, HER-2 negative breast cancer. It concluded that in node-negative disease only Prosigna, BCI and EndoPredict

were able to significantly predict the risk of overall and late distant recurrences (77). Another study (35) looking specifically at BCI in node-positive women in the aTTom-trial found that women with a high BCI-score derived significant benefit from receiving tamoxifen over a 10-year period compared to five years of tamoxifen. Those with a low BCI-score derived no significant benefit from 10 years of tamoxifen compared to five years despite having node-positive disease. Furthermore, there was no significant association between the degree of hormone receptor positivity and extended treatment with tamoxifen (35). See figure 3. An expanded analysis of this material was published in 2022 (79), showed consistent results where node-positive patients with a high BCI-score derived significant benefit from 10 years of tamoxifen treatment. Node-positive patients with a low BCI-score did not gain any benefit from extended treatment with tamoxifen. The total study population and the node negative-subgroup were underpowered due to the low event rate in the node negative subgroup (79).

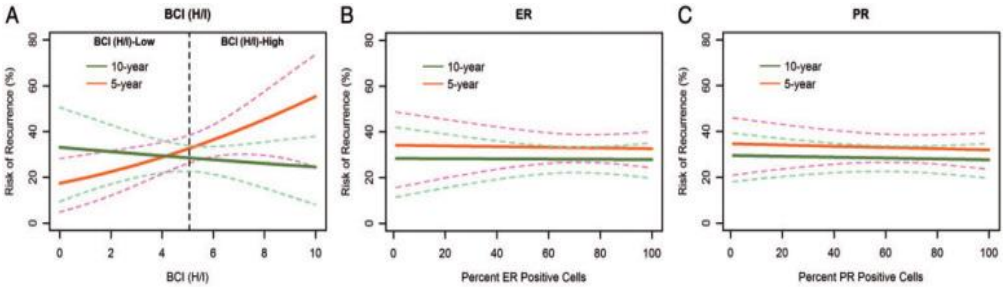

Figure 3. Risk of recurrence of node-positive disease in relation to Breast Cancer Index (BCI), oestrogen receptor status and progesterone status for patients treated with 5 or 10 years of tamoxifen (35).
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5.2.7 Side-effects of antihormonal treatment

It has become common to switch from tamoxifen to an AI as part of the planned treatment regimen. However, often a switch in the antihormonal treatment becomes inevitable due to the development of troublesome side effects. While both tamoxifen and AIs are generally well tolerated (55, 74), their side effects are well recognized. These can vary from minimal complaints to severe side effects leading to non-adherence and therefore the potential for a poorer outcome for the patient. In extremely rare cases, adverse effects may be fatal. Extended treatment up to 10 years often means prolonged duration of experienced side effects. However, women who have already completed five years of antihormonal treatment are less at risk of developing new symptoms than those who are starting the treatment (75, 80). Tamoxifen and aromatase inhibitors have similar, yet varying side effect profiles which are important in the clinical setting. Also, for those women who have received cytotoxic treatment, which may induce an early menopause, the side effects of the antihormonal therapy may be exacerbated.

Tamoxifen

The most frequent side effects of tamoxifen include vasomotor symptoms (hot flushes and night sweats), gynaecologic symptoms (vaginal dryness, vaginal discharge), sleep disturbances, weight gain and depression/irritability/mood swings. Less common, but more severe side effects include venous thromboembolic disease and endometrial cancer (80, 81). The risk of developing severe side effects increases with duration of treatment. However, the absolute risk of death due to severe side effects is low at <0.5% (75).

Most endometrial cancers attributed to tamoxifen are low-grade stage 1 cancers, rarely high-grade sarcomas may occur (55). Tamoxifen entails a 2-3-fold increased risk of developing endometrial cancer compared to an age-matched population (82). It has been shown that routine gynaecological examinations of asymptomatic women taking tamoxifen has a low specificity and a poor positive predictive value. This type of screening will also lead to unnecessary surgical interventions (83). The American College of Obstetricians and Gynecologists (ACOG) published a committee opinion in June 2014 stating that routine gynaecological examinations of women taking tamoxifen is not necessary in the absence of gynaecological symptoms (82).

The relative risk of venous thromboembolic disease following tamoxifen use is increased 2-7-fold. Incidence is highest the first two years of treatment and a deep venous thrombosis (DVT) is more common than pulmonary embolism (PE). Interestingly, a study comparing tamoxifen and raloxifene showed that raloxifene had a 30% lower risk of venous thromboembolic disease compared to tamoxifen (84).

The agonist effects of tamoxifen may also have beneficial effects. Tamoxifen is shown to decrease bone demineralization and increase bone mineral density in postmenopausal women, thereby preventing osteoporosis. Also, tamoxifen decreases low-density lipoprotein (LDL) and increase high-density lipoprotein (HDL) levels in postmenopausal women. Some studies have shown tamoxifen to be cardioprotective, however other studies have not been able to prove this beneficial effect (85).

Studies have been undertaken trying to predict who will develop side effects. A cross-sectional analysis of 241 women taking tamoxifen showed that significant predictors of developing side effects include: younger age, taking tamoxifen for less than 12 months, previous use of postmenopausal HRT and higher serum endoxifen levels (81). Another study of women taking tamoxifen showed that women aged 75 years and older and those with better emotional health were less likely to experience side effects of the treatment (86).

Aromatase inhibitors

The most frequent side effects of AIs are vasomotor symptoms (hot flushes and night sweats), gynaecological symptoms (vaginal dryness and dyspareunia), musculoskeletal symptoms (arthralgia, myalgia), osteoporosis and fractures (59, 80). When anastrozole was compared to tamoxifen in the ATAC-trial, it was shown that anastrozole was associated with significant reductions in hot flushes, vaginal discharge/bleeding, ischaemic cerebrovascular events, venous thromboembolic events and endometrial cancer. However, anastrozole was associated with significantly more musculoskeletal disorders and fractures (55). An extended

follow-up analysis of the ATAC-trial showed that in postmenopausal patients with early-stage breast cancer, anastrozole was better tolerated than tamoxifen, led to fewer adverse events, and resulted in lower recurrence rates than tamoxifen (87).

With the increased incidence of osteoporosis in those taking AIs, comes an increased risk of fractures. The ATAC and BIG 1-98 trials both showed an increased risk of developing bone fractures with an AI compared to tamoxifen (55, 59). However, the risk associated with AIs may have been overestimated as tamoxifen itself has a bone protective effect. Calcium and vitamin D supplements are recommended while taking an AI (85).

In a prospective cohort study of 12,904 postmenopausal women receiving an AI who did not have a previous history of cardiovascular disease or venous thromboembolic disease, showed that the use of an AI was associated with at least 41% decreased risk of developing venous thromboembolic events compared to tamoxifen (88). The MA.17-trial showed no significant difference in cardiovascular events when comparing the letrozole group with the placebo group and there were no cases of drug-related hypercholesterolemia (71).

The risk of potentially life-threatening side effects (bone fractures for AIs sand pulmonary embolus and endometrial cancer for tamoxifen) increase with longer treatment. However, the absolute risk of death is low at <0.5% (75).

5.2.8 Management of side effects

The side effects of antihormonal treatment range from mild to severe. Both pharmacological and non-pharmacological therapies exist to treat troublesome side effects. Some have well-documented efficacy; others have not been proven to be helpful. The symptoms of the physiological menopause are similar to the side effects of antihormonal treatment. As many of the breast cancer patients are undergoing the changes of menopause at the same time the antihormonal treatment is administered, they often experience a substantial burden of symptoms (80).

Pharmacological approaches

Peroral hormonal therapy

The most effective management of the side effects induced by antihormonal therapy would be oestrogen replacement therapy. This is contraindicated as it would counteract the effect of the antihormonal treatment and increase the risk of breast cancer recurrence. The Swedish HABITS-trial tested this hypothesis randomizing 434 women with previous breast cancer and menopausal symptoms to either HRT or to best symptomatic treatment without hormones. Treatment with tamoxifen was allowed. The trial was terminated in December 2003 due to an unacceptable high risk of breast cancer in those treated with HRT compared to those who did not receive HRT (89).

Local hormonal therapy

There has been, and still is, some controversy regarding the use of vaginal hormonal therapy in breast cancer patients. Studies have shown that vaginal oestrogen therapy significantly

increases circulating oestrogen levels (90). However, there is also evidence that it only occurs in some women and its clinical relevance is uncertain (80). One study (91) comprised 13,479 women, of whom 2,673 received an AI, 10,806 received tamoxifen and 271 used vaginal oestrogen therapy. The study concluded that using vaginal oestrogen therapy simultaneously with tamoxifen or an AI, did not cause an increased risk of breast cancer compared to the control group. However, the results were mainly driven by the tamoxifen-group as the AI-group lacked statistical power (91). As AIs acts by lowering oestrogen levels and tamoxifen competitively inhibits the oestrogen receptor, it has become increasingly accepted that vaginal oestrogen therapy can be given (at lowest effective dose) in combination with tamoxifen (80). Non-hormonal local moisturizers and lubricants should be tested prior to commencing local hormonal therapy.

Antidepressants

Antidepressant such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are used in the treatment of hot flushes both for healthy menopausal women and for women experiencing hot flushes as a side effect of antihormonal treatment. A large review of 11 randomized controlled trials looking at healthy (non-breast cancer) menopausal women showed that SSRIs were associated with a significant decrease in frequency and severity of hot flushes compared to placebo (92). Evidence shows that even a low dose of venlafaxine is effective in treating hot flushes in patients taking tamoxifen (93, 94). The concomitant use of tamoxifen and an SSRI could potentially reduce the bioavailability of tamoxifen metabolites, thereby reducing the effectiveness of tamoxifen and increasing the risk of breast cancer recurrence (45, 80). Selective serotonin reuptake inhibitors and SNRIs are inhibitors of the CYP2D6-enzyme. Medications within these groups of antidepressants inhibit the CYP2D6-enzyme to various extent. Paroxetine and fluoxetine are potent inhibitors of the CYP2D6-enzyme, while venlafaxine and citalopram are weak inhibitors of the enzyme (43, 95). There is some varying evidence regarding the safety of using these medications in conjunction with tamoxifen. Some studies states that it is safe to do so, even when prescribing potent CYP2D6-inhibitors with tamoxifen (96, 97). However, there is strong evidence that potent CYP2D6-inhibitors and tamoxifen should not be prescribed simultaneously (43-45, 98-100). It is important to bear in mind that other medications also might affect the CYP2D6 metabolism. Examples of other medications known to be moderate to potent CYP2D6-inhibitors include cardiac medications (quinidine, ticlopidine), antipsychotics (perphenazine, pimozide) and cinacalcet (45).

Anticonvulsants

Anticonvulsants, such as gabapentin and pregabalin, have been described to be helpful in treating hot flushes. A randomized, double-blind trial included 420 women with breast cancer experiencing ≥2 episodes of hot flushes per day to receive either placebo, 300mg of gabapentin or 900mg of gabapentin a day for eight 8 weeks. For each group, 75%, 68% and 69% of the women were taking concomitant tamoxifen respectively. At 8 weeks, placebo reduced the severity of hot flushes by 15%, for gabapentin 300mg/day this value was 31% and for gabapentin 900mg/day it was 46%. The study concluded that 900mg/day of gabapentin significantly reduces both frequency and severity of the experienced hot flushes

(101). Another randomized controlled trial compared gabapentin 900mg/day with vitamin E in 115 women with breast cancer. 87% of those in the gabapentin-arm were concurrently taking tamoxifen and 86% of those in the vitamin-E arm were taking tamoxifen. With gabapentin, the frequency of hot flushes decreased with 57% and the severity of hot flushes decreased with 67%. For vitamin E, the effect was small with a decrease in frequency of hot flushes of 10% and severity of 7% (102).

Clonidine

A meta-analysis looked at the effectiveness of clonidine in treating hot flushes both in breast cancer patients and non-breast cancer patients. Of 10 trials, half of them reported significant reduction in the frequency or severity of hot flushes. However, only 3 of the trials were classified as fair-quality trials and a combined estimation of these showed that clonidine approximately causes a reduction of one hot flush per day (103).

Other agents

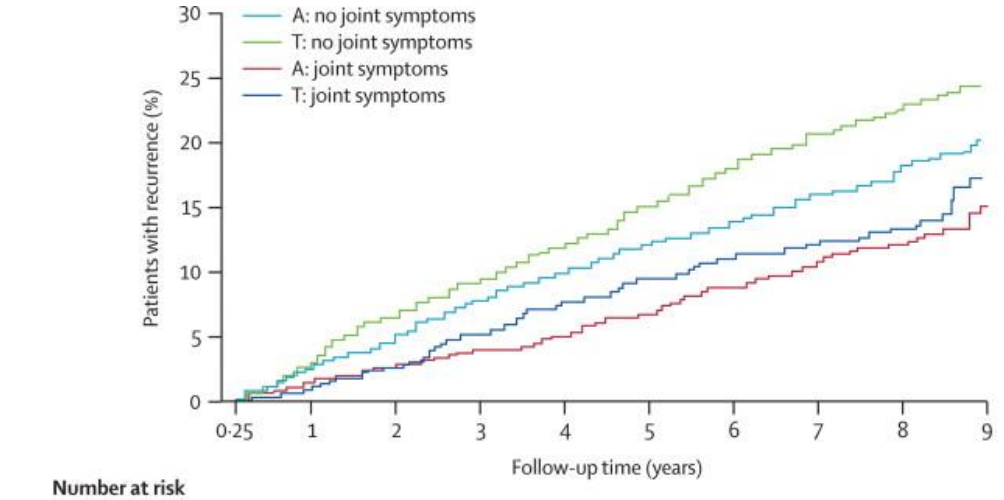
Natural health products such as phytoestrogens, black cohosh and St. John's wort do not seem to be effective in treating hot flushes. There are safety concerns regarding the use of phytoestrogen as they have weak oestrogenic effects and thereby potentially can cause breast cancer and endometrial hyperplasia. Also, black cohosh has been shown to interfere with the activity of tamoxifen (80, 100). Other agents such as vitamin E, omega 3 and magnesium have not been proven to be effective in treating hot flushes. Glucosamine might have a role in treating musculoskeletal complaints (80).

Non-pharmacological approaches

Cognitive behavioural therapy (CBT), hypnosis, acupuncture, weight control and stellate ganglion blockade might all have a role in the management of hot flushes. Physical activity does not seem to have a direct effect on hot flushes; however, it has a beneficial effect on musculoskeletal symptoms. As an alternative to local hormonal agents, moisturizers and lubricants are safe, although less effective, options (80).

5.2.9 Side effects and recurrence

There is some evidence that the presence of side effects might predict the efficacy of antihormonal treatment. A study (104) of 1,551 women with early breast cancer showed that women who reported hot flushes secondary to tamoxifen treatment were less likely to develop breast cancer recurrence. The authors suggest that the side effects are an indirect measure of the enzyme CYP2D6 activity, this activity correlates with endoxifen levels which is the active metabolite of tamoxifen (104). It has been suggested that endoxifen levels might predict both the occurrence of side effects and the risk of recurrence. However, the CYP2D6 genotype does not seem to be a good predictor of recurrence as endoxifen levels also are affected by medications that inhibit the CYP2D6 enzyme (81).



Number at risk						
A: no joint symptoms	1302	1190	1083	909	643	199
T: no joint symptoms	1417	1273	1154	966	624	181
A: joint symptoms	665	646	615	545	376	114
T: joint symptoms	580	563	523	460	333	96

Figure 4: Breast cancer recurrence according to treatment group and whether joint symptoms (with or symptoms) were reported at the 3-month follow-up visit in women without endocrine symptoms at entry.
A=anastrozole. T=tamoxifen (105).

A retrospective study (105) of 3,964 women in the ATAC-trial showed a significant lower recurrence of breast cancer in those women reporting vasomotor or joint symptoms within the first 3 months of antihormonal treatment (Figure 4). This was true both for those taking tamoxifen and for those treated with anastrozole. Non-adherence due to troublesome side effects is a well-recognised problem. This finding might be of value when encouraging women to adhere to their prescribed antihormonal treatment (105).

5.2.10 Quality of life and side effects

Being diagnosed with breast cancer and the subsequent treatment imposes a substantial impact on the patient's life, both physically and psychologically. This is further intensified by the side effect(s) of the treatment(s) given. Many of these patients are initially treated with surgery +/- radiotherapy +/- chemotherapy which may induce various side effects. Subsequently adding antihormonal treatment may further exacerbate these symptoms, but also introduce new troublesome side effects. When the side effects of a given treatment become so troublesome that they impair quality of life (QoL), this may subsequently affect the patient's adherence to that treatment.

In one study of 404 patients treated for early-stage breast cancer, the patients were treated with radiotherapy (72%), chemotherapy (49%), antihormonal treatment (57%) and axillary dissection (21%). Here, 93% of the patients reported one or more health problems up to five years after diagnosis (106). A patient may choose to take a prescribed medication or

chose not to. Whether or not the patient is willing to start such treatment is highly dependent on the information given by the clinician regarding why the treatment is started, available options, expected therapeutic gain and side effects, but also largely dependent on their own expectations and prior knowledge about the treatment. How a medication affects a person's QoL is an important factor determining whether the patient will persist with the recommended treatment regimen over time (107).

The ATAC-trial randomized 9,366 postmenopausal women who had completed primary treatment for breast cancer to receive 5 years of adjuvant therapy with either tamoxifen, anastrozole or a combination of these (55). A 5-year follow up study of the ATAC-trial looked at health-related QoL in women treated with tamoxifen (n=347) and anastrozole (n=335). This study concludes that there was no significant difference between tamoxifen and anastrozole at five years and that QoL for both groups slightly improved during the treatment period. Those taking tamoxifen experienced more cold sweats and vaginal discharge, while those taking anastrozole experienced more vaginal dryness, dyspareunia and loss of libido (108).

Another study looking at the QoL is the IES-study. This study randomized women who had initially been taking tamoxifen for 2-3 years to either continue with tamoxifen or to switch to exemestane to complete a course of 5 years of antihormonal therapy (63). Comparing these two groups revealed that there were no significant differences in QoL. The only variable that differed between the two groups was vaginal discharge that was more prevalent in those taking tamoxifen. There was a gradual, slight improvement of symptoms over time. Although there were no differences in QoL between the two groups, it is important to recognise that the symptoms described were described as severe, this was especially true for hot flushes, sweating and sleep disturbances (109).

Decreased QoL following cancer treatment might not be a direct result of the given oncological treatment. One study compared 196 postmenopausal breast cancer patients (treated with curative surgery, chemotherapy, radiotherapy and/or antihormonal therapy) with 101 controls (blood donors). The majority (76%) of the women with breast cancer reported health complaints similar to those reported by the controls. Significant predictors of these complaints were fatigue, anxiety and depression, not the given oncological treatment(s) (110). Depression and anxiety are known side effects of antihormonal treatment. However, these symptoms might also occur as a result of menopause itself (111) and/or due to the burden of being diagnosed with cancer (112). Treating depression, regardless of cause, is important.

The expectations to antihormonal treatment have been proven to affect both side effects and QoL reported by the patients. After 2 years of antihormonal treatment, the relative risk of side effects was higher in those with negative expectations at baseline than those who did not have these negative expectations (RR=1,833, CI 95% 1,032-3,256) (113). Many cancer-patients overestimate their risk of recurrence, this might also affect their QoL. In a study of newly treated breast cancer patients with a good prognosis, 30.4% of the patients overestimated their risk of recurrence to be more than twice their actual risk. This overestimation was significantly associated with decreased QoL (114). Expectations to the treatment and patients perceived risk of recurrence are important factors to bear in mind as these are potentially modifiable.

When considering QoL in relation to the side effects of a given treatment, one should be aware of how the side effects and QoL were recorded. Antihormonal treatment is often described as “well tolerated” (55, 115). However, there is evidence that these medications are less “well tolerated” than they appear in clinical studies. Qualitative studies have shown that there is large discrepancy between the side effects reported by clinicians in medical records compared to women’s own reports in research interviews (107). A study of 75 premenopausal women with early breast cancer receiving tamoxifen, goserelin or both compared the side effects documented in the medical records with an interview of the women focusing on the side effects experienced. The study showed that there were significant differences in the recorded frequency of side effects in the medical records compared to the patients’ self-report in the interview (116). This is a potentially serious issue as underestimation of side effects in medical records might lead to a misleading side effect profile.

5.3 Adherence

"Keep a watch also on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die. What they have done never results in a confession, but the blame is thrown upon the physician" Hippocrates, Decorum (117).

Hippocrates (about 460BC – 370BC). The father of modern medicine (118).

"Drugs don't work in patients who don't take them" C. Everett Koop, M.D.

Charles Everett Koop (1916-2013). American paediatric surgeon. Appointed as Surgeon General of the United States under President Ronald Reagan from 1982-1989 (119).

5.3.1 Definitions

Various definitions of adherence, compliance and persistence exist and there has been opposing views how to best define each one of them. Persistence describes the time from initiation to discontinuation of therapy or, in more general terms, whether the patient stays on the prescribed treatment or not (120).

Adherence and compliance both describe the extent to which a patient follows a treatment regimen. Often, these terms are used interchangeably and synonymously (121, 122). With increasing research in this field, there has been a shift in the preferred terminology. Compliance, being the oldest term, has become less popular and adherence has become the preferred term. Compliance refers to the more passive behaviour in which the patient merely follows instructions. Compliance denotes a paternalistic approach to patient care where patient autonomy often is disregarded. The term compliance also has other meanings (such as mechanical compliance and compliance with regulations/good clinical practice) which further limits its use (123-126).

In 2003, the World Health Organization (WHO) stated that it is important to differentiate between adherence and compliance. WHO defines adherence as:

"The extent to which a person's behaviour -taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider". (127).

Increased focus on patient autonomy has probably contributed to the shift in terminology where adherence is preferred (128). Adherence describes the active and agreed choice a patient makes in collaboration with the clinician where they agree upon a suitable treatment after discussion in a non-paternalistic manner (123). The WHO emphasizes that adherence requires that the patient agrees to the recommendations made, the importance of patients

being active partners with health professionals and that good communication is paramount (127).

Non-adherent patients can be subclassified into being primary non-adherent (PNA) or secondary non-adherent (SNA). Primary non-adherence refers to those patients who never initiate a prescribed treatment, that is, they don't consume any of the treatment. Secondary non-adherence refers to those patients who initiate a treatment, but subsequently discontinue it (125, 129, 130).

5.3.2 Adherence in general

"In every situation in which patients are required to administer their own treatment, nonadherence is likely".

WHO (127).

Close to 50% of all patients does not adhere to prescribed medical treatment (122, 131, 132). Poor adherence prevents medications from exerting their full beneficial effect and thereby resulting in increased morbidity and mortality (125, 133, 134). As an example, poor adherence is the main cause of poor blood pressure control in the population. Less than 25% of patients undergoing treatment for high blood pressure achieves satisfactory blood pressure (127). Less than 50% of patients takes their blood pressure medication one year after initiating the treatment (135).

Adherence is not a binomial value where the patient is either adherent or non-adherent. It is rather a continuous variable ranging from being fully non-adherent, to partially adherent to completely adhere to the recommended treatment (123). Adherence often vary during the course of a treatment. An example of this is the phenomenon "white coat adherence". Here, adherence typically increases around the time before and after a doctor's appointment (125).

Adherence has three components: initiation, implementation/execution and discontinuation. Initiation occurs as the patient takes the first dose of the prescribed treatment. Implementation or execution is the extent to which a patient follows the dosing regimen correctly. Discontinuation occurs when the patient takes his/hers last tablet (126, 136). Suboptimal execution is often recurrent and will frequently lead to treatment discontinuation. Figure 6 shows non-initiation/primary non-adherence (the initial abrupt drop at zero time) and persistence in seven medical conditions (a) and in relation to execution (b) (126).

Poor adherence also includes overdosing or taking doses too close together. This might lead to risk of toxicity and this is especially true for medications with accumulative pharmacodynamics and/or low toxicity threshold. Elderly patients are especially at risk due to altered pharmacodynamics. Certain medications, if taken in too high doses, may lead to dependency, examples include diazepam and opioids (127, 137).

It is important to consider the difference between intentional and non-intentional non-adherence. Intentional non-adherence occurs when the patients choose not to take their

medication or alter the dose to suit their needs. Non-intentional non-adherence usually occurs when the patient forgets to take the medication or has misunderstood the instructions. Research has shown that intentional non-adherence can be predicted by the patient's own opinions regarding the medication. Nonintentional non-adherence is more strongly related to patient characteristics such as age, ethnicity and educational level (138, 139).

5.3.2 Adherence in the global perspective

The impact of non-adherence in the global perspective is quite substantial. In developing countries this problem is magnified and complicated by scarce health care resources and often poor access to health care. As an example, tuberculosis (TB) is a major global health problem. In 2021, 10.6 million people got infected with TB and 1.6 million people died worldwide (140). A standard short course of treatment lasts six months for new patients and for those who need re-treatment the course typically lasts eight months. Close to 50% of all patients with TB do not finish their prescribed treatment regimen. As this is an infectious disease, this leads to increased spread of the infection, as well as drug resistance, relapse of the disease and death (141). It is reported that 37-83% of patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) do not adhere to their antiretroviral therapy (depending on the type of medication given and the characteristics of the study population) (127). In sub-Saharan Africa, there are rather high rates of TB-HIV coinfection, which further complicates the matter (141). Poor adherence represents a major concern in the global health perspective as successful treatment is largely determined by the adherence to long-term therapies (127).

5.3.3 Measurement of adherence

Measurement of adherence is challenging. Several methods exist, but they all have their limitations. Many of the methods used are subject to bias because of the "Hawthorne effect". This describes the tendency of patients to improve their adherence when they know that their adherence-behaviour is being monitored. This is often done to please the observer (137). Measurement of adherence is important to identify patients that would benefit from improved adherence and as an aid to understand which factors affect adherence. Also, assessment of adherence is highly important when evaluating clinical and economical outcomes related to a treatment (120).

Measurement of adherence can be achieved using direct and indirect methods (159, 169). Direct measurements include the detection of the medication, or one of its metabolites, in the blood, urine or other bodily fluids. It can also be the detection of a biological marker added to the drug formulation. These methods are often expensive and laboursome. Although direct measurements can be a good alternative for assessing adherence, they give no information about the timing of the doses taken. Also, these measures are affected by varying pharmacokinetics in different individuals which may make the results difficult to interpret (124, 137, 142). In order to make sure an individual actually takes the medication as prescribed, directly observed therapy (DOT) is an alternative. This is the most accurate method for ensuring adherence. Here, one observes the ingestion of every dose taken. It is extremely resource-intensive and is not routinely used. However, it has been used by

authorities for the treatment of diseases that impose a high public health risk, such as TB (143).

Indirect measurements are more commonly reported in the literature and include patient interviews, questionnaires, medication diary, pill counts, assessing clinical response, electronic medication monitors and refilling of prescriptions. The use of questioning or diaries are relatively simple measurements to perform but are often biased due to over-reporting of adherence. Pill counts might give an incorrect picture of adherence as pills may be thrown away prior to a doctor's appointment. Assessing clinical response might be confounded by many factors which can affect the clinical outcome and not be attributable solely to the given medication. Electronic monitors called medication event monitoring systems (MEMS) have been available for a long time, but because of the high cost, they are mainly used in clinical research. These are monitors attached to, for example a pill bottle or an inhaler, and records date and time for when the pill bottle was opened or when the inhaler was used. This gives accurate information about when the medicine bottle was opened. However, it does not verify that the medication was consumed or that the correct dose was taken (124, 125, 127, 137, 142).

Another indirect measure of adherence is the registration of prescription filling. These assume that refilling of prescriptions corresponds to the actual adherence-behaviour. This method provides an accurate and objective measure of adherence in a large population over a long period of time. Also, the Hawthorne effect is avoided (124, 125, 137).

The medication possession ratio (MPR) is the most frequently used measure for adherence (144, 145). It measures the proportion of days a medication is at hand during a specified time interval:

$$MPR = \frac{Days\ supply}{Length\ of\ observed\ period}$$

A weakness of this measurement is that it does not tell if the medication actually is ingested by the patient. Therefore, MPR may overestimate adherence (125, 146, 147). It is important to recognize that adherence statistics can vary greatly and is dependent on which method of measurement is used (134). Regardless of which method used, various thresholds for defining "good" and "bad" adherence exists. However, there is lack of evidence to support these levels of threshold (127, 133). An 80% cut-off is commonly used (146, 148). This cut-off has been shown to be valid for many chronic diseases (149), it remains controversial.(150).

5.3.4 Consequences of poor adherence

"Medication adherence is America's new drug problem".

Carolyn Clancy, MD. Former director of the Agency for Healthcare Research and Quality.

Patient outcomes

Poor adherence may result in effective treatments being judged ineffective. Unnecessary prolongation and/or intensification of the treatment may be implemented (125, 126, 131). Also, unnecessary, and often expensive, diagnostic procedures may be ordered when a patient does not respond to a given treatment (125). Hospital admissions of patients that do not adhere to their regular medications may potentially lead to dangerous situations such as hypotension and hypoglycaemia when they are re-started on medications as prescribed, when in reality they had been non-adherent prior to admission. Good adherence in chronic conditions will prevent or delay the onset of complications, prevent hospital admissions and reduce health care costs (131).

A meta-analysis of 21 studies involving 46,847 patients showed that good adherence (this was variously defined and measured in the included studies, mainly ranging from ≥66% - ≥95% as a threshold for "good" adherence) to the recommended treatment decreased mortality by half when compared to those with poor adherence. Interestingly, the same result was shown for those patients who had good adherence when given placebo. This can be explained by the "healthy adherer effect" where good adherence is believed to act as a surrogate marker for a healthy behaviour/lifestyle and therefore decreased mortality (151).

Economy

Poor adherence does not only lead to poor health care outcomes, but also contributes to significant health care costs (129, 134, 136). In the US, it is estimated that costs related to non-adherence range from $100-$300 billion each year. This represents 3-10% of the total health care expenditures (131). Twenty-three percent of all admissions to nursing homes and 10% of all hospital admissions can be related to poor adherence (142). Improvement of poor adherence can directly contribute to savings for the health care system, exemplified by reduced hospital admissions and the prevention of relapses of disease. More indirect savings are seen as patients will preserve or even improve their QoL and are able to maintain their work capacity (121, 127, 143).

Clinical trials

In clinical trials participating patients are followed closer than in real life. Together with the often-careful selection of patients, this might lead to artificial high adherence rates in the study-setting. However, poor adherence is also a major concern here. Four to five per cent of participants in clinical studies never initiate the treatment. In clinical trials of chronic conditions, adherence rates of 43-78% have been reported (124, 135). Especially dose-response relationships may be miscalculated. This may in certain cases lead to incorrect conclusions. These conclusions are often based on underestimation of treatment effect, underestimation of side effects and overestimation of dosing requirements. Furthermore, the economic analyses may be distorted (125, 126). As a result, there should be greater emphasis on documenting the extent of adherence in relation to treatment effect in clinical trials (151).

5.3.5 How to improve adherence?

«There is growing evidence to suggest that because of the alarmingly low rates of adherence, increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments"

WHO, 2003 (127).

How well a patient adheres to a prescribed regimen is dependent on several factors. A good relationship between the patient and clinician is essential to capture which factors might affect adherence for each individual patient. Communication is strongly related to adherence (152). Good communication with accurate and understandable information about why the treatment is given, expected effect, possible side effects, how the treatment should be administered and for how long is important to convey to the patient (124, 132). Patients often obtain information from several sources, these might include: another doctor, nurses, brochures, pharmacists, media, books, family/friends and the internet. A study of 328 patients showed that 80.1% had received conflicting information from various sources and that this significantly reduced adherence (153). How much time a doctor spends with a patient also affects adherence. Short consultations negatively affect adherence (127). Good continuity of care positively affects adherence (131). Adherence will often be at its best just before and after a doctor's appointment, this is also known as "white coat adherence" (124, 125). Therefore, close follow-up will improve adherence. Other factors that have been shown to negatively affect adherence include stress, forgetfulness, uncertainty about the diagnosis, concerns regarding possible side effects, low expectations to the effect of the treatment, fear of dependency and poor understanding about the health risks of not taking the medication. These factors all strengthen the importance of providing good information to the patient. Other factors that also affect adherence include low socioeconomic status, poverty, low educational level, unemployment, lack of social network, long distance to health care institutions, costs related to the treatment and cultural and other beliefs that conflict with traditional medicine (127, 154).

Some patient groups are more prone to poor adherence than others. Those above 60 years of age are increasing in numbers. They often suffer from chronic illnesses and are frequently prescribed complex treatment regimens. Some patients in this group also experience varying degrees of both functional and/or cognitive impairment which further increases the risk of poor health and poor adherence. Patients above 60 years of age consume about 50% of all prescriptions or three times as much as the general population (127). Another group of patients that often exhibits poor adherence are patients with psychiatric illnesses. This group also shows low adherence for medications taken for non-psychiatric conditions (132, 155). Even subclinical depression is a risk factor for poor adherence (131). Some patients tend to periodically forget to take their prescribed medications. The effect of this can be reduced by, when its possible, to prescribe "forgiving drugs". These are medications where the half-life is long in relation to the dose interval, in this way the treatment effect will persist even though a dose is postponed or forgotten (124, 136).

Reduced adherence is more common in certain situations and more attention to this could help improve adherence. Poor adherence is more common in conditions that are asymptomatic and where medications are used prophylactically. An example is the use of statins. Close to one in six patients never start on prescribed statin-treatment and less than 60% take the treatment two years after initiating it. Adherence is worse when a medication is

prescribed for primary prophylaxis as compared to secondary prophylaxis (136). Adherence is better for acute conditions as opposed to chronic conditions. After six months of treatment adherence rates often drops significantly (124). It has been shown that adherence increases with decreasing frequency of tablet administration per day. In a meta-analysis of 76 studies, adherence rates of medications taken once daily were 79% falling to 65% for medications taken three times daily (156). See figure 5.

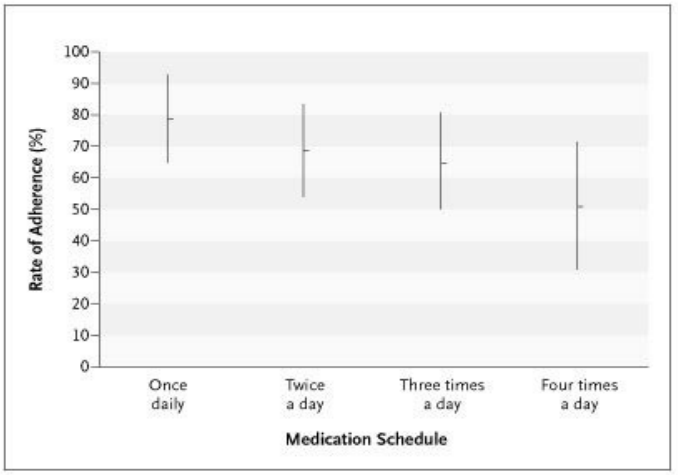


Figure 5: Adherence to medication according to frequency of doses.
Reproduced with permission from (124) Copyright Massachusetts Medical Society.

For many patients, the use of a medication-taking device might be helpful to increase adherence. Often involvement of family members or community health services is necessary (124). Non-supportive family members have been shown to negatively affect adherence. There are also numerous applications available on smart phones to help patients remember to take their medications (131). Some patients will also need practical help to be able to take their prescribed medications such as opening a box of tablets/blister pack, administer eye drops or correctly use an inhaler. The pharmacist can play an important role in improving adherence rates. A study where patients were given individualized medication education along with the use of a medication taking device and two-month follow ups by a clinical pharmacist showed improved adherence rates (157).

Interestingly, placebo-controlled trials have shown that patients being adherent have better outcomes regardless of whether they were given placebo or real treatment. This is called the “healthy adherer effect” and shows that good adherence itself is a marker for better outcomes. This suggests that good adherence might be a surrogate marker for overall healthy behaviour, but also that good adherence can improve health through the “placebo effect” and positive expectations (132, 151).

In any situation where the given treatment does not produce the expected effect, reduced adherence should be considered before implementing other measures (124). Interventions to improve adherence for each individual patient can be implemented. However, further research regarding slow-release (depot) medications, implantable

medications, medications with fewer side effects and even cure for diseases (that will render medications redundant) will all help improve adherence (122).

Studies have shown that doctors generally overestimate the adherence of their patients (126). Also, doctors tend to overestimate their skills in communication as well as the patients' understanding of their explanations (131). More attention regarding poor adherence among clinicians will be beneficial. A simple question, in a non-judgemental manner, such as: "I know it is difficult to remember to take all your medications. Do you sometimes have problems with this?" might reveal decreased adherence (121, 155).

No single intervention for improving adherence has been shown to be a success (127, 131, 134, 136). Many of the strategies for improving adherence to long-term medications are complex and costly and has not proven to be very effective (122, 124, 134). The cause of non-adherence is often multifactorial (121, 125, 158) making effective interventions difficult to design.

5.4 Antihormonal treatment and adherence

"A lady with growth neoplastic
thought castration was just a bit drastic.
She preferred that her ill could be cured with a pill.
Today it's no longer fantastic".

Elwood Jensen and V. Craig Jordan (159).

With the development of antihormonal medications, recurrence- and mortality rates have been greatly reduced for hormone receptor positive breast cancers (54, 55, 59). With increasing survival, adherence to adjuvant treatments becomes increasingly important. Despite being faced with a potential life-threatening diagnosis, adherence-rates have shown to be suboptimal to these medications. Reported non-adherence rates to antihormonal therapy in breast cancer ranges from 10.8% (160) to 55% (154). This wide range can be explained by varying methodological approaches such as different duration of observation and type of measurement of adherence used. Another important reason for these varying rates is the use of different definitions of adherence, compliance and persistence (133, 145, 161).

5.4.1 Predictors of non-adherence to antihormonal therapy

Side effects are major factors determining adherence to antihormonal treatment (154, 162-165). Side effects caused by these groups of medications are common. One study showed that side effects were the most frequently reported reason for non-adherence to tamoxifen (almost half the participants reported this), with hot flushes and night sweats being the most troublesome adverse effects (166). Side effects are often a driver of poor adherence, but they can also at times be a driver of good adherence. Adverse effects of tamoxifen in the initial period of treatment have been shown to be a predictor of non-adherence. However, side effects of tamoxifen over time have been linked to good adherence. In the latter case, side effects are often seen as an indicator that the medication is working and therefore promotes good adherence (138). Asking women about experienced side effects is important and may detect many patients with poor adherence. Prescribing ameliorative treatments for troublesome side effects will often be very beneficial (154, 163).

Age has also been shown to affect adherence to antihormonal treatment. Studies have shown associations between poor adherence and old age (162, 167), younger age (168, 169) and both (163, 170, 171). The extremes of age therefore seem to exert an effect on adherence. The younger, premenopausal women often develop troublesome side effects when an early menopause is induced (169). Also, these women may have a wish to become pregnant during the course of treatment and therefore discontinue the medication (128). This is of increasing relevance with the extended duration of treatment to 10 years. Elderly patients frequently suffer from comorbidities and these illnesses may lead to polypharmacy and complex treatment regimens increasing the likelihood of non-adherence. Additionally, the elderly may suffer from both functional and/or cognitive impairment further increasing the risk of non-adherence (158).

Various other factors have been shown to affect adherence, these include patient characteristics, tumour characteristics, type of antihormonal treatment and patient concerns and beliefs about the treatment. In general, adherence seems to improve with increasing severity of the breast cancer (162, 172). Sociodemographic factors have been shown to affect adherence. Women with perceived low social support and high levels of distress at onset of treatment were more likely to become non-adherent. Also, women from ethnic minority groups have been shown to exhibit poor adherence (138). Anastrozole has by some been shown to be associated with better adherence than tamoxifen (55), others have not been able to show this association (171). Concerns that the risk of the treatment outweighs its benefits has been shown to promote poor adherence (138). The most common concerns among patients are lack of belief of the necessity of the treatment and fear of adverse effects (161).

5.4.2 Can adherence to antihormonal treatment be improved?

Patients need varying degree of support while taking antihormonal treatment. More emphasis on factors that can improve adherence to antihormonal treatment is important. This could improve adherence rates and therefore also improve outcomes for the patients.

In addition to the above-mentioned ways of improving adherence in general (pages 35-37), there are some specific points that can help improve adherence to antihormonal treatment. Side effects are among the major contributing factors to poor adherence for this group of medications (154, 162-164, 173). Asking women about experienced side effects will help highlight this issue. As mentioned earlier, time spent with the patient explaining the rationale for prescribing the medication is important. Prescribing ameliorative treatments for troublesome side effects would help many patients adhere to the prescribed treatment (154, 163). One study of antihormonal treatment showed that 76% of patients experienced side effects that limited functions of daily life and that 60% of clinicians did not react to these side effects (173). Furthermore, it is shown that negative expectations to the potential side effects of antihormonal therapy at baseline significantly increases the chance of becoming non-adherent (113).

As it is the young and the elderly that are at greatest risk of non-adherence to antihormonal treatment these groups would benefit from extra attention with regards to adherence. Follow-up after the initiation of the treatment is important. As many patients discontinue the treatment in the initial part of the treatment period, this is a time where close follow-up is important. Also, mode of follow-up is of importance. A study of 567 patients showed that those followed-up by a general practitioner tended ($p = 0.07$) to be less adherent to antihormonal treatment than those followed-up by an oncologist (161).

It is important to provide comprehensible information to the patients that will enable them to make informed choices and to understand the rationale for prescribing the treatment. A study of 547 postmenopausal women with early breast cancer from nine European countries showed that 41% of the women were not in any way involved in the decision to start antihormonal therapy and that 10% were fully involved. Furthermore, only 57% received information about possible side effects and 26% received information regarding the risk of recurrence. Older patients and those with low educational level and were less likely to receive information or to be involved in the decision-making process. Patients who are

actively involved in the decision-making process are more likely to adhere to the treatment (174).

Negative beliefs about the treatment related to its potential risks versus benefit has been shown to affect adherence. This can possibly be overcome as shown in a study of 33 women with suboptimal adherence to tamoxifen enrolled in a four-week programme receiving written material containing educational information regarding tamoxifen, and a series of CBT activities and behavioural change techniques. Improvements were seen in adherence, QoL, medication beliefs and distress (175). However, merely providing written material regarding the antihormonal treatment has been shown to be an ineffective measure to improve adherence (173). The former study might have been successful in improving adherence as it included CBT and behavioural change techniques in addition to simply providing facts about the medication. A randomised trial examining the effect of twice weekly text-messages to patients prescribed aromatase inhibitors, did not show an effect on adherence (176). Improving adherence to oral anticancer medications with a smartphone application (containing medication plan with reminders, symptom-reporting and patient education) has not been successful in improving adherence (177).

Addressing intentional and non-intentional non-adherence as two separate entities would be beneficial when trying to understand and improve adherence rates. Research has shown that non-adherence to tamoxifen mainly is unintentional (138), see figure 6. However, in a study of 211 women two to four years after their breast cancer diagnoses revealed that of the 22% who were non-adherent, 14% were intentional non-adherent and 8% were unintentional non-adherent (178). Interventions to improve intentional non-adherence should target their effort on each individual's specific reasons for not adhering, while efforts to improve non-intentional non-adherence should focus their efforts on making sure these patients remember to take their medications (138, 139).

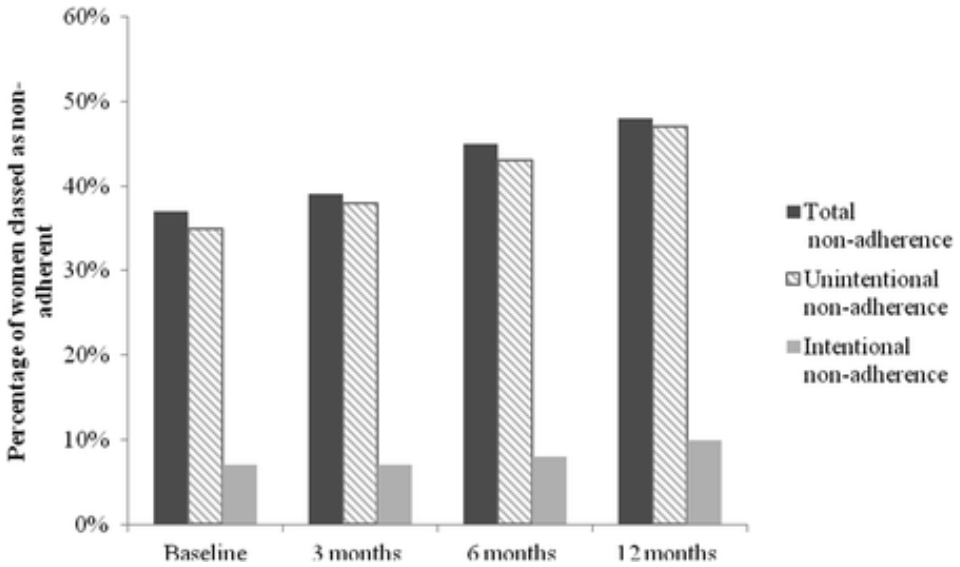


Figure 6: Percentage of women (n = 345) classified as non-adherent to tamoxifen. Women can be classified as both intentionally and non-intentionally non-adherent (138).

Reasons for non-adherence may be multifactorial. Developing strategies to improve adherence is complex. However, time spent with each patient, especially addressing side effects, as well as close personalised follow-up seem to be important.

5.5 Overtreatment

"Though the doctors treated him, let his blood, and gave him medications to drink, he nevertheless recovered".

Leo Tolstoy, War and Peace.

5.5.1 Overtreatment in general

Overtreatment is a pervasive worldwide problem. It refers to medical and surgical interventions that will not improve the outcome for a patient. Overtreatment also occurs when the risk of an intervention is likely to outweigh any benefit the patient may receive. Related terminology includes: overtesting (excessive use of investigations), overuse (services that are unnecessary), overdiagnosis (diagnosis based on findings that will not affect a person's prognosis or QoL if left untreated) and low-value care (test or treatment that will not benefit the patient or where there is evidence of more harm than benefit). Although difficult to measure, it has been estimated that overtreatment account for up to 30% of health care costs (179-181).

"…more care may not necessarily result in a better outcome" (179)

Several factors contribute to overtreatment. With the constant evolution of modern medicine, more knowledge, better technology and more sensitive tests often leads to more patients being labelled as "sick". Also, the definitions of many diseases have widened leading to a larger proportion of persons being defined as having a disease. An example includes the lowering risk-threshold for treating hypercholesterolaemia with the subsequent increased prescription of lipid-lowering medications. Patient-related factors driving overtreatment includes the patients' (and sometimes their families') expectations. Patients are generally more satisfied when they receive more diagnostic procedures and more treatments as they feel these interventions will benefit them. The discomfort of uncertainty might drive doctors to order unnecessary diagnostic procedures or prescribe treatments that are futile. This uncertainty can also drive patients to demand further interventions. Fear of complaints is a factor that may drive doctors to overtreatment. Complaints regarding doctors' care are mostly related to what diagnostic procedures and/or treatments a patient did not receive rather than complaints of overtreatment. Overtreatment is also affected by how the health care is provided. Especially in private practice, the remuneration of doctors can affect their clinical decisions and practice. Also, in many countries the pharmaceutical industry spends large amounts of money on influencing health care professionals as well as on advertising its products to the population (179, 181, 182).

Often the clear demarcation between the appropriate and highly beneficial interventions and the more inappropriate non-beneficial interventions is unclear leaving most interventions in a grey zone of ambiguity (Figure 7). Most tests and treatments fall into this ambiguous category. Here, an intervention may offer some benefit to the patient. The balance

between benefit and harm might vary between patients and the evidence in favour of the intervention may be weak (181).

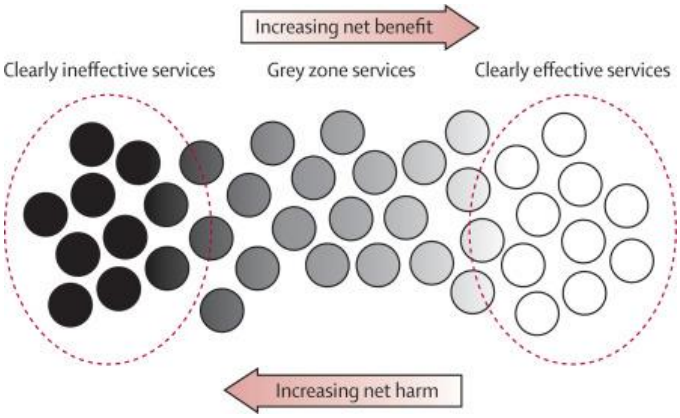


Figure 7: Grey zone services (181).
Reuse with permission, license number: 5500080762852.

The consequences of overtreatment affect both the individual patient, but also the health care system. Inappropriate interventions may harm the patient. This may be direct adverse events or psychological harm such as anxiety. Furthermore, financial costs may negatively affect the patient. Also, overtreatment increases the workload on doctors and other health care professionals. Overtreatment leads to large, unnecessary, expenditure. It diverts health resources away from where they are needed. It has been estimated that in 2013, the US spent $270 billion on care that could be defined as overtreatment. At the same time, millions of Americans do not have adequate access to basic health care services (179, 181).

5.5.2 Overtreatment in breast cancer

In breast cancer, overdiagnosis mainly refers to the detection of low-grade tumours by mammography screening. Overdiagnosis frequently leads to overtreatment. Increased emphasis on overtreatment has led to more focus on treatment de-escalation. Here, less invasive surgery, limited radiotherapy and more tailored chemotherapy has shown not to affect oncological outcomes. With more knowledge, there is a shift towards de-escalation and individualised treatment (183).

The management of the axilla is one example of de-escalation within breast cancer surgery. Treatment recommendations are now being made increasingly based on tumour biology rather than nodal status (183). Axillary lymph node dissection (ALND) was for a long time the standard procedure of the axilla. With the introduction of the SLNB, the use of ALND decreased. This change of practice was mainly due to the ACOSOG Z0011-trial that demonstrated no benefit of ALND in patients with one to two axillary metastases at SLNB undergoing breast conserving surgery with subsequent whole breast irradiation and systemic therapy (184). In recent years, guidelines have recommended omitting SLNB in patients over

70 years of age with hormone receptor positive tumours less than 20 mm (185). Another example of de-escalation within breast cancer surgery is the shift from performing mastectomies to mainly performing breast conserving surgery (186). Furthermore, there has been a decrease in re-excision rates for invasive cancer treated with breast conserving surgery and whole breast irradiation. Here, a consensus statement led to the shift away from supporting margins over 1cm towards allowing for no ink on tumour as the standard acceptable margin width for breast conserving surgery (187). Less chemotherapy is now being prescribed in the adjuvant setting due to the omission of chemotherapy in selected low-risk patients based on gene expression analysis (188).

There is an ongoing debate regarding the diagnosis and treatment of ductal carcinoma in situ (DCIS). Some argue that DCIS is both being overdiagnosed and overtreated. Mammography screening along with the sometimes widespread practice of taking biopsy of calcifications has led to a rise in the number of DCIS-cases diagnosed (189). There is no consensus internationally on how to best manage DCIS. Treatment ranges from no treatment to mastectomy with or without radiation therapy and/or antihormonal treatment (190). As up to 40% of DCIS will develop into an invasive cancer (191), there is a need to distinguish which patients are at high risk of developing invasive cancer and who are unlikely to do so. Studies have shown that clinical factors, tumour factors and treatment factors all influence the risk of local recurrence of DCIS and/or the progression to an invasive breast cancer after breast conserving surgery for DCIS (192). If we in the future can predict what cases of DCIS will develop into invasive cancer, overtreatment of many cases of DCIS can be prevented.

6 Aims

The overall aim of this thesis was to achieve an in-depth understanding of adherence to antihormonal treatment in patients with breast cancer. Specifically, we wanted to quantify the incidence of poor adherence to antihormonal treatment in our cohort and also look at the effects of poor adherence on survival. Furthermore, the plan was to investigate how survival varied among the different luminal subtypes of breast cancer. To be able to classify the patients into these subtypes, assessment of Ki67 in cases prior to 2010 was necessary. As work progressed, we realised that this would not be possible. Therefore, paper 3 had to be altered. Paper 3 raises the issue of adherence in relation to a guideline that has not been widely implemented by clinicians.

The aims of the three papers included in this thesis were:

Paper 1

The aim of this study was to examine adherence to adjuvant antihormonal treatment in breast cancer patients. Putative predictors affecting adherence were studied. Furthermore, non-adherent patients were subclassified into PNA and SNA, and persistence was calculated.

Paper 2

The primary aim of this study was to examine the effect of poor adherence to adjuvant antihormonal treatment on survival in breast cancer patients. Patients with poor survival was subclassified into being PNA or SNA. Overall survival and breast cancer specific survival (BCSS) were calculated according to adherence status.

Paper 3

The main aim of this study was to examine why the de-implementation of the sentinel lymph node procedure in elderly low-risk breast cancer patients has not been successful. Emphasis has been placed on axillary lymph node metastases and adherence to antihormonal treatment.

7 Materials and methods

7.1 Study population

Paper 1 and 2

All patients in study 1 and study 2 underwent surgery following a diagnosis of hormone receptor positive breast cancer. Surgery was performed at St Olav's University Hospital, Trondheim in the period 01.01.2004 to 31.12.2013. The patients were subsequently prescribed five years of adjuvant antihormonal treatment. Patients with histological grade 1 tumours less than 20mm were excluded as these patients were not recommended antihormonal treatment according to national guidelines at the time. Also, patients with oestrogen receptor positivity of $\geq 1 < 10\%$ diagnosed before 2011 were excluded as these patients were not prescribed antihormonal treatment according to national guidelines at the time. All women were followed to the date of death from breast cancer, death from any other cause or to the end of follow-up at 31.12.2019.

The study populations in study 1 and study 2 are largely the same. Article 1 contains 1,192 patients and study 2 comprises 1,176 patients. The reason for this discrepancy is different inclusion criteria. In study 1, patients were included if they collected their first prescription within the study period. However, in study 2, patients were included if they were diagnosed within the study period.

Paper 3

Patients in paper 3 originate from the study population described above (papers 1 and 2). All patients were diagnosed with oestrogen receptor positive breast cancer and subsequently underwent surgery in the period 01.01.2004 to 31.12.2013. All included patients were aged $\geq$ 70 years and had tumours measuring less than 20 mm in diameter (T1-tumours) according to the postoperative pathology report. All patients were prescribed five years of adjuvant antihormonal treatment.

7.2 Registers

Norway has long traditions of national health registries. The National Leprosy Registry of Norway was the world's first national registry for any disease. It was established in 1856. In 2001, it was included in UNESCO's heritage list: "Memory of the World" (193).

In Norway, reporting to the national health registries is mandatory. These registries therefore contain detailed medical information about the population. Upon birth, each resident is assigned a unique personal identification number. In Norway, these numbers were introduced in 1964 and were originally used to control and monitor tax payments. The number encodes date of birth and the sex of the individual. In registry-based research these numbers allow for follow-up of individuals within the registries, linkages can be made between different registries and also between registries and other data sources (194, 195).

The Cancer Registry of Norway

The Cancer Registry of Norway (CRN) commenced its registration in 1952 and is one of the oldest population-based registries in the world. It has an estimated completeness of over 95%. In 2002, a Health Registry Act came into force, this included statutory regulations for the CRN. The Act required all hospitals, laboratories and general practitioners in Norway to report new precancerous and cancerous cases to the registry (196-198).

The Norwegian Cause of Death Registry

The public registration of deaths started in 1685 in Norway. Local vicars were required to register births, marriages and deaths in their local parishes. More systematic statistics were organised from 1853, and from the 1920s these reports included over 90% of all deaths. The Norwegian Cause of Death Registry was founded in 1951 and contains information on deaths and causes of death. It includes persons that reside in Norway at the time of death and also persons that die abroad who have a registered address in Norway. For all deaths, a death certificate is completed by a doctor. The certificate conforms to the principles established by the WHO. Causes of death have since 1951 been coded according to the International Classification of Diseases (ICD)-classification system (199, 200).

The Norwegian Prescription Database

In October 2003, the King in the Council of State passed the final regulation on The Norwegian Prescription Database (NorPD). The NorPD was subsequently established in 2004. The NorPD contains information regarding prescribed medications that has been distributed from pharmacies since 2004. This information includes data regarding the patient, the person who wrote the prescription, type of medication, dosage and where and when the prescription was collected (201, 202).

7.3 Medication possession ratio

The medication possession ratio (MPR) is a commonly used measure for adherence (144, 145). It is calculated as a fraction where the total number of days a medication is at hand is summarised over the treatment duration. It is expressed as a percentage (124, 125, 146). In this material a patient was considered adherent if MPR reached 80% or more.

7.4 Statistical analysis

Paper 1

Differences between subgroups were calculated using logistic regression. Odds ratios and their 95% confidence intervals were calculated. Furthermore, adherence was predicted as a

function of age by including a second-degree polynomial age term in the logistic regression. This term was also used when adjusting for the effect of age.

Paper 2

Pearson's chi square (χ^2) was used to describe differences in distribution of the variables. Overall survival and BCSS for the three categories of adherence (adherent, PNA and SNA) were assessed using Kaplan Meier curves and cox regression with adherence state as a time-dependent covariate.

Paper 3

Kaplan Meier curves were designed to show overall survival and BCSS for according to axillary lymph node metastases and adherence status.

Statistical analyses were performed using SPSS version 28, Stata version 17.0 and R version 3.6.3.

7.5 Ethical approval

Committees handling questions regarding research ethics were first established in the mid-1960s. In 1975 the Declaration of Helsinki stated that: "any experiment involving human beings (…) must be submitted to an especially appointed, independent committee for review, comments and guidance". In 1977, the Norwegian Medical Association submitted a specific proposal to establish ethical research committees in Norway. It was not until 1987 the full set of regional ethical committees were established. In 2006 the Research Ethics Act was introduced, this ensured sufficient funding for the committees (203).

Paper 1 and 2

These papers were approved by the Regional Committee for Medical and Health Research Ethics (REK), South-East Norway (#2017/1356) and the Regional Data Protection Office according to the Declaration of Helsinki.

Paper 3

Approved by the Regional Committee for Medical and Health Research Ethics (REK), Central Norway (#561970).

8 Results

Paper 1

The total study population comprised 1,192 patients. Amongst these, 75.8% (903/1,192) were adherent and 24.2% (289/1,192) were non-adherent to the prescribed antihormonal treatment. Of the non-adherent patients, 8.5% of the total study population (101/1,192), were classified as PNA.

The youngest (<40 years) and oldest (≥80 years) in the study population showed significantly lower adherence than those aged 50-59 years. Those with metastases to the axillary lymph nodes were more likely to be adherent compared to those with no axillary lymph node metastases. Patients treated with radiotherapy and/or chemotherapy were also more likely to be adherent than those who did not receive these treatment modalities. Patients who switched to an AI or from an AI or who were treated with AI monotherapy were more likely to be adherent than those treated with tamoxifen monotherapy. Also, those who switched treatment regimen at two years, according to guidelines at the time, were more likely to be adherent.

Patients in the PNA-group tended to have a better prognosis than the adherent patients. A large proportion of the PNA-patients had tumours measuring ≤ 20mm (T1) and no axillary lymph node metastases. Furthermore, most of the PNA-patients were not treated with chemotherapy indicating less serious disease. Persistence was measured and the SNA-patients tended to discontinue the antihormonal therapy in the initial part of the treatment period.

Paper 2

A total of 1,176 patients were included in this study. Of these, 75.6% (889/1,176) were adherent to the prescribed antihormonal treatment, while 8.5% (100/1,176) were classified as PNA and 15.9% (187/1,176) were SNA. At the end of follow-up, the proportions of patients alive were 79.1% (703/889) in the adherent group, 76% (76/100) in the PNA-group and 55.6% (104/187) amongst the SNA-patients. Of the patients who died from breast cancer, 12.4% (110/889) were adherent to the antihormonal treatment, 4% (4/100) were PNA and 23% (43/187) were SNA.

The PNA-patients showed similar overall survival to the adherent patients. The SNA-patients showed poorer survival compared to the adherent patients. Breast cancer specific survival was better among the PNA-patients and poorer among the SNA-patients compared to the adherent patients. The low-risk PNA-patients tended to have better BCSS compared to the low-risk adherent patients. SNA-patients with a high-risk profile had worse overall survival and BCSS when compared to the high-risk adherent patients. SNA-patients showed poorer overall survival compared to the adherent patients regardless of age. Furthermore, the SNA-group of patients had worse BCSS compared to the adherent patients for those aged less than 69 years.

Paper 3

The total study population comprised 98 patients. Of these, 66.3% (65/98) were adherent to the prescribed adjuvant antihormonal treatment, 11.2% (11/98) were PNA and 22.4% (22/98) were SNA. According to the postoperative pathology report, 59.2% (58/98) did not have axillary lymph node metastases, 25.2% (25/98) were diagnosed with 1-3 axillary lymph node metastases and 8.2% (8/98) had ≥4 axillary lymph node metastases. The PNA-patients tended to have better overall survival than the adherent patients. The SNA-patients tended to have worse overall survival compared to the adherent patients. Both overall survival and BCSS tended to be poorer with increasing number of axillary lymph node metastases.

9 Discussion

9.1 Papers

Paper 1 and 2

Medications must be taken correctly in order to exert their beneficial effects. Poor adherence leads to poorer outcomes for the patients (125, 133, 134) and imposes a great economic burden for the health care systems (136, 144, 168). Much work has been done on the issue of adherence, both amongst researchers, but also larger institutions. An example of the latter is the EU-project: "Ascertaining Barriers for Compliance: policies for safe, effective and cost-effective use of medicines in Europe" (204). The aim of the study was: "…to produce evidence-based policy recommendations for improving patient compliance and subsequent better use of medicines by Europeans". The project ran from 2009 to 2012 and had a budget of almost €3 million (205). In 2003, the WHO published an extensive report about adherence describing it as a worldwide problem. The main aim was to improve adherence rates. It focuses on five dimensions that affect adherence: 1) Patient-related factors 2) Condition-related factors 3) Health system-related factors 4) Therapy-related factors 5) Socioeconomical factors (127). Despite much work on the issue of adherence, it needs more awareness. Adherence is of relevance in all clinical specialities. More attention both among health care workers and patients will improve adherence rates.

In both papers, almost one quarter of the patients were non-adherent. Close to 10% of the total study population never initiated the treatment. About 50% of all patients with chronic conditions do not take their medications as prescribed (122, 131, 132). Adjuvant antihormonal treatment prescribed to breast cancer patients has been shown to reduce the risk of recurrence and improve survival (53-55, 59, 61, 206). Although cancer patients have a potentially life-threatening disease, many still choose not to take the antihormonal treatment, or worse, do not initiate the treatment at all. With the evolvement of modern cancer therapy, there is a shift towards more oral medications being taken at home (207). Simultaneously, there is a trend towards less hospital follow-up (178). This further emphasizes the need for interventions to improve adherence rates.

Many studies have shown that side effects are the main cause of non-adherence to antihormonal treatment (154, 162-165). However, it is interesting that this might not be the case for all patients. Research has shown that in the elderly, discontinuation of antihormonal treatment did not improve QoL, implying that the side effects are not the cause of reduced QoL (208). Also, side effects might for some be a motivating factor, indicating that the treatment is working.

In general, classifying non-adherent patients into being intentional non-adherent (linked to patients' beliefs and preferences) and non-intentional non-adherent (more strongly associated with socio-demographic factors) may be useful. Non-intentional non-adherence occurs when the patient wants to adhere but is unable to. This is usually due to forgetfulness but can also be because the patient has misunderstood the instructions or can't afford to pay for the medication (139, 178). Economy is not a factor influencing adherence in this material as the costs are reimbursed. However, this has been shown to affect adherence in other parts of the world, such as the US (209). Intentional non-adherence includes those beliefs that the

patient considers relevant and finds important, perhaps ignoring important arguments for adhering to a treatment regimen. These beliefs can broadly be divided into two main categories: perceptions about the personal *need* for the treatment and *concerns* about possible adverse consequences of the treatment. In simple terms, interventions for improving intentional non-adherence should be targeted towards better information and spending time on explaining the rationale for prescribing the treatment. Interventions for improving non-intentional non-adherence should focus on helping the patients to remember to take their medications. As reasons for non-adherence often are multifactorial, improving poor adherence is often a complex matter that needs to be individualised for each patient (139, 210, 211).

Paper 3

The guideline stating that it is safe to omit SLNB in low-risk elderly breast cancer patients was first published in 2016 by the Choosing Wisely Campaign (212). This has later been reaffirmed in updated versions and also by ASCO in 2021 (185). Despite evidence stating the safety of omitting the SLNB-procedure (213-216), it is still being widely performed as many clinicians are reluctant to forego this procedure (217, 218). This paper looks at some aspects that might explain why the omission of SLNB-procedure in low-risk elderly breast cancer patients have not been widely implemented. The recommendation states that in order to omit the SLNB-procedure, the preoperative clinical examination of the axilla must reveal no axillary lymph node metastases and furthermore, the patients should be treated with adjuvant antihormonal treatment.

We show that about one third of the patients have axillary metastases. This number is in concordance with other studies (219, 220). The CALBG 9343-trial, and other similar studies, have shown that axillary evaluation does not affect survival. Despite this, clinicians are reluctant to omit the SLNB-procedure in these patients. Omitting the SLNB-procedure means missing the opportunity to treat potential axillary lymph node metastases. As the SLNB-procedure is largely considered to be a safe and accurate procedure with few complications (221, 222), it often not considered to impose much of a burden to the patient. This will especially be true if the patient is a fit and healthy female in her 70's with few or no comorbidities. The diversity of fitness and health is large in this group of patients. We therefore suggest that a more individualised approach for the selection of omitting the SLNB-procedure should be applied. For the frail, elderly patient with several comorbidities it would be sensible to omit the SLNB-procedure thereby probably avoiding a general anaesthetic, shortening the surgical trauma and allow for a faster recovery. Furthermore, a fit and healthy patient would tolerate the SLNB-procedure very well. The same will be true for the potential treatment for any axillary metastases. An individual assessment of these patients is important. Additionally, biomarker profiling will probably help guide the selection process of these patients in the future.

Non-adherence to the prescribed antihormonal treatment was seen in approximately one third of the patients in this material. Adherence in these patients cannot be assumed. It is likely that patients in the CALBG-9343-trial also were non-adherent to the prescribed antihormonal treatment, this did not affect the survival. However, better adherence could have resulted in even better survival rates. As we see a shift where more treatments are being

delivered at home, more awareness and focus must be placed on adherence, both among health care personnel and patients (223, 224).

Guidelines are made with the intention to assemble as much up to date evidence as possible to be able to guide clinicians to provide the best care for their patients (225). Reasons for clinicians not adhering to new guidelines are multifactorial and often complex. Several factors can contribute to this: lack of awareness of new guideline, lack of agreement, lack of ability to perform the guideline in practice, lack of outcome expectancy, lack of motivation, patient factors, guideline factors (e.g. too complex to follow) and environmental factors (e.g. organisational constraints) (226, 227). Guidelines are mere recommendations that clinicians may or may not follow. The fear of leaving potential axillary metastases untreated is probably an important factor explaining why the procedure is still widely performed. Also, the SLNB is a well-established procedure that is considered to be safe. Furthermore, the suboptimal adherence-rates to the antihormonal therapy will mean that a significant proportion of the patients will be left with little or no adjuvant therapy.

9.2 Registers

The Nordic countries are privileged to have extensive population-based registries that provide individual and health data with close to complete follow-up and exact censoring information. These registries together with universal tax-funded health services and personal identity numbers, allows for linkage at the individual-level between the registries. This gives unique possibilities for research on large populations with long follow-up (195).

Although these population-based registers provide an excellent opportunity for research, it is a time-consuming task to conduct this type of research. This is important to consider when planning such studies. After the ethical approval is in place, one must contact each registry which will then process the application. After the application(s) are approved and the personal identity numbers of the participants are transferred to the respective registries, there is usually at least a two months processing period. The data returned from the registries does not come in the same format, therefore ensues a long process of "cleaning up" the files and finally merging them. Finally, the analysis of the data can start.

Using population-based registers for research has some potential disadvantages. This is mainly related to validity and completeness. Validity refers to whether a given variable measures the intended event. Completeness relates to whether all individuals with a diagnosis in the population is recorded in the registry (195). The bottom line is that data output is only as good the data entered into the database.

9.3 Limitations

All three studies in this paper have rather low number of included participants. Further studies are therefore needed to validate the findings of this thesis.

As with all types of indirect methods of measuring adherence, one cannot be sure that the patient actually consumed the medication of interest. There is no confirmed information stating that the patient ingested the correct dosage of the medication with the right frequency.

One can only assume that the patient has consumed the medication correctly. However, we consider it unlikely that a patient repeatedly would collect a medication at the pharmacy without ingesting it. Direct methods of measuring adherence would be needed in order to confirm that the medication actually was consumed correctly. However, direct measurements are expensive, laboursome and susceptible to the "Hawthorne effect" whereby the patients improve their medication taking behaviour because they know they are being observed. Adherence data obtained from patient self-reported methods such as questionnaires or patient diaries have been shown to overestimate adherence rates. Adherence data retrieved from prescription refill databases have been shown to be a precise method of determining adherence. However, it has been shown that the most accurate estimate of adherence occurs when one uses two or more methods of measurements (124, 132).

Paper 1 studied only a selected number of possible predictors of adherence to antihormonal treatment. It did not include socioeconomic factors, side effects or patient beliefs about the treatment. All these factors are important contributors affecting adherence. As causes of non-adherence often are multifactorial and complex, one must be aware of all possible causes of non-adherence. However, it was beyond the scope of the paper to study all possible causative factors.

Although commonly used, the 80% cut-off of defining "good" and "poor" adherence is somewhat arbitrary. It has been defined as a reasonable cut-off (149). However, it is not known at what exact level of non-adherence the antihormonal medications stop exerting their beneficial effects. It is likely that this cut-off in reality is distinct for each specific antihormonal medication. The pharmacokinetics of each medications determines its "forgivingness" in terms of missed or delayed doses. Missed or delayed doses will have less impact on the effectiveness of the treatment for medications with a long half-life (124, 228). Aromatase inhibitors have shorter half-life than tamoxifen indicating that strict adherence to AI's is perhaps more important in order to achieve their beneficial effects as compared to tamoxifen (206). Overcoming this issue of using an arbitrary cut-off for adherence would be possible if detailed information regarding adherence data for each specific antihormonal medication was linked to clinical outcomes and simultaneously using a continuous measure of adherence rather than a binominal categorical cut-off (132, 228).

10 Conclusions

The main findings of the papers presented in this thesis may be summarized as follows:

- Adherence to antihormonal treatment is suboptimal.
- Special attention should be paid to the young and elderly as these age groups show poorer adherence than the other age groups.
- Patients with more severe disease, as shown by axillary lymph node metastases and treatment with chemotherapy, seem to have better adherence than those with less severe disease.
- PNA-patients tend to have a better prognosis than the adherent patients.
- SNA-patients tend to terminate the treatment in the initial part of the treatment period.
- The poorest survival is seen amongst the SNA-patients.
- About one third of low-risk elderly breast cancer patients have axillary metastases as confirmed on the postoperative pathology report.
- Non-adherence is seen in about one third of low-risk elderly breast cancer patients.
- The presence of axillary lymph node metastases and suboptimal adherence-rates are likely to, at least partly, explain why the de-implementation of the SLNB-procedure has been unsuccessful in the low-risk elderly breast cancer patients.

11 Future perspectives

This thesis will hopefully help highlight the importance of adherence in clinical medicine. The WHO has stated that non-adherence is likely in every situation where patients are required to administer their own medication. This is of increasing relevance as we see a shift towards more treatments being administered at home outside of the hospitals. Whenever a patient does not respond as expected to a treatment, non-adherence should be considered. Increased awareness and knowledge about non-adherence are essential in order to improve adherence-rates in the future.

Individualised treatment has rapidly become an important aspect of modern cancer management. Stratifying patients according to risk profile and thereby tailoring their treatment regimen is highly important in order to avoid overtreatment. There is evidence to suggest that breast cancer patients with oestrogen receptor positive disease and a low-risk profile are being overtreated with antihormonal treatment. Biomarker profiling is already in use in these patients in order to de-escalate the adjuvant antihormonal treatment. Also, individualised follow-up of breast cancer patients based on biomarker profiling is likely to become more prevalent.

In the future, it is likely that less SLNB-procedures will be performed in carefully selected patients. This selection will probably be based on biomarker profiling along with an individualised assessment of comorbidity.

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Paper I

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RESEARCH

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Predictors of adherence and the role of primary non-adherence in antihormonal treatment of breast cancer

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Abstract

Background: Antihormonal treatment for hormone receptor (HR) positive breast cancer has highly beneficial effects on both recurrence rates and survival. We investigate adherence and persistence in this group of patients.

Methods: The study population comprised 1192 patients with HR-positive breast cancer who were prescribed adjuvant antihormonal treatment from 2004 to 2013. Adherence was defined as a medical possession ratio (MPR) of ≥80.

Results: Of the 1192 included patients, 903 (75.8%) were adherent and 289 (24.2%) were non-adherent. Primary non-adherence was seen in 101 (8.5%) patients. The extremes of age (< 40 and ≥ 80 years) were associated with poor adherence. Patients with metastasis to axillary lymph nodes and those who received radiotherapy and/or chemotherapy were more likely to be adherent. Better adherence was also shown for those who switched medication at 2 years after diagnosis. Primary non-adherence seems to be associated with cancers with a good prognosis.

Conclusion: Adherence to antihormonal therapy for breast cancer is suboptimal. Primary non-adherence occurs among patients with a relatively good prognosis. Non-adherent patients tend to terminate their antihormonal therapy in the initial part of the treatment period. Targeted interventions to improve adherence should be focused on the first part of the treatment period.

Keywords: Breast cancer, Antihormonal treatment, Tamoxifen, Aromatase inhibitors, Adherence, Primary non-adherence

Background

Antihormonal treatment is one of the main treatment modalities in the adjuvant treatment of hormone receptor (HR) positive breast cancer. With increasing knowledge, their use has greatly expanded; from initially being used only in the palliative setting [1], tamoxifen is now prescribed for up to 10 years in the curative setting [2]. The efficacy of both tamoxifen [3–5] and aromatase inhibitors (AI's) [6–8] has been well documented. Despite this, many patients terminate their treatment prematurely or never initiate the treatment at all.

The World Health Organization emphasizes that adherence presumes the active participation and collaboration of the patient in the treatment process [9]. Adherence may be defined as the extent to which the patient takes a medication as prescribed [10]. Primary non-adherence (PNA) is defined as failure of the patient to fill the first and subsequent prescriptions at the pharmacy. Secondary non-adherence (SNA) refers to failure to take the prescribed medication as directed after the first prescription has been collected [11–13]. Persistence describes the time from initiation of therapy to discontinuation or,

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in more general terms, whether the patient stays on the treatment as prescribed [14, 15].

Awareness of the importance of adherence to medical treatment has increased in recent decades. However, it has been reported that close to 50% of all patients do not adhere to prescribed medical treatment irrespective of diagnosis [16–18]. Poor adherence prevents medications from exerting their full beneficial effect thereby resulting in unnecessary morbidity and mortality [9–11, 14, 18, 19]. In addition to its effect on the individual patient, it also has a vast effect on health economy leading to increased health care expenditures [19–22].

While there is no doubt that antihormonal treatment in breast cancer is highly beneficial, non-adherence continues to be a challenge. Varying rates of non-adherence to antihormonal treatment have been reported, ranging from 10.8% [23] to 55% [24]. Different definitions of adherence and varying methodological approaches to measuring adherence account for this wide range [14, 25, 26]. Poor adherence to antihormonal treatment has been shown to negatively affect recurrence rates and mortality, and also leads to increased medical costs and reduced quality of life [4, 8, 20, 27, 28].

Side effects of antihormonal treatment is one of the strongest predictors of poor adherence to antihormonal treatment [24, 27, 29–31]. Therefore, identifying patients at risk of poor adherence prior to the onset of the treatment provides an opportunity for early intervention. Predictors of adherence including patient characteristics, tumour characteristics, type of antihormonal treatment and other adjuvant treatment modalities, have previously been studied, however, the results are not entirely concordant. Age seems to be an important factor affecting adherence. A number of studies have shown associations between poor adherence and old age [27, 32], younger age [20, 33], and both [29, 34, 35]. In general, adherence seems to improve with increasing severity of disease [27, 36]. While anastrozole has been shown to be associated with better adherence than tamoxifen by some [6], others have failed to demonstrate a similar association [35]. While acknowledging previous research on adherence to antihormonal treatment, further knowledge on how to best identify patients at risk of poor adherence is needed.

The aim of this study was to examine adherence, and specifically PNA, in a series of Norwegian patients with breast cancer. All patients were diagnosed pre-operatively with HR-positive breast cancer and subsequently underwent surgery at St Olav's Hospital, Trondheim University Hospital, Trondheim, Norway. All patients were prescribed adjuvant tamoxifen or an AI, either as monotherapy or as a switch regimen. Associations with age, tumour characteristics, nodal status, radiation therapy and chemotherapy were studied as putative factors affecting adherence. Non-adherent patients were subclassified into primary non-adherent or secondary non-adherent. Furthermore, persistence was calculated for these patients.

Materials and methods

Study population

The study population comprised all patients with HR-positive breast cancer who underwent surgery at St Olav's University Hospital in the period 01.01.2004 to 31.12.2013 and subsequently were prescribed antihormonal treatment as part of their adjuvant therapy. Patients with histological grade 1 tumours less than 20 mm in diameter (T1) were excluded from the material. These patients were not prescribed antihormonal treatment according to national guidelines in the study period. A total of six patients diagnosed before 2011 had tumours showing oestrogen receptor positivity $\geq 1 < 10\%$ and were therefore excluded from the study as guidelines prior to 2011 stated that oestrogen positivity $< 10\%$ did not warrant antihormonal treatment (Fig. 1). All patients in this study were recommended 5 years of antihormonal treatment according to national guidelines operative at the time of diagnosis.

Data regarding tumour characteristics and treatment were retrieved from the hospital medical records. These data were linked to the Norwegian Prescription Database (NorPD) where pharmaceutical records were collected for all patients. After the data were linked, patient identity was replaced by a serial number. The NorPD includes information regarding each dispensed medication, the month and year it was dispensed, the total number of tablets dispensed each time, gender, year of birth, and month and year of death. Data in NorPD covered the time period from 01.01.2004 through 31.12.2019. The long follow-up time ensured at least 5 years of follow-up for all patients. All patients had a one-year follow-up appointment at the surgical out-patient clinic. Thereafter, yearly follow-up by their general practitioner for 10 years. Patients with metastasis at time of primary diagnosis were followed more closely by an oncologist.

Outcomes

Adherence was determined by the medical possession ratio (MPR). MPR is a recognized and commonly used method to estimate adherence [21, 26]. It is determined by the number of days a medication is at hand within a given time interval [10, 11, 37]. We used the total amount of tablets dispensed as the nominator, this equals the number of days of treatment as the tablets, regardless of type of antihormonal treatment, are taken once daily. The denominator was 5 years for all patients except for those who died during the five-year treatment period. The

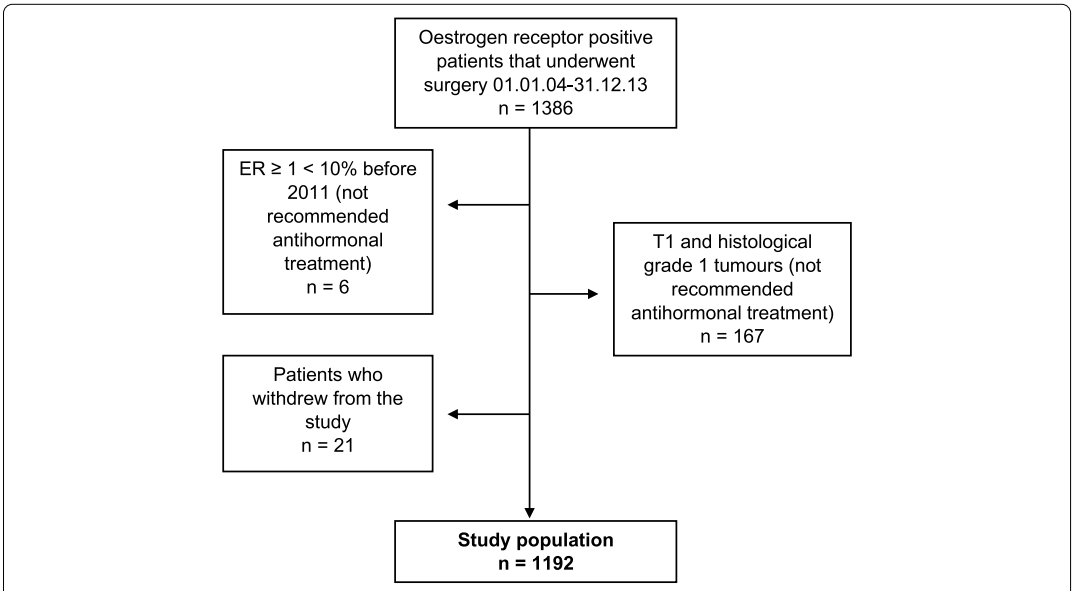

Fig. 1 Overview of included and excluded patients

MPR for patients who died during their five-year course of antihormonal treatment was also included. MPR for these patients were calculated based on the length of time they were alive after commencing the treatment. Patients were considered adherent to the given treatment if MPR reached 80% or more. This cut-off is widely used for differentiating between adherence and non-adherence [37–39]. Adherence was correlated to tumour characteristics (tumour stage, histopathological type and grade, nodal status) and treatment modalities (neoadjuvant treatment, type of antihormonal treatment, radiation therapy, chemotherapy). Persistence was calculated from the date of the first prescription to the date when the supply of the last prescription ended. Pauses in antihormonal treatment of greater than 180 days were regarded as discontinuation of the treatment. Primary non-adherence was defined as failure of the patient to fill the first and subsequent prescriptions of antihormonal treatment.

Statistical analysis

The differences between subgroups were calculated using logistic regression. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. In the univariate analysis we included all clinicopathological data. Predictors of adherence were age, tumour stage, histopathological type, histological grade, axillary lymph node metastasis, neoadjuvant treatment, type of antihormonal treatment, switch of antihormonal treatment at 2 years, radiation therapy and chemotherapy. Furthermore, adherence was predicted as a function of age by including a second-degree polynomial age term in the logistic regression. This term was also used when adjusting for the effect of age. Statistical analyses were performed using SPSS version 28 and Stata version 17.0.

Results

A total of 1386 patients with HR-positive breast cancer underwent surgery during the study period (Fig. 1). Of these, 22 were diagnosed with breast cancer twice within the study period. In these cases, the first cancer was chosen. Patients with T1, histological grade 1 tumours were excluded ($n = 167$ patients). Six patients diagnosed before 2011 had tumours with oestrogen receptor positivity of $\geq 1 \leq 10\%$ and were excluded. Twenty-one patients opted not to participate in the study and were therefore excluded. This leaves a total study population of 1192 patients (1182 females and 10 males).

During the five-year follow-up, a total of 903 patients (75.8%) were adherent (MPR $\geq$ 80%) to the antihormonal treatment they were prescribed (Table 1). Two hundred and eighty-nine (24.2%) patients were classified as non-adherent. Of these, 101 patients never initiated the treatment and were classified as PNA. A total of 659 (55.3%) had a MPR rate of > 100% indicating that they remained on antihormonal treatment for longer than 5 years.

Table 1 Patient characteristics and estimated probability of adherence

Characteristics	Adherent/total	Adherent % (95% CI)	Non-adherent/total	Non-adherent % (95% CI)
	903/1192	75.8 (73.2-78.1)	289/1192	24.2 (21.8-26.8)
Age at diagnosis				
< 40	36/59	61.0 (47.4-73.5)	23/59	39.0 (26.5-52.6)
40-49	164/195	84.1 (78.2-88.9)	31/195	15.9 (11.1-21.8)
50-59	282/350	80.6 (76.0-84.6)	68/350	19.4 (15.4-24.0)
60-69	269/350	76.9 (72.1-81.2)	81/350	23.1 (18.8-27.9)
70-79	104/138	75.4 (67.3-82.3)	34/138	24.6 (17.7-32.7)
≥ 80	48/100	48.0 (37.9-58.2)	52/100	52.0 (42.8-63.1)
Tumour stage				
T1	508/686	74.1 (70.6-77.3)	178/686	25.9 (22.8-29.6)
T2	275/356	77.2 (72.5-81.5)	81/356	22.8 (18.5-27.5)
T3-T4	28/32	87.5 (71.0-96.5)	4/32	12.5 (3.5-29.0)
Unknown[a]	92/118	78.0 (69.4-85.1)	26/118	22.0 (14.9-30.6)
Histopathological type				
Ductal	712/943	75.5 (72.5-78.1)	231/943	24.5 (21.8-27.3)
Lobular	122/153	79.7 (72.5-85.8)	31/153	20.3 (14.2-27.5)
Other	64/89	71.9 (61.4-80.9)	25/89	28.1 (19.1-38.6)
Unknown	5/7	71.4 (29.0-96.3)	2/7	28.6 (3.7-71.0)
Histological grade				
Grade 1	76/104	73.1 (63.5-81.3)	28/104	26.9 (18.7-36.5)
Grade 2	507/686	73.9 (70.4-77.0)	179/686	26.1 (23.0-29.7)
Grade 3	229/285	80.4 (75.3-84.8)	56/285	19.6 (15.2-24.7)
Unknown	91/117	77.8 (69.2-84.9)	26/117	22.2 (15.1-30.8)
Axillary lymph node metastasis				
0	473/665	71.1 (67.4-74.4)	192/665	28.9 (25.6-32.6)
1-3	280/334	83.8 (79.4-87.6)	54/334	16.2 (12.4-20.6)
≥ 4	119/143	83.2 (76.1-88.9)	24/143	16.8 (11.1-23.9)
Unknown	31/50	62.0 (47.2-75.3)	19/50	38.0 (24.7-52.8)
Neoadjuvant treatment				
No	764/1017	75.1 (72.3-77.7)	253/1017	24.9 (22.2-27.7)
Yes	139/175	79.4 (72.7-85.2)	36/175	20.6 (14.8-27.3)
Type of antihormonal treatment				
Tamoxifen only	169/231	73.2 (67.0-78.8)	62/231	26.8 (21.2-33.0)
Tamoxifen ➔ AI	298/343	86.9 (82.8-90.3)	45/343	13.1 (9.7-17.2)
AI only	284/336	84.5 (80.2-88.2)	52/336	15.5 (11.8-19.8)
AI ➔ Tamoxifen	93/111	83.8 (75.6-90.1)	18/111	16.2 (9.9-24.4)
More than one switch	59/70	84.3 (73.6-91.9)	11/70	15.7 (8.1-26.4)
No antihormonal treatment registered	0/101	0 (0- 3.6)	101/101	100 (96.4-100)
Switch at two years				
No[b]	208/253	82.2 (76.9-86.7)	45/253	17.8 (13.3-23.1)
Yes	245/276	88.8 (84.4-92.2)	31/276	11.2 (7.8-15.5)
Monotherapy	450/562	80.1 (76.5-83.3)	112/562	19.9 (16.7-23.5)
No antihormonal treatment registered	0/101	0 (0- 3.6)	101/101	100 (96.4-100)
Radiation therapy				
No	234/345	67.8 (62.6-72.7)	111/345	32.2 (27.2-37.4)
Yes	669/847	79.0 (76.1-81.7)	178/847	21.0 (18.3-23.9)
Chemotherapy				
No	379/576	65.8 (61.8-69.7)	197/576	34.2 (30.5-38.4)
Yes	524/616	85.1 (82.0-87.8)	92/616	14.9 (12.2-18.0)

[a] 108/118 received neoadjuvant therapy. Hormone status was determined on core needle biopsy[b]Switch at other time point than 2 years (+/− 6 months)

The extremes of age (< 40 years and ≥ 80 years) showed significantly lower adherence (OR = 0.4, [95%CI: 0.2-0.7]; $p = 0.001$) and (OR = 0.2, [95%CI: 0.1-0.4]; $p = < 0.001$) respectively compared to patients aged 50-59 years (Table 2). Adherence predicted by a second-degree polynomial age term gives similar results also when grouped by chemotherapy (Fig. 2). Patients with metastasis to axillary lymph nodes as determined by sentinel lymph node biopsy and/or axillary clearance were more likely to be adherent to antihormonal treatment than those without axillary lymph node metastasis, (OR = 2.1, [95%CI: 1.5-3.0]; $p = < 0.001$) for those with 1-3 affected axillary lymph nodes and (OR = 2.0, [95%CI: 1.3-3.2]; $p = 0.004$) for those with ≥4 axillary lymph node metastasis). Similar results were seen when adjusting for age. Patients who switched to an AI (OR = 2.4, [95%CI: 1.6-3.7]; $p < 0.001$) those who received an AI only (OR = 2.0, [95%CI: 1.3-3.0]; $p = 0.001$), and the patients who started their treatment with an AI (OR = 1.9, [95%CI: 1.1-3.4]; $p = 0.031$) were all more likely to be adherent than those who received tamoxifen monotherapy. Those who switched type of antihormonal treatment (tamoxifen to AI or AI to tamoxifen) after 2 years were more likely to be adherent (OR = 1.7, [95%CI: 1.0-2.8]; $p = 0.033$) than patients on monotherapy. Patients who received chemotherapy showed better adherence (OR = 3.0, [95%CI: 2.2-3.9]; $p < 0.001$) than those who did not. This effect was observed for all ages (Fig. 2). Patients who received radiation therapy were also more likely to be adherent (OR = 1.8, [95%CI: 1.3-2.4]; $p < 0.001$). When adjusting for age, increasing tumour-stage was associated with a greater likelihood of adherence (OR = 1.5, [95%CI: 1.1-2.1]; $p = 0.011$) for T2-tumors and (OR = 3.7, [95%CI, 1.2-11.2]; $p = 0.023$) for T3- and T4-tumors. Furthermore, we found that after adjusting for age, those who received chemotherapy showed better adherence (OR = 3.8, [95%CI: 2.6-5.5]; $p < 0.001$).

In the primary non-adherent group, 82.2% had T1 tumours compared to 56.3% in the adherent group (Table 3). Those without axillary lymph node metastasis comprised 89.1% of the PNA-group as opposed to 52.4% of the adherent group. Among patients who did not receive chemotherapy, 95.0% were PNA as opposed to 42.0% in the adherent group ($p < 0.001$).

For the non-adherent patients, persistence was measured as the period from initiation to termination of therapy (Fig. 3). Patients who never initiated the recommended treatment (PNA) account for 34.9% of the non-adherent patients. Furthermore, 21.5% of the patients discontinued treatment during the first year. Thereafter, 15.6, 16.6, 9.7 and 1.7% discontinued treatment during year two, three, four and five respectively.

Discussion

In this study we found that close to a quarter of the patients (24.2%) did not adhere to prescribed treatment. Our main findings show that adherence varies with age, nodal status, type of treatment regimen and whether radiotherapy and/or chemotherapy were administered. Patients with primary non-adherence appears to have a less serious cancer-diagnosis compared to the rest of the study-population.

Poor adherence is a major challenge negatively affecting patient outcomes. It prevents medications from exerting their full beneficial effect [9–11, 14, 22]. With the use of oral medications taken at home, patients are increasingly rendered to themselves to tackle obstacles that might prevent good adherence. As antihormonal therapy in the setting of breast cancer treatment has proven to reduce the risk of recurrence and improve survival [3, 4, 8, 20, 27, 28, 40], there is no doubt that their effect is highly beneficial. This is further emphasized by the fact that current guidelines have extended the duration of treatment from five to 10 years.

A total of 659 patients (55.3%) were registered as having a MPR > 100%. These patients stayed on the antihormonal treatment beyond the recommended five-year treatment period. Some may have used antihormonal treatment for only a short period of time beyond the specified five-year recommendation. However, this finding may reflect emerging evidence at that time of the beneficial effects of antihormonal treatment given for more than five years [41–43].

The present study shows that patients aged < 40 years and ≥ 80 years are more likely to be non-adherent to antihormonal treatment. Pre-menopausal women treated with tamoxifen often develop troublesome side effects that could explain the low adherence rates in this group. Also, some of these women may have had a wish to become pregnant during the treatment period and therefore discontinued their treatment. This would be of increasing relevance with the current ten-year treatment recommendations. Patients above the age of 80 are more likely to be non-adherent due to comorbidities. These illnesses often entail complex treatment regimens. Some elderly patients suffer from varying degrees of both functional and/or cognitive impairment which further increases the risk of poor adherence [9, 44].

Our study shows that patients with metastasis to axillary lymph nodes are significantly more likely to be adherent compared to those without metastasis. This is also true when adjusting for age. Patients receiving

Table 2 Predictors of adherence

Characteristics	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
	Unadjusted		Adjusted for age	
Age at diagnosis				
< 40	0.4 (0.2-0.7)	0.001		
40-49	1.3 (0.8-2.0)	0.306		
50-59	Ref			
60-69	0.8 (0.6-1.2)	0.230		
70-79	0.7 (0.5-1.2)	0.203		
≥ 80	0.2 (0.1-0.4)	< 0.001		
Tumour stage				
T1	Ref		Ref	
T2	1.2 (0.9-1.6)	0.258	1.5 (1.1-2.1)	0.011
T3-T4	2.5 (0.8-7.1)	0.098	3.7 (1.2-11.2)	0.023
Unknown	1.2 (0.8-2.0)	0.368	1.3 (0.8-2.1)	0.286
Histopathological type				
Ductal	Ref		Ref	
Lobular	1.3 (0.8-2.0)	0.256	1.3 (0.9-2.1)	0.188
Other	0.8 (0.5-1.4)	0.454	1.0 (0.6-1.6)	0.915
Unknown	0.8 (0.2-4.2)	0.803	1.0 (0.2-5.8)	0.964
Histological grade				
Grade 1	Ref		Ref	
Grade 2	1.0 (0.7-1.7)	0.858	1.0 (0.6-1.6)	0.992
Grade 3	1.5 (0.9-2.5)	0.124	1.6 (0.9-2.7)	0.108
Unknown	1.3 (0.7-2.4)	0.417	1.2 (0.6-2.3)	0.550
Axillary lymph node metastasis				
0	Ref		Ref	
1-3	2.1 (1.5-3.0)	< 0.001	2.2 (1.6-3.1)	< 0.001
≥ 4	2.0 (1.3-3.2)	0.004	2.1 (1.3-3.4)	0.002
Unknown	0.7 (0.4-1.2)	0.175	1.3 (0.7-2.6)	0.415
Neoadjuvant treatment				
No	Ref		Ref	
Yes	1.3 (0.9-1.9)	0.220	1.4 (0.9-2.1)	0.098
Type of antihormonal treatment				
Tamoxifen only	Ref		Ref	
Tamoxifen ➔ AI	2.4 (1.6-3.7)	< 0.001	1.6 (1.0-2.6)	0.034
AI only	2.0 (1.3-3.0)	0.001	1.5 (0.9-2.4)	0.099
AI ➔ Tamoxifen	1.9 (1.1-3.4)	0.031	1.3 (0.7-2.4)	0.484
More than one switch	2.0 (1.0-4.0)	0.060	1.3 (0.6-2.8)	0.437
No antihormonal treatment registered	0	0.996	0	0.995
Switch at two years				
No[a]	Ref		Ref	
Yes	1.7 (1.0-2.8)	0.033	1.5 (0.9-2.4)	0.141
Monotherapy	0.9 (0.6-1.3)	0.473	1.0 (0.7-1.5)	0.988
No antihormonal treatment registered	0	0.995	0	0.995
Radiation therapy				
No	Ref		Ref	
Yes	1.8 (1.3-2.4)	< 0.001	1.2 (0.9-1.7)	0.209
Chemotherapy				
No	Ref		Ref	
Yes	3.0 (2.2-3.9)	< 0.001	3.8 (2.6-5.5)	< 0.001

[a] Switch at some other point in time (+/− 6 months)

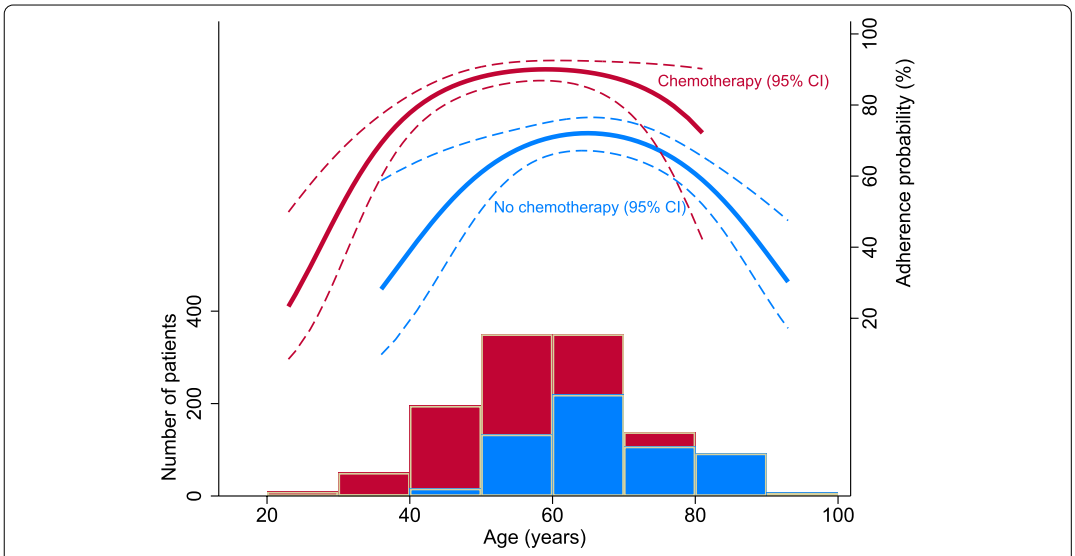

Fig. 2 Predicted adherence as a function of age and chemotherapy

Table 3 Characteristics of patients related to adherence

	Primary non-adherent (%)	Secondary non-adherent (%)	Adherent (%)	*P*-value (χ^2 Pearson's)
Tumor stage				
T1	83 (82.2)	95 (50.5)	508 (56.3)	< 0.001
T2	14 (13.9)	67 (35.6)	275 (30.5)	
T3-T4	2 (2.0)	2 (1.1)	28 (3.1)	
Unknown	2 (2.0)	24 (12.8)	92 (10.2)	
Histological grade				
Grade 1	3 (3.0)	25 (13.3)	76 (8.4)	< 0.001
Grade 2	87 (86.1)	92 (48.9)	507 (56.1)	
Grade 3	10 (9.9)	46 (24.5)	229 (25.4)	
Unknown	1 (1.0)	25 (13.3)	91 (10.1)	
Axillary lymph node metastasis				
0	90 (89.1)	102 (54.3)	473 (52.4)	< 0.001
1-3	7 (6.9)	47 (25.0)	280 (31.0)	
≥ 4	1 (1.0)	23 (12.2)	119 (13.2)	
Unknown	3 (3.0)	16 (8.5)	31 (3.4)	
Radiation				
No	39 (38.6)	72 (38.3)	234 (25.9)	< 0.001
Yes	62 (61.4)	116 (61.7)	669 (74.1)	
Chemotherapy				
No	96 (95.0)	101 (53.7)	379 (42.0)	< 0.001
Yes	5 (5.0)	87 (46.3)	524 (58.0)	
Neoadjuvant treatment				
No	99 (98.0)	154 (81.9)	764 (84.6)	< 0.001
Yes	2 (2.0)	34 (18.1)	139 (15.4)	

adjuvant radiotherapy and/or chemotherapy are also significantly more likely to be adherent to antihormonal treatment than those who did not receive this treatment. These findings may reflect that more severe disease motivates patients to maintain adherence throughout the scheduled treatment period. However, most young patients receive chemotherapy and most elderly do not. In our material 96.6% of those < 40 years and 91.8% in the 40-49 year age group received chemotherapy compared to 1% ≥ 80 years and 22.5% within the 70-79 year age group. Paradoxically, despite the fact that young patients receive chemotherapy, they are more likely to non-adherent compared to older patients.

Most patients, with the exception of those with distant metastasis at the time of diagnosis, had a one-year follow-up appointment at the surgical out-patients clinic, thereafter yearly follow-up by their general practitioner for 10 years. Close follow-up has been linked to improved adherence [10, 17]. However, several studies have shown greater adherence among patients followed by an oncologist as compared to those followed by their general practitioner [23, 25, 29, 30]. As this factor is modifiable, it will be important when strategies for improving adherence are considered.

The type of treatment regimen has an impact on adherence. Some patients were recommended monotherapy and others were recommended to switch endocrine treatment (tamoxifen to AI or AI to tamoxifen) at 2 years. Our material shows significantly better adherence for those

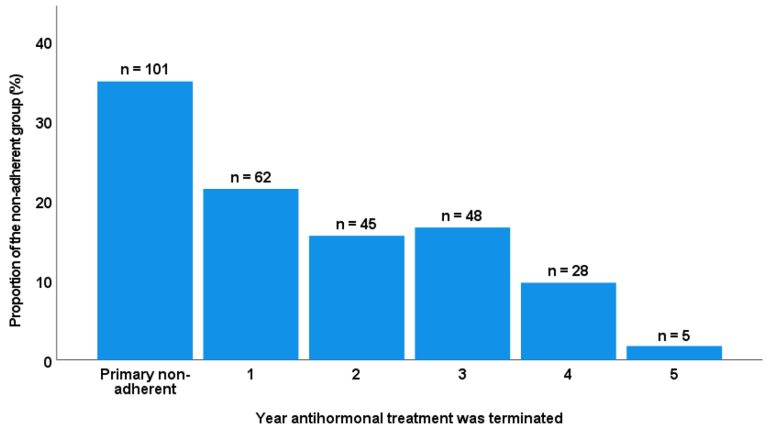

Fig. 3 Non-adherence according to year of patient-initiated termination of treatment

who switched at 2 years compared to those who received tamoxifen only. Some of the switches at 2 years may have been the result of side effects at the time. Although side effects are most intense in the first year of treatment, many of these patients may have continued the prescribed treatment for 2 years in the hope of fewer side effects after the planned switch at 2 years. We believe these are highly motivated patients who wish to continue the treatment despite troublesome side effects. We also observed that those who received AI as monotherapy had better adherence than those who were treated with tamoxifen monotherapy. This is in keeping with previous research [6], but is more difficult to explain but suggests that age may be a contributory factor as most women receiving AIs are postmenopausal and mainly in the age groups 60-79 years.

Of the non-adherent patients, 35.3%, or 8.5% of the total population, never initiated the treatment they were recommended. This is particularly worrisome as these patients stand to gain no benefit from the treatment. Previous research has shown that taking tamoxifen for only one to two years significantly reduces recurrence rates and breast cancer death rates [5, 45]. Motivating patients to initiate and continue their recommended treatment would therefore be advantageous in an attempt to improve adherence rates.

Of those initiating treatment, most patients with poor adherence discontinue within the first year of treatment. Thereafter, the numbers gradually decrease during the five-year treatment period. This may partly be explained by the occurrence of side effects. Research has shown that women treated with tamoxifen report fewer and less severe side effects after the first year of treatment [46]. Once the prescription is handed over to the patient, it is the patient's responsibility to follow the recommended treatment regimen. Information about why the treatment is given, expected benefit and possible side effects are important factors to communicate to the patient in a comprehensible manner [10, 18]. Close follow-up, especially during the first year of treatment, might prevent patients from becoming non-adherent. This is exemplified by the fact that adherence often will be at its best just before and after a consultation [10, 11]. The five patients who discontinued treatment during the fifth year may have been deemed satisfactorily treated and advised to terminate their treatment as they were close to the five-year mark.

Degree of adherence may be related to certain patient characteristics. Patients with cancers with a good prognosis not warranting chemotherapy, are more frequent in the PNA-group. We failed to find a clear distinction between secondary non-adherent patients and adherent patients. The influence of other factors such as side effects and co-morbidities may have contributed to patients discontinuing their treatment earlier than recommended. However, the study of these factors was beyond the scope of this study. Our findings suggest that patients who never initiate recommended treatment have less serious cancers. A possible explanation could be that these patients fail to see the need for antihormonal treatment given their favourable diagnosis. Several factors may contribute to this misconception. Often little time is spent on explaining the importance of good adherence. In a busy clinical working day, there is often limited time available to give the patient in-depth information regarding the treatment and the prescription may be handed

over to the patient with little further explanation. Important issues such as why the treatment is given, possible side effects and duration of treatment are often not adequately addressed. Clinicians may "oversell" the favourable diagnosis and prognosis to such an extent that the treatment is deemed unnecessary by the patient. Some patients may have negative expectations to antihormonal treatment [47], and this combined with a "non-serious" cancer, may increase the likelihood of not initiating the treatment. Cost of the medication is unlikely to be a contributing factor as these costs are reimbursed to the patients and do not impose a large expense. However, in some study populations, socioeconomic status may exert influence on patient adherence behaviour [48].

Our study shows that 75.8% of the patients are adherent to antihormonal treatment. This is consistent with several other studies [20, 36, 49]. We have shown that the extremes of age and less severe disease characteristics increases the risk of non-adherence. Although these are non-modifiable factors, they are important in order to identify patients at risk of poor adherence. PNA or "lack of "initiation" to antihormonal treatment has been described in previous research [23, 50, 51]. However, more in-depth knowledge about this particular group is important. In this paper we show that the PNA-patients tend to have a better prognosis and postulate that their non-initiation might be linked to how clinicians communicate. If this is the case, greater awareness among clinicians on how we communicate the need for antihormonal treatment, regardless of a good prognosis, may be a way of improving adherence rates among PNA-patients. This study has also shown that most non-adherent patients discontinue the treatment in the initial part of the treatment period, this is in keeping with previous research [38]. This finding is of value as targeted interventions for improving adherence could benefit from focusing their efforts in the initial part of the treatment period. Increased awareness of non-adherence, both among clinician and patients, will ultimately lead to better outcomes for these patients.

The present study does not investigate subjective factors affecting adherence. Side effects are one of the major factors determining adherence to antihormonal treatment [24, 27, 29–31]. One study showed that almost half the participants reported side effects as the reason for non-adherence to tamoxifen [52]. It is important to ask patients about their experience of side effects to detect poor adherence. Prescribing ameliorative treatments for troublesome side effects will often be very beneficial [24, 29], and may prevent poor adherence. Patients' expectations to antihormonal therapy before initiating the treatment have been proven to affect both side effects and quality of life. After 2 years of antihormonal treatment the relative risk of side effects was higher in those with negative expectations at baseline than those with low negative expectations (RR = 1.833, [95%CI: 1.0-3.3]) [47]. Patients who have been treated with chemotherapy have already been exposed to low oestrogen levels [53], this may be a contributary factor as to why these women show better adherence compared to those who did not receive chemotherapy.

Assessing adherence is challenging and complex. Several methods of measurement exist. Using prescription refill registers has been shown to be an objective and reliable way of assessing adherence. This is especially true for medications intended for long-term therapy [10, 15]. However, relying on register data, we cannot be sure that the patients consumed the medications dispensed at the pharmacy. However, we consider it unlikely that patients have repeatedly refilled their prescriptions without actually taking them. Research supports this assumption as it has been shown that the rate at which patients refill their prescriptions is consistent with the rate at which they consume their medications [54]. Furthermore, it has been shown that there is concordance between serum tamoxifen levels and rates of discontinuation [55]. Although widely used, the 80% cut-off for "good" and "poor" adherence is an arbitrary value that is poorly documented in relation to specific diseases and classes of medications [14, 56].

There are some limitations to this study. Reasons for poor adherence were not recorded. Non-adherence may be a patient choice and therefore represent intentional non-adherence. However, the decision to stop a medication may also be made by the clinician based on intercurrent illness or other factors. The unavailability of reasons for non-adherence in this study is therefore a weakness. Another drawback is the fact that data regarding antihormonal treatment prescribed to patients admitted to hospital or residing in a nursing home is not included in the data from the NorPD. The numbers in the younger and elderly subgroups are relatively small, therefore, one should be cautious in drawing firm conclusions. While some studies have shown similar adherence-rates in relation to age [29, 35], others have shown this association only for the younger age group [20, 24, 25]. A potential limitation of this study is whether the results are transferable to other patient populations. Study population profiles vary with regard to demographics, access to treatment and public health systems. However, we believe that our results contribute to our understanding of patient adherence.

Strengths of this study include its population-based design including all women that underwent surgery at

St Olav's Hospital during the study period. We have collected prescription data from the NorPD rather than relying on self-reported data from the patients. Data from prescription databases have been shown to be superior to self-reported adherence data [54] and are particularly advantageous for the evaluation of medications intended for long-term therapy [15]. Compared to many other studies with shorter periods of follow-up [28, 34, 38, 57–60], we have evaluated adherence for the full length of the recommended five-year treatment period. Furthermore, we have differentiated between treatment with tamoxifen and AIs.

Conclusion

We conclude that adherence to antihormonal therapy for breast cancer is suboptimal. Special attention should be paid to the young and elderly as these subgroups show poorer adherence than the other age groups. The relatively large group of patients with primary non-adherence is of particular interest. It appears that these patients have cancers with a relatively good prognosis. This is a somewhat surprising finding, and we hope future research will focus more on this group of patients. Non-adherent patients tend to terminate their antihormonal therapy in the initial part of the treatment period. This means that targeted interventions to improve adherence should be focused on the initial part of the treatment period. Better adherence will improve patient outcomes and reduce health care expenditures.

Abbreviations

HR: Hormone receptor; MPR: Medical Possession ratio; AI: Aromatase inhibitor; NorPD: Norwegian Prescription database; OR: Odds ratio; CI: Confidence interval.

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Authors' contributions

ID: Data collection. Analysis and interpretation of the data, drafting the article, final approval. AMB: Interpretation of the data, drafting the article, final approval. HS: Drafting the article, final approval. GT: Statistical analysis, drafting the article, final approval. MJE: Conceptualization, analysis and interpretation of the data, drafting the article, final approval. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due to reasons of sensitivity and limitations imposed in the conditions for approval by the Ethics Committee but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study, including an outline of the statistical methods used, was approved by the Regional Committee for Medical and Health Research Ethics, South East Norway (# 2017/1356) and the Regional Data Protection Office according to the Declaration of Helsinki. Informed consent was obtained from all participants in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Paper II

Adjuvant antihormonal treatment in breast cancer. Understanding how poor adherence affects survival

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Adjuvant antihormonal treatment in breast cancer. Understanding how poor adherence affects survival

Introduction

Adherence to antihormonal treatment is known to be suboptimal. The beneficial effects of antihormonal treatment are well documented. We investigate how poor adherence affects survival.

Methods

This single-centre retrospective cohort study included 1176 patients diagnosed with breast cancer from 2004-2013. These patients were all prescribed antihormonal treatment as part of their adjuvant treatment regimen. Adherence was calculated based on the medical possession ratio (MPR) where patients were defined as adherent if they reached a MPR ≥80%. Non-adherent patients were further subclassified into secondary non-adherent (SNA) where MPR measured 0.1-80% or primary non-adherent (PNA) where MPR was zero.

Results

A total of 24.4% (287) of the patients were non-adherent. Secondary non-adherent patients had poorer breast cancer specific survival (hazard ratio [HR] 3.04, 95% confidence interval [CI] 2.12-4.36) compared to adherent patients. Primary non-adherent patients had better breast cancer specific survival compared to adherent patients (HR 0.27, 95% CI 0.10-0.75).

Conclusion

Subdividing non-adherent patients into primary non-adherent or secondary non-adherent provides valuable insight into how different adherence-behaviours affect survival. Based on the favourable survival rates of the low-risk primary non-adherent patients, we suggest that some low-risk patients currently are being overtreated with antihormonal treatment.

Abbreviations

MPR	Medical possession ratio
SNA	Secondary non-adherent
PNA	Primary non-adherent
HR	Hazard ratio
CI	Confidence interval
OS	Overall survival
BCSS	Breast cancer specific survival

Adjuvant antihormonal treatment in breast cancer. Understanding how poor adherence affects survival

Introduction

Adherence to medical treatment affects survival (1-6). Already well-established and highly effective treatments must be taken correctly in order to exert their full pharmacological effects. Failure to take medication as prescribed often leads to poorer patient outcomes, and for some patients, this means shorter survival.

Adherence may be defined as the extent to which a patient follows the given instructions when prescribed a treatment (4, 7). A patient is adherent if they follow treatment as prescribed. Primary non-adherent characterises patients who never fill their first or subsequent prescriptions at the pharmacy. Secondary non-adherent describes those who initiate the prescribed treatment but subsequently fail to take the medication as directed (5, 8-10).

Antihormonal treatment for hormone receptor positive breast cancer (oestrogen and/or progesterone receptor positive breast cancer) includes tamoxifen and aromatase inhibitors. The beneficial effects of antihormonal treatment on both recurrence and survival are well documented (11-14), and most patients with hormone receptor positive disease are prescribed antihormonal treatment for up to 10 years (15). Several studies have shown that adherence to antihormonal treatment is suboptimal (11, 16-24). However, previous studies have often classified all non-adherent patients as a single group, perhaps masking any differences there may be between PNA and SNA. As many patients never initiate, or prematurely discontinue their prescribed treatment, it is important to gain a better understanding of the effects of both PNA and SNA on survival.

The aim of this study was to examine the effect of poor adherence expressed as PNA and SNA on overall survival and breast cancer specific survival in a group of patients who underwent surgery for hormone receptor positive breast cancer in the period 2004-2013.

Materials and methods

Study population

A total of 1370 patients were diagnosed with hormone receptor positive breast cancer and underwent surgery at St Olav's Hospital, Trondheim University Hospital in Norway from 01.01.2004 to 31.12.2013. They were subsequently prescribed adjuvant antihormonal therapy. A total of 167 patients with tumours that were T1 (<20mm) and histopathological grade 1 were excluded as they did not qualify for antihormonal therapy according to national guidelines operative at the time of diagnosis. Six patients with tumours that showed oestrogen receptor positivity of ≥1<10% diagnosed prior to 2011, were excluded from the study as they were not prescribed antihormonal treatment for the same reasons. A further 21 patients did not wish to participate in the study. The final study population comprised a total of 1176 patients (Fig. 1).

Patient data including date of birth, tumour characteristics and treatment modalities, were collected from the hospital medical records. Detailed information regarding antihormonal treatment was retrieved from the Norwegian Prescription Database. Date of death and cause of death (death from breast cancer or other causes) were retrieved from the Cancer Registry of Norway and the Norwegian Cause of Death Registry respectively. Follow-up ended on the 31.12.2019.

Outcomes

Participants were assigned to one of the following categories: adherent, PNA and SNA according to their degree of adherence to the prescribed treatment. Adherence was calculated based on the medical possession ratio (MPR). In the present study, the MPR was defined as the number of days a medication is available during a specified time interval (5, 25). The MPR was calculated as a fraction where the numerator was the days of medication supply obtained and the denominator was fixed at five years. For those who died during the five-year course of antihormonal treatment the denominator was adjusted to the length of time they were alive after initiating the treatment. Patients with an adherence rate ≥80% were regarded as adherent and those < 80% were deemed non-adherent. The 80% cut-off is commonly used (20, 26). Non-adherent patients were further subdivided into PNA (MPR = 0) and SNA (MPR 0.1-80%). Patients were further classified as low-risk or high-risk based on the occurrence of axillary lymph node metastases. Low-risk patients were defined as having no axillary lymph node metastases according to the postoperative pathology report and high-risk patients as being diagnosed with one or more axillary metastasis.

The three categories of adherence were correlated to age, tumour characteristics (tumour-stage, histopathological type, histopathological grade and, axillary lymph node status) and treatment modalities (neoadjuvant treatment, type of antihormonal treatment, radiation therapy and chemotherapy). Hazard ratios with 95% CI's were calculated for categories of adherence according to overall survival (OS) and breast cancer specific survival (BCSS).

Statistical analysis

Pearson's chi square (χ^2) was used to describe differences in distribution of the variables in table 1. Overall survival and BCSS for the three categories of adherence (adherent, PNA, and SNA) were assessed using Kaplan Meier curves and cox regression with adherence state as a time-dependent covariate. Statistical analyses were performed using SPSS version 28 and R version 3.6.3.

Results

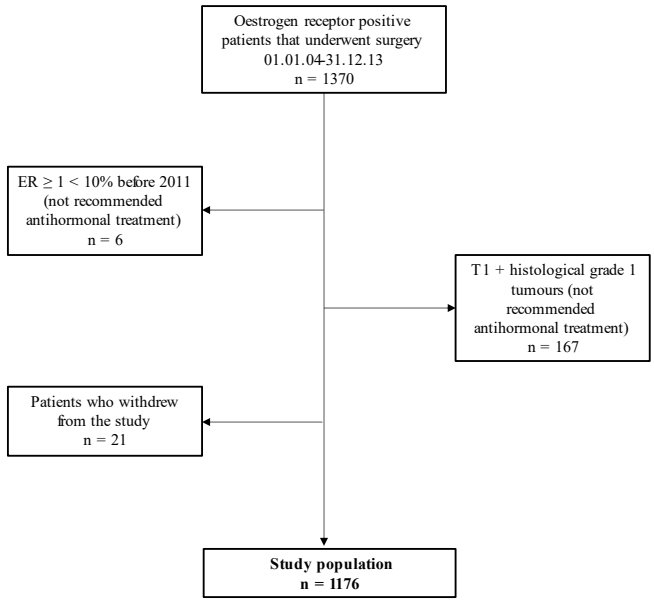
Patient characteristics, histopathological status and treatment modalities according to adherence are shown in table 1. The study population comprised 1176 patients, 1166 females and 10 males. The median age at diagnosis was 59 years (range 23-93). Median follow-up from diagnosis to end of study was 129 months (range 72-225). A total of 75.1% (883/1176) patients were still alive at end of follow up. The patient selection is summarized in Figure 1.

Table 1: Characteristics of the study population according to adherence					
	Total study population	Adherent (%)	Primary non-adherent (%)	Secondary non-adherent (%)	P-value (χ^2 Pearson's)
N	1176	889 (75.6)	100 (8.5)	187 (15.9)	
Alive at end follow-up	883 (75.1)	703 (79.1)	76 (76)	104 (55.6)	<0.001
Breast cancer mortality	157 (13.4)	110 (12.4)	4 (4)	43 (23)	
Death from other causes	136 (11.6)	76 (8.5)	20 (20)	40 (21.4)	
Age at diagnosis					
<40	57 (4.8)	34 (3.8)	2 (2)	21 (11.2)	<0.001
40-49	191 (16.2)	161 (18.1)	7 (7)	23 (12.3)	
50-59	342 (29.1)	275 (30.9)	29 (29)	38 (20.3)	
60-69	348 (29.6)	267 (30)	37 (37)	44 (23.5)	
70-79	138 (11.7)	104 (11.7)	9 (9)	25 (13.4)	
≥80	100 (8.5)	48 (5.4)	16 (16)	36 (19.3)	
Tumour stage					
T1	678 (57.7)	502 (56.5)	82 (82)	94 (50.3)	<0.001
T2	353 (30)	272 (30.6)	14 (14)	67 (35.8)	
T3-T4	32 (2.7)	28 (3.1)	2 (2)	2 (1.1)	
Unknown*	113 (9.6)	87 (9.8)	2 (2)	24 (12.8)	
Histopathological type					
Ductal	930 (79.1)	701 (78.9)	85 (85)	144 (77)	0.209
Lobular	151 (12.8)	120 (13.5)	11 (11)	20 (10.7)	
Other	88 (7.5)	63 (7.1)	4 (4)	21 (11.2)	
Unknown	7 (0.6)	5 (0.6)	0	2 (1.1)	
Histological grade					
Grade 1	104 (8.8)	76 (8.5)	3 (3)	25 (13.4)	<0.001
Grade 2	677 (57.6)	500 (56.2)	86 (86)	91 (48.7)	
Grade 3	283 (24.1)	227 (25.5)	10 (10)	46 (24.6)	
Unknown	112 (9.5)	86 (9.7)	1 (1)	25 (13.4)	
Axillary lymph node metastasis					
0	661 (56.2)	470 (52.9)	89 (89)	102 (54.5)	<0.001
1-3	332 (28.2)	278 (31.3)	7 (7)	47 (25.1)	
≥4	142 (12.1)	118 (13.3)	1 (1)	23 (12.3)	
Unknown	41 (3.5)	23 (2.6)	3 (3)	15 (8)	
Neoadjuvant treatment					
No	1005 (85.5)	754 (84.8)	98 (98)	153 (81.8)	<0.001
Yes	171 (14.5)	135 (15.2)	2 (2)	34 (18.2)	
Type of antihormonal treatment					
Tamoxifen only	231 (19.6)	169 (19)	0	62 (33.2)	<0.001
Tamoxifen → AI	334 (28.4)	289 (32.5)	0	45 (24.1)	
AI only	331 (28.1)	279 (31.4)	0	52 (27.8)	
AI → Tamoxifen	110 (9.4)	93 (10.5)	0	17 (9.1)	
More than one switch	70 (6)	59 (6.6)	0	11 (5.9)	
No antihormonal treatment registered	100 (8.5)	0	100 (100)	0	
Switch at two years					
No**	249 (21.2)	204 (22.9)	0	45 (24.1)	<0.001
Yes	270 (23)	240 (27)	0	30 (16)	
Monotherapy	557 (47.4)	445 (50.1)	0	112 (59.9)	
No antihormonal treatment registered	100 (8.5)	0	100 (100)	0	
Radiation therapy					
No	334 (28.4)	224 (25.2)	39 (39)	71 (38)	<0.001
Yes	842 (71.6)	665 (74.8)	61 (61)	116 (62)	
Chemotherapy					
No	566 (48.1)	370 (41.6)	95 (95)	101 (54)	<0.001
Yes	610 (51.9)	519 (58.4)	5 (5)	86 (46)	

*105/113 received neoadjuvant therapy. Hormone status was determined on core needle biopsy.

**Switch at time point other than at 2 years (+/- 6 months).

Figure 1: Flow chart of study population



Of the total study population, 75.6% (889/1176) remains adherent to the prescribed treatment, 8.5% (100/1176) were classified as PNA and 15.9% (187/1176) were classified as SNA (Table 1 and Figure 2). At the end of follow-up, the percentages of patients still living were 79.1% (703/889), 76% (76/100) and 55.6% (104/187) in the adherent, PNA and SNA groups respectively. During follow-up, a total of 12.4% (110/889) of the adherent patients died of

breast cancer in contrast to 4% (4/100) among PNA and 23% (43/187) among SNA-patients. Death due to other causes was seen in 8.5% (76/889) of adherent patients, 20% (20/100) of PNA and 21.4% (40/187) of SNA-patients.

Figure 2: Adherence rates

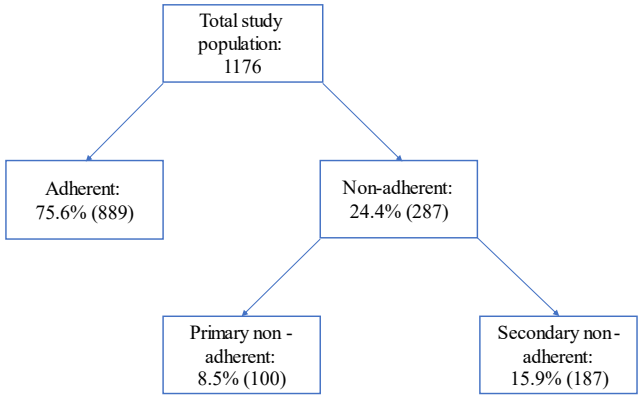


Table 1 also shows that patients in the PNA-group tend to have a better prognosis than the other patients in the study population. Among the PNA-patients, 82% (82/100) had T1-tumours (tumours < 20mm) falling to 50.3% (94/187) among SNA-patients and 56.5% (502/889) in the adherent group. Similarly, 86% (86/100) of the PNA-patients were diagnosed with histopathological grade 2 tumours falling to 48.7% (91/187) in the SNA-group and to 56.2% (500/889) in adherent patients. Furthermore, 89% (89/100) of PNA patients had no axillary lymph node metastases, falling to 54.5% (102/187) in the SNA group and 52.9% (470/889) in the adherent group.

Overall survival among PNA was similar to that of adherent patients (HR 1.05, 95% CI 0.69-1.62) (Table 2). Overall survival was poorer among SNA compared to adherent patients (HR 3.48, 95% CI 2.68-4.53). Breast cancer specific survival was better among PNA- (HR 0.27, 95% CI 0.10-0.75) and poorer among SNA-patients (HR 3.04, 95% CI 2.12-4.36) compared to adherent patients. Low-risk SNA-patients had poorer OS than low-risk adherent patients (HR 3.41, 95% CI 2.16-5.40). The PNA-patients with a low risk profile tended to have better BCSS than the low-risk adherent patients (HR 0.21, 95% CI 0.03-1.54). High-risk SNA-patients had a poorer OS and BCSS compared to high-risk adherent patients (HR 3.50, 95%

CI 2.43-5.06) and (HR 4.42, 95% CI 2.83-6.60), respectively. Survival curves are shown in Figure 3.

Table 2: Adherence status according to survival

	Total HR (CI)	**Low risk HR (CI)**	**High risk HR (CI)**	**Age <50 HR (CI)**	**Age 50-69 HR (CI)**	**Age ≥70 HR (CI)**
Overall survival						
Adherent (ref)	-	-	-	-	-	-
PNA	1.05 (0.69-1.62)	1.37 (0.77-2.42)	2.56 (1.05-6.23)	2.59 (0.77-8.73)	0.93 (0.48-1.79)	0.78 (0.41-1.46)
SNA	3.48 (2.68-4.53)	3.41 (2.16-5.40)	3.50 (2.43-5.06)	4.76 (2.43-9.35)	3.03 (1.91-4.80)	1.98 (1.37-2.87)
Breast cancer specific survival						
Adherent (ref)	-	-	-	-	-	-
PNA	0.27 (0.10-0.75)	0.21 (0.03-1.54)	0.85 (0.16-4.51)	1.83 (0.42-7.88)	0*	0.28 (0.07-1.16)
SNA	3.04 (2.12-4.36)	1.91 (0.82-4.46)	4.42 (2.83-6.60)	5.03 (2.49-10.17)	2.76 (1.52-5.02)	1.50 (0.82-2.73)

*No patients died in this category.

Overall survival is poorer among SNA-patients compared to adherent patients regardless of age. This is illustrated in table 2 where SNA-patients <50 years of age (HR 4.76, 95% CI 2.43-9.35), aged 50-69 years (HR 3.03, 95% CI 1.91-4.80) and those 70 years or older (HR 1.98, 95% CI 1.37-2.87) have poorer OS than the adherent patients. Furthermore, BCSS is poorer among SNA-patients compared to adherent patients for the age groups <50 years (HR 5.03, 95% CI 2.49-10.17) and 50-69 years (HR 2.76, 95% CI 1.52-5.02).

Figure 3: Overall survival and breast cancer specific survival

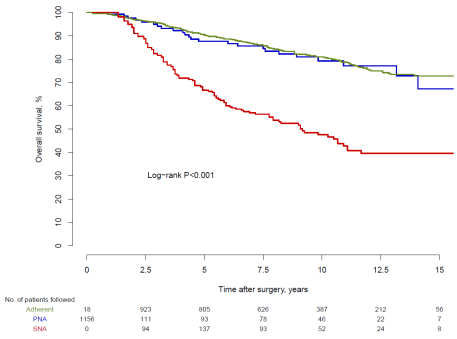


Figure 3a: Overall survival

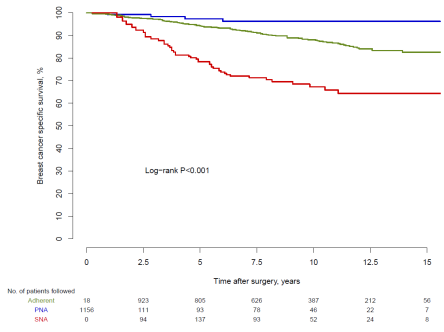


Figure 3b: Breast cancer specific survival

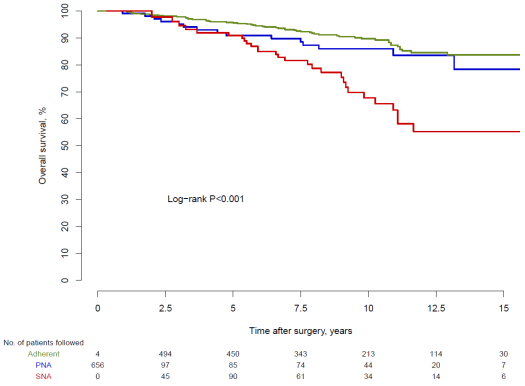


Figure 3c: Overall survival, low risk

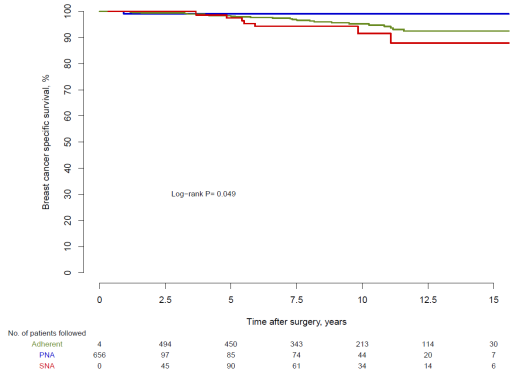


Figure 3d: Breast cancer specific survival, low risk

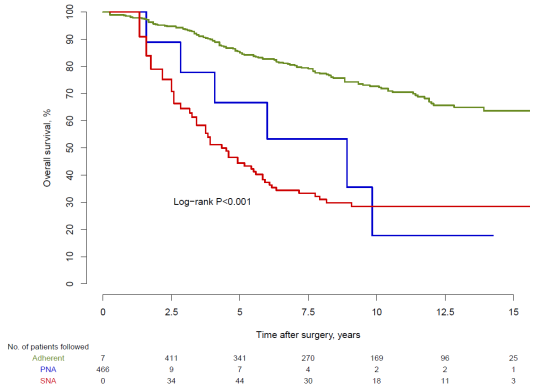


Figure 3e: Overall survival, high risk

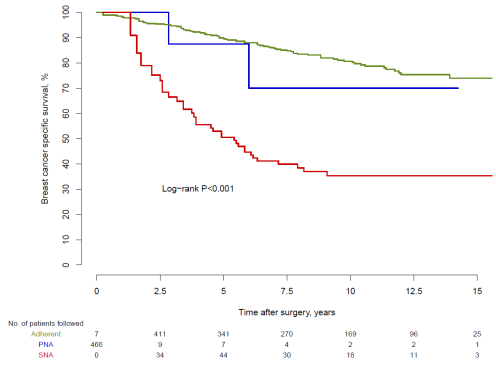


Figure 3f: Breast cancer specific survival, high risk

Low risk: Patients with no axillary metastases. High risk: Patients with axillary metastases.

Discussion

In this study of 1176 patients with breast cancer, we show that 24.4% patients did not take their antihormonal treatment as prescribed. Of the total population, 15.9% initiated the treatment, but subsequently failed to reach a MPR of 80% and 8.5% of the patients never filled their first or subsequent prescriptions at the pharmacy. Patients who initiated treatment but failed to reach a MPR of 80% (SNA), had poorer survival compared to those who followed the prescribed treatment regimen. Interestingly, we show that patients who never initiated their prescribed treatment (PNA) had a similar overall survival to those who took their medication as directed.

There is no doubt antihormonal treatment is highly beneficial in the treatment of hormone receptor positive breast cancer (11-14, 27, 28). As expected, SNA-patients showed poorer survival compared to adherent patients in this study. This could simply be explained by the fact that patients with poor adherence discontinued their antihormonal treatment prematurely, thereby failing to gain the full benefit of the treatment. However, some patients may have discontinued due to other serious medical conditions, where the antihormonal treatment was deemed less important. Furthermore, it is possible that SNA-patients tend to show poor adherence to other medications affecting their OS in a negative manner.

Patients who never initiated their treatment had a better BCSS than those who remained adherent to their prescribed treatment. While more difficult to explain, we suggest this may be governed by the characteristics of the patients in the PNA-group. In our study population, PNA-patients tended to have a better prognosis compared to SNA and adherent patients. We suggest this to a certain extent steers how we, as clinicians, communicate with our patients. In an attempt to ease some of the stress a cancer-diagnosis entails, clinicians may "oversell" a more favourable prognosis to their patients. This could in some cases result in the patient failing to appreciate the need for antihormonal therapy. Good, comprehensible information regarding the prescribed treatment is paramount in establishing optimal adherence (4, 29). Furthermore, in a busy working day, clinicians may under-communicate the intention of antihormonal treatment, thereby contributing to poor adherence. "Lack of physician recommendation" has been shown to be an important factor negatively affecting adherence (30). While PNA-patients have an excellent BCSS, their OS is somewhat lower. This might be explained by the probable non-initiation of other types of therapies not related to the breast cancer diagnosis. We observed little difference in OS between the PNA group and the

adherent group indicating that the assumption of the good long-term prognosis in patients with favourable prognostic factors is probably correct. On the other hand, we cannot exclude that PNA-patients could have achieved better survival had they followed their prescriptions as recommended. Our finding of a low-risk profile among PNA-patients needs to be validated in other PNA-cohorts.

All patients in our study population were prescribed antihormonal treatment for a period of five years in accordance with treatment guidelines at time of diagnosis. It is now known that ten years of antihormonal treatment has beneficial effects for many patients (31-36). It is particularly high-risk patients that benefit most from this extended duration of therapy (15, 37). In the present study, patients were stratified into low and high-risk groups based on axillary lymph node status. As expected, high-risk, non-adherent patients showed the poorest survival. These patients would have benefitted from the antihormonal treatment they never initiated or did not take as prescribed. Follow-up of these patients should also focus on adherence to the prescribed antihormonal treatment in an effort to optimise their survival.

Based on our findings, we propose that antihormonal treatment regimens should be stratified according to the individual patient's prognostic profile. Gene profiling has contributed to a more precise stratification of patients with regards to risk of recurrence and likely response to treatment (38). There is evidence that many patients are currently being overtreated with antihormonal therapy (39, 40). De-escalation of treatment has already been implemented in other aspects of breast cancer treatment. A relatively recent example is the omission of chemotherapy for selected low-risk patients (41-44). Furthermore, the replacement of axillary lymph node dissection with sentinel lymph node biopsy represents a major improvement in the treatment of breast cancer patients. (45-47). Emerging evidence shows that carefully selected low-risk patients could be treated with limited antihormonal treatment, or perhaps, no treatment at all (39, 40, 48, 49). Shorter duration of treatment will lead to shorter duration of potentially troublesome side effects, and this might in itself be a motivating factor for remaining adherent throughout the treatment period. "One-size-fits-all" is less accepted in modern cancer medicine and an individualized approach should be employed also for antihormonal treatment. Our study supports the de-escalation of antihormonal treatment by showing excellent survival for the low-risk PNA-patients.

Many patients experience side effects impacting their quality of life to such an extent that it leads to reduced adherence (16, 19, 50-54). Side effects have been shown to be one of the

main causative factors of non-adherence to antihormonal treatment (55, 56). As SNA-patients have initiated the treatment but subsequently not taken the therapy as prescribed, one may assume that they had an intention of taking the treatment in the first place. Previous research has shown that SNA-patients tend to terminate their treatment in the initial part of the treatment period (20, 24, 37, 55). This could be explained by the fact that side effects are most frequent and more severe during the first year of treatment (57). Addressing side effects early in the treatment process might therefore contribute to improved adherence.

This study has limitations. Some of the subgroups in the study have low numbers which decreases their statistical strength. This cohort comprised of 1176 patients, of whom 100 were PNA. Our findings should be validated in larger cohorts. Risk stratification based on Luminal A and B subtypes was not possible as Ki67 and HER-2 status were not available for a large proportion of the cohort. We have not included recurrence-data or contralateral breast cancers in our study.

A strength of this study is that we have used registry-based data to obtain information about prescription-filling. This method of gaining data regarding adherence has been shown to be superior to self-reported adherence data, as the latter will often overestimate adherence-rates (4, 7, 58, 59). As the present study shows, subdividing non-adherent patients into PNA and SNA provides more in-depth knowledge about these patients and may subsequently contribute to improving patient outcome.

Conclusion

This study shows that, in breast cancer, about a quarter of patients do not take their prescribed antihormonal treatment. Secondary non-adherent patients have poorer survival outcomes than the rest of the study population. Primary non-adherent patients do better than anticipated, probably due to their low-risk profile. Good communication between patient and clinician is paramount in establishing good adherence. A more personalized approach stratifying patients according to risk profile seems to be appropriate when prescribing antihormonal treatment. This form of personalized antihormonal treatment will ultimately lead to less overtreatment, improved adherence, and better quality of life for many patients.

Statements and Declarations

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Competing interests The authors declare that they have no competing interests.

Authors' contributions ID: Data collection. Analysis and interpretation of the data, drafting the article, final approval. AMB: Interpretation of the data, drafting the article, final approval. HS: Drafting the article, final approval. ØS: Statistical analysis, drafting the article, final approval. MJE: Conceptualization, analysis and interpretation of the data, drafting the article, final approval. All authors have read and approved the final manuscript.

Data availability Data that support the findings of this study are available from the Norwegian Prescription Database. Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Patient data collected from the medical records in the hospital are not available due to patient confidentiality.

Ethics approval The study, including an outline of the statistical methods used, was approved by the Regional Committee for Medical and Health Research Ethics, South East Norway (# 2017/1356) and the Regional Data Protection Office according to the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all participants in the study.

Consent to publish Not applicable.

Acknowledgements A preprint has previously been published (60).

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Research Article

How to Optimize Deimplementation of Sentinel Lymph Node Biopsy?

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Background. The omission of sentinel lymph node biopsy in low-risk elderly breast cancer patients has been introduced in several guidelines. Despite evidence to support its safety, this recommendation has not been implemented by many clinicians. We have examined two aspects of this recommendation that may explain why sentinel lymph node biopsy continues to be performed in most of these patients. Firstly, we quantified the proportion of patients diagnosed with axillary metastases postoperatively. Secondly, we examined adherence to antihormonal therapy in the same group of patients. *Methods*. In this single-centre retrospective cohort study, the study population comprised 98 patients with breast cancer. Patients were aged ≥70 years and diagnosed with hormone receptor positive breast cancers less than 20 mm (T1). All patients underwent surgery and were subsequently prescribed five years of adjuvant antihormonal treatment. *Results*. Axillary lymph node metastases, as confirmed by the postoperative histology report, were seen in 36.3%. Nonadherence was seen in 33.7% of the patients. Primary nonadherence, that is, patients that never collect their first or subsequent prescriptions at the pharmacy, comprised 11.2% of the total study population. *Conclusion*. The high proportion of axillary metastases demonstrated suggests that clinical examination of the axilla alone is not sufficient in the preoperative assessment of the axilla. The less-than-optimal adherence rates show that adherence in these patients cannot be taken for granted. We suggest that these factors reflect some of the reluctance among clinicians to omit the sentinel lymph node procedure in these patients.

1. Introduction

Focusing on the challenge of overtreatment in breast cancer has led to the deescalation of previously well-established therapies. Overtreatment can be defined as treatment that does not convey a benefit to the patient but rather may cause harm. Moreover, unnecessary treatment leads to unnecessary costs for health care systems [1–3]. This pervasive problem has gained increasing attention in recent years. Minimising overtreatment is of particular importance in elderly breast cancer patients where comorbidities and frailty frequently occur [4]. The population is aging [5], and over 30% of new breast cancer diagnoses in the US occur in women ≥70 years [6].

The *Choosing Wisely Campaign* was established in the US in 2012 with a goal to reduce unnecessary medical testing and treatment by engaging clinicians and patients in conversations about the topic. Since its inception, many countries around the world have adapted and implemented the campaign [7, 8]. The *Choosing Wisely* initiative published the following recommendation in 2016: "Don't routinely use sentinel node biopsy in clinically node negative women ≥70 years of age with early stage hormone receptor positive, HER-2 negative invasive breast cancer." This has later been

reaffirmed in updated versions in 2019, 2020, and 2021 [9]. The same recommendation was made by the American Society of Clinical Oncology (ASCO) in 2021 [10]. Both recommendations state that these patients should be treated with adjuvant antihormonal treatment. These recommendations were made mainly based on the findings in the Cancer and Leukaemia Group B 9343 (CALBG 9343) clinical trial published in 2004 [11] with a follow-up study in 2013 [12]. These trials demonstrated similar survival in women who received radiotherapy and tamoxifen compared to those who received tamoxifen only following breast conserving surgery. Omitting SLNB, and therefore radiotherapy, has consequently been deemed safe by the *Choosing Wisely Campaign* and ASCO. Other studies have showed concordant results [13–16].

Although there is extensive evidence showing that omitting sentinel lymph node biopsy (SLNB) and radiotherapy in these patients is safe, the implementation of this recommendation remains to be embraced by most clinicians treating breast cancer [13, 17–20]. Retrospective data have shown that between 68% [21] and over 80% [22, 23] of patients eligible for omission of SLNB according to the abovementioned recommendations still undergo the procedure. The explanation for this is multifactorial showing that effective deescalation relies on more than evidence from clinical trials [24–26].

We propose that there are two prerequisites to this recommendation that may explain its unsuccessful implementation. Firstly, preoperative examination of the axilla must verify the absence of axillary metastases (cN0), and secondly, the patient is expected to adhere to adjuvant antihormonal treatment for five years after diagnosis. The main aims of the present study were to quantify the proportion of patients in whom axillary lymph node metastases are detected postoperatively and to examine adherence to antihormonal treatment in this specific group of patients. Furthermore, we examine how adherence and axillary lymph node status relate to survival for these patients.

2. Materials and Methods

The study population comprised all patients aged ≥70 years at the time of diagnosis who underwent surgery for estrogen receptor positive breast cancer at St. Olav's University Hospital in the period 01.01.2004 to 31.12.2013. Information regarding age, tumour characteristics, lymph node status, and treatment modalities were collected from the hospital medical records. Patients underwent breast conserving treatment (BCT) or mastectomy of the tumour with SLNB and/or axillary lymph node dissection (ALND). Tumours were confirmed to be estrogen receptor positive and less than 20 mm in diameter (T1 tumours) according to the postoperative pathology report. All patients were prescribed adjuvant antioestrogen treatment for five years. Patients with tumours that were of histological grade 1 and TI were excluded from the material if national guidelines operative at the time of diagnosis did not recommend antihormonal treatment. Also, patients with estrogen receptor low-positive tumours (≥1% < 10%) diagnosed prior to 2011 were excluded as these patients were not recommended antihormonal treatment at that time. Patients who received neoadjuvant treatment were excluded. All patients were followed for at least five years.

Preoperative evaluation of the axilla consisted of clinical examination and axillary ultrasound. All SLNB were performed using dual tracer with radioactive isotope and blue dye. Lymph node positivity was defined as any detected metastases within a lymph node. During the study period, frozen sections were performed on all lymph nodes removed during the SLNB procedure. An axillary dissection was performed if any metastases ≥2 mm were detected.

Detailed information regarding the prescribed antihormonal treatment was retrieved from the Norwegian Prescription Database. Adherence was determined by the medical possession ratio (MPR). MPR was measured as a fraction where the numerator was the total amount of tablets dispensed. The denominator was five years. Patients were defined as nonadherent if the MPR was <80%. For those who died during the five-year course of antihormonal treatment, the denominator was adjusted to the length of time they were alive after commencing the treatment [27].

Nonadherent patients were further subclassified into primary nonadherent (PNA) or secondary nonadherent (SNA). Primary nonadherence occurs when a patient is prescribed a treatment but fails to collect the first and subsequent prescriptions at the pharmacy. Secondary nonadherence is defined as failure to take the medication as prescribed after the first prescription has been collected, with a measured MPR of <80% [28–30].

Overall survival and BCSS were assessed using Kaplan–Meier curves. Statistical analyses were performed using SPSS version 28.

3. Results

A total of 98 patients (Figure 1), 97 females and one male, were included in the study. The median age at diagnosis was 77 (range 70–93). Of the total study population, 66.3% (65/98) were adherent, 11.2% (11/98) were PNA, and 22.4% (22/98) were SNA to the prescribed antihormonal treatment (Table 1). No axillary lymph node metastases (pN0) were found in 59.2% (58/98), 1–3 axillary metastases were found in 25.5% (25/98), and ≥4 in 8.2% (8/98) of the study population.

At the end of the follow-up, 12.2% (12/98) of patients had died due to breast cancer, 30.6% (30/98) had died of causes other than breast cancer, and 57.1% (56/98) were alive (Table 2).

Figure 2 shows that the PNA patients tend to have better overall survival (OS) than the adherent patients (HR 0.61, 95% CI 0.18–2.02). SNA patients may be more likely to have worse OS compared to the adherent patients (HR 1.5, 95% CI 0.78–3.01). Figure 3 shows a worsening survival with an increasing number of axillary metastases. Overall survival was poorer for those with ≥4 metastases (HR 5.1, 95% CI 1.8–14.2) compared to patients with no axillary metastases.

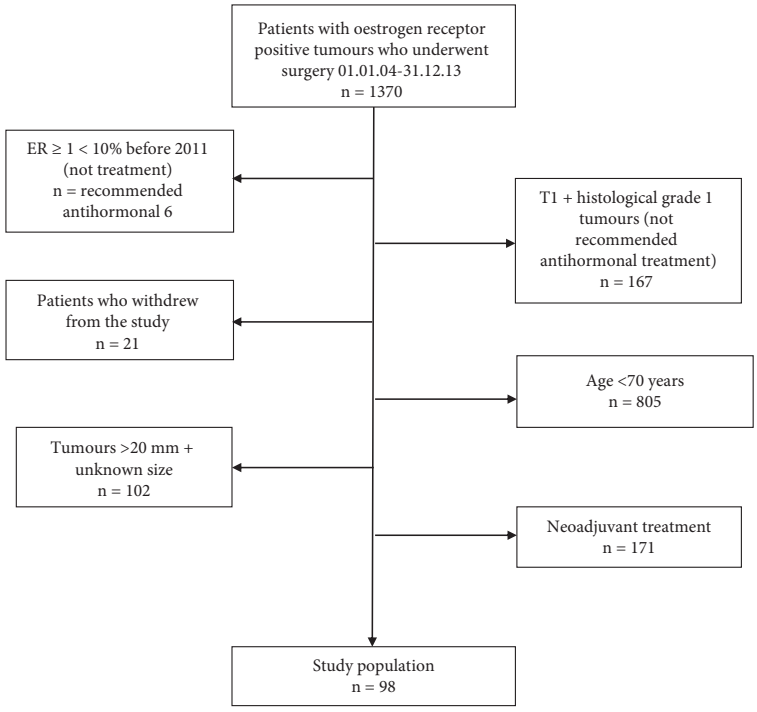

Figure 1: Flow chart of study population.

4. Discussion

In this study, we found that about one-third of the patients had axillary lymph node metastases as documented on the postoperative pathology report. Nonadherence to the prescribed treatment was seen in approximately one-third of patients, and of these, one-third failed to collect their first and subsequent prescriptions.

In the CALBG 9343-trial [11], the majority of women had estrogen receptor positive T1 tumours, and all were ≥70 years of age. A total of 636 women were randomized to either breast conserving treatment with adjuvant radiotherapy and tamoxifen or breast conserving treatment and tamoxifen alone. In both arms, about one-third of the patients underwent axillary lymph node dissection (ALND). The study concluded that the two arms had similar survival and a similar risk of distant metastases. The only significant difference between the two groups was an increased risk of local or regional recurrences at five years for those who did not receive radiotherapy (4% risk for those not receiving radiotherapy and 1% risk for those receiving tamoxifen and radiotherapy). A long-term follow-up study of the CALBG 9343-trial published in 2013 [12] showed similar results. This study also demonstrated that the slightly increased risk of local recurrences in those treated without radiotherapy did not result in decreased survival.

Of the 91 patients in our study with known axillary status, 36.3% (33/91) had axillary metastases confirmed on the postoperative pathology report. According to the abovementioned guidelines, omitting SLNB is only done if the preoperative clinical examination of the axilla reveals no signs of metastases. It has been shown that the clinical evaluation of the axilla is inaccurate with regard to detecting axillary lymph node metastases [31, 32]. Similar to our results, a study of 5125 patients with negative preoperative clinical examinations of the axilla who underwent axillary dissection revealed that 34% had axillary metastatic disease according to the histopathological report [33]. A further study among women with no palpable axillary lymph nodes revealed that 32% had axillary metastases on histopathological examination [34].

Preoperative clinical data were unavailable to us. However, considering the rather low detection rates of axillary metastases by clinical examination alone, it is highly likely that metastases would have been missed. With the concomitant use of axillary ultrasound, a higher number of metastases would be detected. The use of both clinical examination and axillary ultrasound should therefore be encouraged [35, 36]. Some argue that axillary ultrasound should replace clinical examination of the axilla as they show that ultrasound has significantly higher sensitivity and accuracy than clinical examination alone [37]. However, ultrasound of the axilla is highly examinator dependent with a positive predictive value ranging from 77 to 83% and a negative predictive value between 52 and 67% [38, 39]. Furthermore, the necessity of axillary ultrasound in this

Table 1: Patient characteristics.

	Total	Adherent	PNA	SNA
N (%)	98	65 (66.3)	11 (11.2)	22 (22.4)
Age at diagnosis				
70–79	66 (67.3)	52 (80)	6 (54.5)	8 (36.4)
≥80	32 (32.7)	13 (20)	5 (45.5)	14 (63.6)
T-stage				
pT1a	1 (1)	1 (1.5)	0	0
pT1b	15 (15.3)	8 (12.3)	6 (54.5)	1 (4.5)
pT1c	82 (83.7)	56 (86.2)	5 (45.5)	21 (95.5)
Histopathological type				
Ductal	74 (75.5)	50 (76.9)	8 (72.7)	16 (72.7)
Lobular	13 (13.3)	8 (12.3)	2 (18.2)	3 (13.6)
Other	10 (10.2)	7 (10.8)	1 (9.1)	2 (9.1)
Unknown	1 (1)	0	0	1 (4.5)
Histopathological grade				
Grade 1	14 (14.3)	9 (13.8)	1 (9.1)	4 (18.2)
Grade 2	65 (66.3)	42 (64.6)	9 (81.8)	14 (63.6)
Grade 3	17 (17.3)	13 (20)	1 (9.1)	3 (13.6)
Unknown	2 (2)	1 (1.5)	0	1 (4.5)
HER-2 status				
Negative	66 (67.3)	44 (67.7)	8 (72.7)	14 (63.6)
Positive	12 (12.2)	10 (15.4)	1 (9.1)	1 (4.5)
Unknown	20 (20.4)	11 (16.9)	2 (18.2)	7 (31.8)
Axillary lymph node metastases				
0	58 (59.2)	37 (56.9)	9 (81.8)	12 (54.5)
1–3	25 (25.5)	19 (29.2)	1 (9.1)	5 (22.7)
≥4	8 (8.2)	7 (10.8)	0	1 (4.5)
Unknown	7 (7.1)	2 (3.1)	1 (9.1)	4 (18.2)
Radiotherapy				
No	56 (57.1)	36 (55.4)	7 (63.6)	13 (59.1)
Yes	42 (42.9)	29 (44.6)	4 (36.4)	9 (40.9)
Chemotherapy				
No	94 (95.9)	61 (93.8)	11 (100)	22 (100)
Yes	4 (4.1)	4 (6.2)	0	0

Table 2: Axillary metastases and adherence according to patient status at the end of follow-up.

	Dead due to breast cancer	Dead due to other cause	Alive
N (%)	12 (12.2)	30 (30.6)	56 (57.1)
Axillary metastases			
0	5 (41.7)	14 (46.7)	39 (69.6)
1–3	5 (41.7)	7 (23.3)	13 (23.2)
≥4	1 (8.3)	4 (13.3)	3 (5.4)
Unknown	1 (8.3)	5 (16.7)	1 (1.8)
Adherence status			
PNA	1 (8.3)	2 (6.7)	8 (14.3)
SNA	1 (8.3)	12 (40)	9 (16.1)
Adherent	10 (83.3)	16 (53.3)	39 (69.6)

setting can be questioned. The ACOSOG Z0011 study has changed the management of axillary metastases allowing for the omission of ALND in patients with one to two positive sentinel lymph nodes. Inclusion criteria in this study allowed patients with no palpable axillary lymphadenopathy eligible without the use of axillary ultrasound [40]. The SOUND trial randomized patients with T1 tumours and a negative axillary ultrasound to undergo SLNB or not. Of those who underwent SLNB, 13.7% had axillary metastases. However, there was no difference in distant disease-free survival or adjuvant treatment recommendations between the two groups [16]. Nevertheless, it must be acknowledged that in current clinical practice, axillary ultrasound is largely regarded to be standard-of-care in the preoperative evaluation [41].

As expected, we show that better survival is seen in patients with the fewest axillary lymph node metastases. Furthermore, studies have shown that a positive SLNB does affect adjuvant treatment decisions [42–44]. Radiation therapy in the CALBG 9343-trial was delivered as whole breast irradiation including axillary level I and II over 25 daily fractions. Due to the relatively low numbers of axillary metastases in these patients and the findings of similar survival for those who did, or did not, undergo axillary evaluation in the CALBG 9343-trials, the guidelines have deemed it safe to omit SLNB. Omitting SLNB means missing the opportunity to treat potential axillary metastases. However, the PRIME II study concluded that it is safe to omit radiotherapy in selected low-risk patients undergoing breast conserving surgery [14]. Omitting radiotherapy altogether might be difficult to accept for many clinicians, especially if the patient is in her early 70s with no or few comorbidities. Some argue that a more appropriate way to deescalate would be to give partial breast radiation to those with unknown axillary status [45]. However, others would be reluctant if axillary status is unknown for fear of missing undiagnosed axillary metastases [46].

Despite evidence that survival is not affected by the omission of SNLB, it might still be difficult to accept forgoing a well-established procedure. SLNB is considered to be safe and accurate and is associated with few complications [47, 48]. It is a relatively minor procedure performed at the same time as the primary breast surgery.

The present study shows that 33.7% (33/98) of the study population were nonadherent at five years of follow-up. Patients in the present study were subclassified into PNA or SNA. Although the numbers are low, over 10% of the patients were PNA. That is, they never initiated the antihormonal treatment they were prescribed. We suspect that these patients' lack of appreciation of the need for antihormonal treatment may be largely due to poor patient-doctor communication. If deescalating in surgery occurs by omitting the SLNB in elderly breast cancer patients, it is highly important that time is spent with the patient explaining the rationale for prescribing the antihormonal treatment in order to minimize both PNA and SNA. We observed that more than 20% of the patients were SNA. That is, they initiated the treatment, but for some reason, they failed to reach a MPR of ≥80%. The main reason for becoming nonadherent to antihormonal treatment is its side effects [49–51]. As many patients experience troublesome side effects affecting their quality of life, some of these patients choose to discontinue the treatment [52, 53]. Treating these side effects will help patients remain adherent to the treatment [52, 54]. We therefore suggest that in the case of deescalation by omitting SLNB, patients should be followed closely in order to uncover troublesome side effects or other reasons for nonadherence.

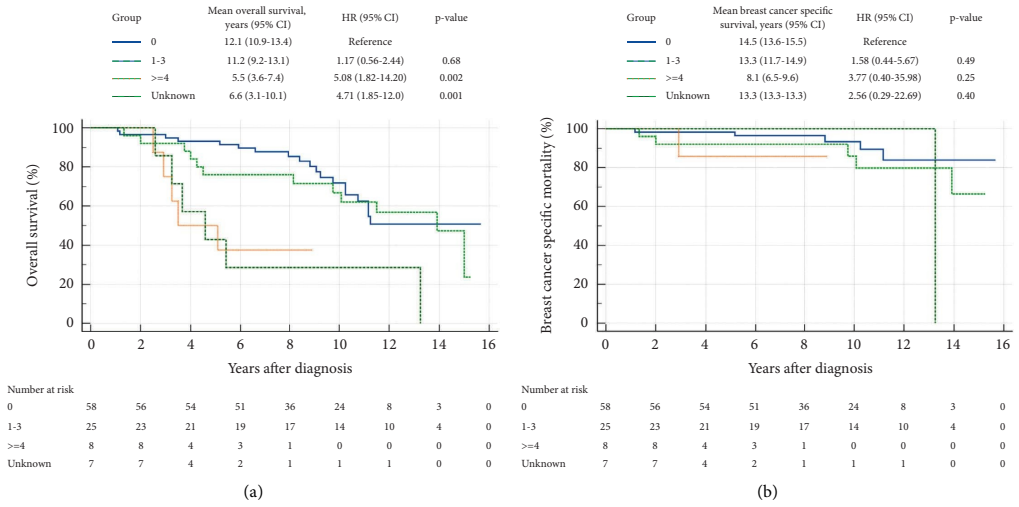

FIGURE 2: Overall survival (a) and breast cancer specific survival (b) according to the number of axillary lymph node metastases.

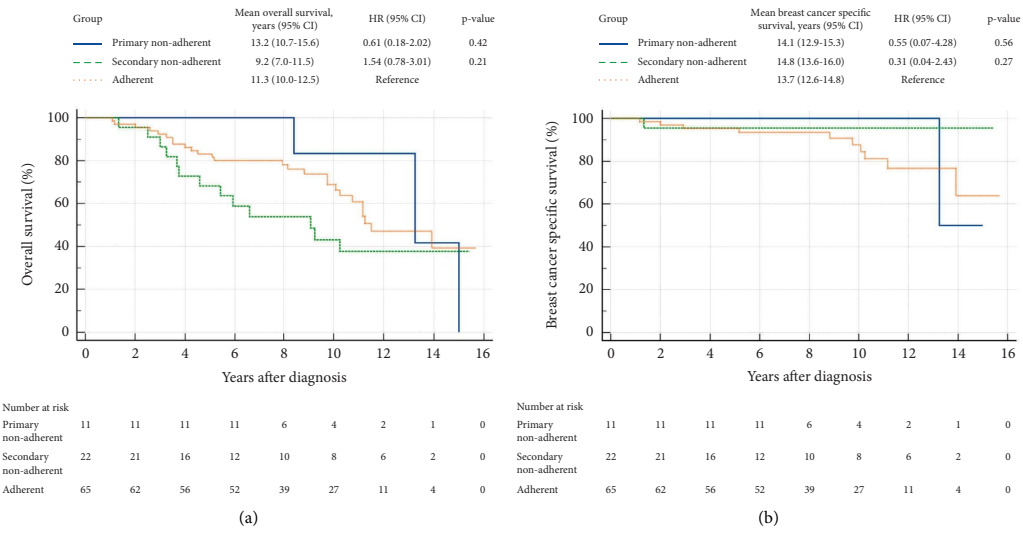

FIGURE 3: Overall survival (a) and breast cancer specific survival (b) according to adherence status.

Various factors have been shown to affect adherence to antihormonal treatment. Advanced age and low-risk disease are known predictors of poor adherence to antihormonal treatment [49, 55, 56]. This puts the patients included in this recommendation at a higher risk of nonadherence compared to many other breast cancer patients. Omitting SLNB could potentially be a motivating factor for remaining adherent to the antihormonal treatment. This would perhaps give higher adherence rates than in the current study. Adherence behaviour is a complex matter, and causes of nonadherence are often multifactorial [57, 58]. It is therefore important to address the issue of adherence early, that is, even before the treatment is commenced.

A prerequisite of the abovementioned guidelines is five years of adherence to antihormonal treatment. However, previous literature has documented that adherence to adjuvant antihormonal treatment is poor [49, 52, 59–62]. Nonadherence rates have been described in the range of 10.8% [63] to 55% [54]. This wide range is probably due to the lack of a uniform definition of adherence and also varying ways of measuring it [64–66]. Based on these figures, it is likely that some of the patients included in the CALBG

9343-trial also were nonadherent. Despite this, survival rates were good. One could therefore argue that adherence to antihormonal therapy is not of importance in this population. However, it is our opinion that as we strive to improve patient care, adherence will continue to be of importance and even better survival rates could have been achieved with optimal adherence. It is therefore of importance to carefully select patients who will benefit from the treatment and avoid unnecessary side effects in those who will have a minimal effect of the treatment. Furthermore, the population is aging [5], and as we see a shift towards increased use of oral anticancer agents taken at home, the impact of poor adherence is likely to become even more important in the years to come [67, 68].

We have previously shown that PNA patients have better prognosis compared to both adherent and SNA patients [61]. Similarly, in the subgroup of patients in the present study, PNA patients tend to have better survival than both the adherent and SNA patients. This adds a contribution to the discussion regarding the possible overtreatment of low-risk patients as the PNA patients had the best survival.

Over the past decades, deescalation of treatments in breast cancer patients has gained increasing attention. As more treatment options become available and our knowledge expands, the need to tailor treatments to each individual patient has become an integral part of modern breast cancer management. Deescalation will spare the patient for potential morbidity associated with treatment and simultaneously reduce expenditure for health care systems [3, 24, 69]. However, deescalation should be carried out with caution and should be based on solid clinical research. Furthermore, implementation of deescalation guidelines should be monitored closely, especially when these guidelines do not seem to be widely accepted by clinicians.

From a financial point of view, health services would benefit from the omission of SLNB [70]. In an already pressurized health care system, the omission of SNLB would free up resources, shorten waiting lists, and allow for resources to be directed elsewhere [46].

In modern breast cancer management, treatment recommendations are increasingly based on tumour biology rather than nodal status [69]. Guidelines based on chronological age might not be the optimal way of stratifying patients. In the future, stratifying patients according to the biomarker profile and comorbidity are likely to become the preferred option in order to determine who is eligible for the omission of SLNB [71, 72].

One of the strengths of this study is the quantification of adherence rates in this specific group of patients and the subdivision of nonadherent patients into PNA and SNA, thus further examining the adherence behaviour of these patients. However, there are several limitations to this study. It is a small and retrospective study. Data regarding whether a patient underwent SLNB and axillary dissection or axillary dissection only were unfortunately not available to us. Patients with HER-2 positive tumours or with unknown HER-2 status were included in this study. These patients could have benefitted from SLNB as proven metastases would have affected adjuvant treatment decisions. Furthermore, patients with pT1 and histological grade 1 tumours were not recommended antihormonal treatment according to the national guidelines operative in the study period. These patients were therefore excluded from the material leaving the study population somewhat skewed towards larger tumours and higher histological grades. Furthermore, molecular subtyping was not available in this study population.

Some of the abovementioned patients with pT1 and histological grade 1 tumours did receive antihormonal treatment. These patients were therefore included in the study. We find this interesting as this group of patients was not treated according to the guidelines operative at the time of diagnosis. This confirms that the guidelines often are mere recommendations and that clinicians in selected cases choose to treat patients on an individual basis and according to the preferences of the patients. This shared decision-making will provide optimal care for each patient [73]. We believe that the individual assessment of each patient, especially with regard to comorbidity, is one of the main reasons for deviation from the guidelines.

5. Conclusion

Despite the small size of this study, it underpins much of the reluctance among clinicians to omit SLNB in elderly low-risk breast cancer patients. While reluctance is both understandable and necessary, the presence of axillary metastases in these low-risk breast cancer patients has not been shown to affect survival. In the future, we suggest that the selection of patients eligible for the omission of SLNB should be personalised based on the principles of shared decision-making including biomarker profiling and assessment of comorbidities.

Data Availability

Data that support the findings of this study are available from the Norwegian Prescription Database. Restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Patient data collected from the medical records in the hospital are not available due to patient confidentiality.

Ethical Approval

The study, including an outline of the statistical methods used, was approved by the Regional Committee for Medical and Health Research Ethics, Central Norway (561970), and the Regional Data Protection Office according to the Declaration of Helsinki.

Consent

Informed consent was obtained from all participants in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

ID has performed the conceptualization of this article along with the data collection, data analysis, and interpretation of the data. Furthermore, she has drafted the article and revised it. AMB, HS, and MJE have contributed to the interpretation of the data, drafted the article, and provided final approval of the article. All authors have read and approved the final manuscript.

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Supplementary Materials

STROBE checklist. STROBE statement: checklist of items that should be included in reports of cohort studies. (*Supplementary Materials*)

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