Adherence to adjuvant hormonal therapy in patients with invasive oestrogen receptor positive breast cancer without distant metastasis

What is the adherence to prescribed adjuvant hormonal therapy over 5 years, causes of discontinuation, factors associated with adherence, and what proportion is prescribed treatment for an additional 5 years?

Version 2

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Abstract

Introduction
Breast cancer is the most common cancer among Swedish women. Adjuvant hormonal therapy (HT) decreases the risk of recurrence and mortality among oestrogen receptor positive (ER+) breast cancer. Adverse events of HT are common and adherence has in previous studies been estimated to around 70%. Additionally, patients with high-risk tumours (lymph node positive cancer) gain further effect from receiving extended therapy (ET) for ten years instead of five.

Aim
To determine adherence to adjuvant HT over 5 years, causes of discontinuation, and factors associated with adherence. What proportion of patients with high-risk tumours is informed on possible gains and risks with ET, and what proportion is prescribed ET.

Methods
A retrospective study evaluating clinical practice at the Oncology Department at Örebro University Hospital, based on examination of medical records. Adherence was defined as taking HT >80% of the prescribed time. Chi-square, Fishers exact, Mann-Whitney-U, and Logrank tests were utilised to determine univariate associations between factors and adherence, and cox regression as multivariate analysis. Factors included: age, tumour size, nodal status, Elston grade, surgery, chemotherapy, and first HT.

Results
The study included 159 patients receiving a breast cancer diagnosis between January 1st 2010 and June 30th 2011, included from the Regional Clinical Quality Breast Cancer Register. Adherence over 5 years, among 143 patients, was 82.5%. Most commonly, discontinuation was caused by adverse events. Significantly increased adherence was found for small tumour size and young age. The analysis of ET, included 55 patients, 44% were prescribed treatment and 71% had a discussion.

Conclusion
Adherence to 5 years of HT was 82 % and compares favourably with previous reports. Lower adherence among older women is consistent with previous studies, although, for tumour size, the results are contradictory. These results indicate potential improvements in support for women taking HT. Adherence to recommendations on ET is considerably lower.
**Abbreviations**

AI – aromatase inhibitors

ER – oestrogen receptor

ET – extended therapy

GNRH – gonadotropin-releasing hormone

HER2 – human epidermal growth factor receptor 2

HT – hormonal therapy

NHG – Nottingham Histologic Grade

PR – progesterone receptor

SERM – selective oestrogen receptor modulator

TNM – tumour size-node-metastasis

VTE – venous thromboembolism
Introduction

Breast cancer is the most common cancer among Swedish women, in 2014 8023 women were diagnosed and 1398 women died from breast cancer [1]. The prognosis of breast cancer depends on several factors. The most important prognostic factor is the TNM-classification, comprised of tumour size (T), lymph node status (N) and distant metastasis (M). Other prognostic factors are age, presence of oestrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2), proliferation rate (Ki67/MIB-1) [2] and histologic grade [3]. For histologic grading, the Nottingham Histologic Grade (NHG) is used. In Sweden NHG is often referred to as Elston grade. NHG is made up of the following criteria: grade of mitosis, differentiation of tubular structure and pleomorphism, each scoring 1 to 3 points, which together translates into an overall prognostic grade [4].

The treatment of breast cancer includes several modalities: excision, chemotherapy, radiotherapy, monoclonal antibodies for HER2-positive tumours, and hormonal therapy (HT). Adjuvant HT is used in patients with primary operable ER+ breast cancer, excluding stage T1a-b tumours (≤10mm). HT prescribed today includes tamoxifen and aromatase inhibitors (AI), and, for premenopausal women with high risk of recurrence, GNRH-analogues are used in combination with tamoxifen [2].

Tamoxifen is a selective oestrogen receptor modulator (SERM), which acts as an antagonist on oestrogen receptors in breast tissue and as a partial agonist in the endometrium and bone [5]. It decreases the risk of breast cancer recurrence and mortality [6-9], however, the agonistic effect on the endometrium increases the risk of endometrial cancer [8,10-14]. Another serious adverse event is increased risk of venous thromboembolism (VTE) [6,12,15].

The second group of drugs used is AI, including three types: anastrozole, letrozole, and exemestane. The aromatase enzyme converts androgen precursors to oestrogen, and inhibition of this enzyme causes the formation of oestrogen to be suppressed. Aromatisation of androgens is the dominant way of oestrogen synthesis in postmenopausal women. Due to extensive suppression of oestrogen by AIs, bone density is decreased[5], thus increasing the risk of osteoporotic fractures [12,15,16]. Further adverse events potentially precipitated by AIs include cardiovascular diseases [16] and joint symptoms [12]. AI is indicated in postmenopausal women but not in
premenopausal women because ovarian production of oestrogen is not dependent on the action of aromatase and thus is not affected by the drug [15].

Presence of oestrogen receptors in tumours is a prerequisite for the use of HT as mentioned above, but is unable to predict which class of HT is preferable [6,15]. Other prognostic markers, such as proliferation and HER2-status, have also failed to show any predictive value in the choice between tamoxifen and AIs [17,18].

Traditionally, tamoxifen was the standard treatment [9], but today AI is recommended to postmenopausal women due to reduced risk of recurrence [19] and prolonged disease free survival in comparison with tamoxifen [13,15,16]. For premenopausal women, tamoxifen is still the conventional treatment [2].

Most commonly tamoxifen or AI is administered as monotherapy for five years [2]. For postmenopausal women, the HT should include an AI, either as five years monotherapy or as sequential therapy, i.e. both AI and tamoxifen is administered to the same patient, the first given for two to three years, then followed by the other, making up a total of five years. For a period of time sequential therapy was primarily employed, since the effect on breast cancer survival for sequential therapy seemed to favourable when compared with monotherapy [19]. However, in a more recent meta-analysis AI monotherapy was proven to be slightly more efficacious than sequential therapy with AI followed by tamoxifen or vice versa [20]. Therefore a change in general practice has occurred and AI monotherapy has become the first choice.

However, due to differences in adverse events between AIs and tamoxifen, a careful assessment of potential contraindications should always be done and likewise, the tolerance to specific adverse events can influence the choice.

Five years of adjuvant HT is the standard treatment [2], although recent studies indicate that a different approach might be preferable. In 2013 the ATLAS trial reported the effects of continued adjuvant treatment with tamoxifen for ten years, compared with the previous standard. Extended therapy (ET) showed a decreased risk of recurrence and breast cancer mortality [21], although the absolute risk reduction was modest, with a decreased breast cancer mortality of 2.8% and a hazard ratio of 0.71. The MA.17 study showed similar results for ET with letrozole after an initial
five years of tamoxifen [22]. Today ET for an additional five years is recommended to all women with high-risk tumours, namely lymph node positive breast cancer [2].

The definition of adherence is the extent to which patients follow the regimen of prescribed drugs. Poor adherence to adjuvant HT in breast cancer has been shown to cause excess mortality [23,24] and increased risk of recurrence [25]. Although the positive effects of the treatment are significant, it has previously been stated that adherence to these drugs is poor. Wigertz et.al. evaluated adherence to adjuvant HT in women with invasive ER+ breast cancer over three years in a Swedish setting, showing an adherence of 69 % [26]. Similar numbers have been replicated by Lash et al. [27], and a further study demonstrated significantly poorer adherence [28].

Adverse events have been shown to be the most common cause of discontinuation [29]. A study by Nekhlyudov et al. showed that women treated with tamoxifen, in comparison to AI, had a higher risk of treatment gaps. Other predictors for treatment gaps were older age, visits to the doctor, and longer duration of inpatient stay [30].

The aim of our study is to further investigate adherence to adjuvant hormonal therapy in patients with invasive oestrogen receptor positive breast cancer, causes of discontinuation, and factors associated with adherence. Furthermore, this study will determine the proportion of patients with high-risk tumours (lymph node positive breast cancer) that were included in a discussion regarding extended therapy for an additional five years, and in turn, the proportion that was prescribed this treatment.

**Material and methods**

**Study population**

All patients diagnosed with ER+ breast cancer at Örebro University Hospital between January 1st 2010 and June 30th 2011 were included. The population was assembled using the Regional Clinical Quality Breast Cancer Register, and limited by following exclusion criteria: carcinoma in situ, primary inoperable tumours, HT as palliative therapy, T4 tumours (present distant metastasis), and follow-up at other care-givers than Örebro University Hospital. Guidelines suggest tumours >10mm should be treated with HT, in case of node-negativity, however, a few patients with smaller tumours are treated due to other risk factors, and therefore all invasive non distant metastasized tumours were included (T1-3N0-2M0).
194 patients were obtained and out of these, some were excluded, shown in Figure 1. Reasons for the 25 patients not receiving treatment were the following: 21 patients had tumours ≤10mm and therefore no indication, three died before start of treatment, and one had advanced age combined with several comorbidities. After these exclusions 159 remained, making up the study population.

**Method**

Following data was included from the register: personal identification number, histologic state (tumours size, number of nodes investigated and with metastasis present), ER-status, Elston grade, chemotherapy, and surgical treatment. Metastatic lymph nodes were separated into macro and micro metastasis. If death occurred, the Register of the Swedish Population was utilised to determine date of death. Personal identification numbers were translated into age at start of HT administration.

An excel-sheet, including all information mentioned above, was created and used while reviewing medical records. Even patients without indication for treatment were examined to determine if they received HT or not. Variables for type of HT, adherence, and ET, were added.

To determine adherence, type of HT and date of start and discontinuation were investigated. If information about exact date of discontinuation was not found, the last date adherence was documented, was used. Endpoints for this study were defined as all causes for ending the prescribed treatment, categorised as: completed treatment, adverse events, recurrence, comorbidity, and others. If patients switched HT from the initial treatment, to alternate therapies, up to four types were recorded against the variables described above. For recurrence, diagnosed secondary tumours were documented as discontinuation even if this caused a switch to another type of HT for
palliative purpose. Only start and stop dates were of interest, shorter periods of discontinuation were not documented, although periods longer than 2 months were registered. Deceased patients, those who relocated, or had recurrence, were censored at time of event for calculation of adherence.

ET for an additional five years was assessed, including: if therapy was discussed with the patient and if it was prescribed. Node-positive tumour is the indication for ET, therefore, these subjects were used for this evaluation.

Out of all patients, by the date of examination, 16 had not yet finished their five years of originally prescribed treatment, due to prolonged time between surgery and initiation, caused by, for example, radiotherapy and chemotherapy. To include these patients, adherence was additionally calculated over three years. For inclusion in the analysis on ET, the initial five-year treatment was due to end before January 1st 2017. Patients planned to finish after this date were excluded from calculations on ET.

Definitions

T₁ was defined as tumours ≤ 20mm, T₂ as 21-50mm and T₃ >50mm [31].

Distant metastasis was defined as dissemination of cancer at time of diagnosis, up until three months after surgery, whereas, recurrence was defined as a distant metastasis found more than three months after surgery.

Metastasis in lymph nodes was defined as either macroscopic or microscopic, corresponding to size, with macroscopic defined as >2mm and microscopic 0.2-2mm [31].

Adherence in a single patient was defined as continuation to prescribed treatment of >80% of the time, and non-adherence as ≤ 80%. These specific parameters were chosen for the purpose of comparing with results from a previous study, investigating adherence to HT in a similar setting [26].

Statistics

IBM SPSS Statistics software version 23 was used for all statistical calculations.
A proportional adherence curve over time was presented using the Kaplan-Meier method, showing time to discontinuation. Patients were censored for completed treatment. Discontinuation due to toxicity, recurrence, or death was regarded as complete observations. The adherence curves were separated for different factors: age, tumour size, nodal status, Elston grade, first HT, chemotherapy, surgery, and number of HTs. Significance for these was calculated using Logrank test. Statistical significance was defined as p value < 0.05, all tests were two-tailed.

Association to five-year adherence was investigated, including the same factors as those mentioned above, using Chi-square, Fishers exact, and Mann-Whitney-U test. For age both Mann-Whitney-U and Chi-square test was performed, with the variable scaled and categorical, separated into ≤50 and >50 years old. The same was done for tumour size, scaled and separated into ≤20mm and >20mm. The potential correlations between discussion about and prescription of ET were investigated with the same method as mentioned above, for: age, lymph node metastasis, and only micro metastasis present.

Cox regression was performed for factors found significant in univariate analyses, and those indicating a trend. Since age and first type of HT are dependent variables, these were not included in the same analysis to exclude a risk of bias. Therefore, two separate analyses were made, one without first type of HT, and one including this variable but only for patients over 55 years old. This was done to avoid the potential bias introduced by the strong correlation between young age and tamoxifen.

**Ethical considerations**

One of the primary considerations for a student conducting this study was reviewing medical records without patients’ informed consent. However, the study will not be published and only used for improvement of clinical practice at the Oncology Department at Örebro University Hospital. Therefore no ethical or patient approval was required.

Secrecy and confidentiality was implemented while completing this study and the patients’ personal identification numbers were removed as soon as possible, and replaced with a corresponding order number. No data is presented on an individual level, all results are on a group level.
Results

The patients included in this section were 159 in total, made up of 158 women and one man. The mean age at start of HT was 63 years, with a range from 30-95 years. The mean tumour size was 21mm, ranging from 3-103mm. Most patients completed their treatment (63%), but as cause for early discontinuation, adverse events were most prevalent (44%).

In table 1, the characteristics of the 143 patients included in the analysis of adherence over five years are shown. Patients excluded were those who had not yet received five-year treatment.

Adherence over five years was estimated to 82.5%, with 118 adherent and 25 non-adherent patients. Association to adherence over five years was found statistically significant for young age contributing to increased adherence. Trends were shown for small tumour size; high Elston grade; and tamoxifen as first type of HT, all increasing adherence (Table 1).

<table>
<thead>
<tr>
<th>5 year adherence</th>
<th>Adherent (n=118)</th>
<th>Non-adherent (n=25)</th>
<th>Total (n=143)</th>
<th>Univariate analysis*§♯</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>25(86)</td>
<td>4(14)</td>
<td>29(100)</td>
<td>0.56*</td>
</tr>
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<td>&gt;50</td>
<td>93(82)</td>
<td>21(18)</td>
<td>114(100)</td>
<td></td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>0.016§</td>
</tr>
<tr>
<td><strong>Tumour size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20mm</td>
<td>77(85)</td>
<td>14(15)</td>
<td>91(100)</td>
<td>0.38*</td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>41(79)</td>
<td>11(21)</td>
<td>52(100)</td>
<td></td>
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<tr>
<td>Continuous variable</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.14§</td>
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<tr>
<td><strong>Nodal status</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>N-</td>
<td>72(84)</td>
<td>14(16)</td>
<td>86(100)</td>
<td>0.64*</td>
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<td>N+, N+micro</td>
<td>46(81)</td>
<td>11(19)</td>
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<td>20(21)</td>
<td>94(100)</td>
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<td>4(8)</td>
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<td>1(100)</td>
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<td>54(81)</td>
<td>13(19)</td>
<td>67(100)</td>
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<td>Breast conserving surgery</td>
<td>63(84)</td>
<td>12(16)</td>
<td>75(100)</td>
<td></td>
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<td>Both</td>
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<td><strong>Chemotherapy</strong></td>
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</table>

Table 1. Patient characteristics. Univariate analysis with Chi-square, Fishers exact and Mann-Whitney-U test.
For three-year adherence, with 159 patients included, 139 were found adherent, making up an adherence of 87.4%. No factors were found significant.

An analysis of all tumours excluded due to no indication for treatment ($T_{1a-b}N_0$) was performed to determine if treatment was prescribed anyway. Out of the 25 patients included, four were treated.

A five-year adherence curve was created using Kaplan Meier technique, showing proportional adherence over time (Figure 2). Statistical significance was found for first HT according to logrank test (Figure 3), indicating that tamoxifen is associated with increased adherence. A trend was noticed for small tumour size increasing adherence.

### Table: First type of hormonal therapy

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<thead>
<tr>
<th>Therapy</th>
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<th>No</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>60(87)</td>
<td>9(13)</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>58(78)</td>
<td>16(22)</td>
</tr>
<tr>
<td>Letrozole</td>
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<tr>
<td>Exemestane</td>
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### Table: Number of hormonal therapy types

<table>
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<tr>
<th>Number of types</th>
<th>1-2 types</th>
<th>3-4 types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>115(82)</td>
<td>3(100)</td>
</tr>
<tr>
<td>No</td>
<td>25(18)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>

* = Chi square
§ = Mann-Whitney-U
♯ = Fishers exact test

Figure 2. Five-year adherence curve. Proportional adherence over 60 months, censored for completed treatment. Truncated at 0.4.
Cox regression analyses were performed for factors found significant or indicating a trend. One analysis included: age, tumour size, and Elston grade (presented in appendix 1). Another, only including patients >55 years old, was performed for factors: tumour size, Elston grade, and first HT (presented in appendix 2).

Significance was found for age in the first analysis (p=0.008), with a HR of 1.03 (95% CI 1.01-1.05). Tumour size was significant in both analyses, HR 1.03 (95% CI 1.01-1.04) and HR 1.03 (95% CI 1.01-1.05) with p<0.001 and p=0.006. Both factors were found significant when ordinally scaled, but not when categorised. To exclude bias for age affecting tumour size, difference in tumour size between age groups was determined. Younger patients were found to have significantly larger tumours than older patients (p=0.009), with a mean size of 26mm and 20mm, respectively.

Although, since tumour size was found to be dependent on age, and age was unevenly distributed, tests for age and tumour size had to be preformed for adherent and non-adherent patients separately, see appendix 3. Significance was found for the adherent group (p=0.008), but not for the non-adherent group (p=1).

Figure 3a-f. Curves showing proportional adherence, separated for factors. P values from Logrank tests included. Panel a) shows age (p=0.26), b) tumour size (p=0.054), c) Elston grade (p=0.90), d) type of surgery (p=0.15), e) chemotherapy (p=0.60), and f) first type of hormonal therapy (p=0.002).
**Extended therapy**

Patients with recurrence, deceased, relocated, or with five-year treatment ending in year 2017, were excluded (see Figure 4). The overall proportion of patients receiving prescriptions was 44%. Discussion about continued treatment took place with 71% of the patients, and in 29% of the cases no discussion was documented. A subgroup analysis, including the factors age and lymph node metastasis, did not show any significant correlations. However, a trend for an increased amount of prescriptions for younger patients was seen (p=0.099). ET was also prescribed to five patients with lymph node negative breast cancer.

**Discussion**

Five-year adherence for the whole cohort was estimated to 82.5%, and this compares favourably to the results shown by Wigertz et al. [26] on a larger cohort, with a three-year adherence of 69%. The improvement seen in our study could partly be explained by a better methodology used by Wigertz et al., where data from the Swedish Prescribed Drug Register was used. In our study, only patient files were examined, and therefore the information on to what extent the medications were dispensed is lacking. Of course neither of the studies have data on the proportion of medication actually taken. However, in the previous study by Wigertz et al., follow-up was only three years, whereas our study covers five-years. Other studies, with follow-up time similar to our study, have shown varied results: van Herk-Sukel et al. [28] reported adherence of 49-66%, and Hershman et al. [32] with adherence of 72%. One possible explanation for the seemingly lower adherence in the latter two studies when compared with our study is the limited out of pocket costs for medication for Swedish patients, since a high cost could adversely affect adherence.

Adverse events were the most prevalent cause of discontinuation, corresponding to 44%. This is in keeping with previous studies [29,33], and indicates there is still need for improvements in this area.

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**Figure 4. Flowchart explaining the exclusion process and results for extended therapy.**
Significant association to adherence was found for age, with increased adherence seen in younger patients, which has previously been shown in a study set in the Netherlands [28]. It has also previously been stated that adherence is poorer in age extremes, such as the youngest and oldest patients [32], which was not identified in this study.

Surprisingly, a significant association between small tumours and increased adherence was found. The opposite has previously been stated by Wigertz et al. [26]. Since our study is smaller than Wigertz’s et al. study, our results may be incidental. Additionally, higher adherence among those with larger tumours, might indicate that patients with a poor prognosis have better insight in the extent of their illness, and therefore are more motivated to be adherent. The same might be considered for mastectomy versus breast conserving surgery, and for receiving chemotherapy, although, no significance was seen for these factors. The association between poor prognosis and increased adherence is scarcely presented in literature, and it is therefore unclear if this fact is important to consider. Further research is thus needed.

An association between the significant factors age and tumour size had to be considered as a cause for the contradicting results for tumour size. If an association between the two was found, where younger patients had smaller tumours, association between the factors and adherence would be difficult to determine. Although, in our study it was found that younger patients on average had larger tumours, which was significant also when compared for the groups separately. This thus indicates that small tumour size is an independent predictor for increased adherence.

Tamoxifen increased adherence in the univariate analysis when compared with AI. It has previously been implicated by Nekhlyudov et al. [30] that AI increases adherence, which contradicts our findings. But since type of HT is affected by age, depending on menopausal state, our results were not considered accurate. And since type of HT, when separated from age in a multivariate regression analysis, was not found significant, this suggests that age is the preponderant factor.

For Elston grade, a trend demonstrated that higher grade increases adherence. A similar trend has previously been shown by Wigertz et al. [26], although there, the grades were categorised in a different manner.
Other factors, including nodal status, surgery, chemotherapy, and number of HTs, were not significant predictors for adherence.

The associations found in this study are important, since all knowledge regarding factors affecting adherence may lead to improved efficacy of HT, and thus a decrease in breast cancer recurrence and mortality [23,34]. Knowledge on specific sub-groups with lower adherence, such as older patients, can help health care workers to target these patient groups with support aiming at improving adherence.

Previous research on ET regarding discussion and prescriptions is scarce. Therefore, our results provide information regarding guideline implementation in a Swedish setting, to improve current practice. A great proportion of the patients had a discussion about their treatment, but only a small number were given a prescription. The small absolute gain of ET together with persisting adverse events are probably important explanations for low adherence. Further research investigating the reasons for this is needed.

**Limitations**

Limitations for this study include the difficulty in determining patient discontinuation using only medical records. The limited number of patients included is also a weakness, this is of major importance when sub group analyses are made and therefore these should be interpreted cautiously.

We had no access to socioeconomic data. Such parameters can be of importance, for instance, the larger Swedish study [26], showed lower adherence in immigrants, possibly mirroring lingual barriers.

Another limitation is that the Logrank test probably is suboptimal for calculating associations to adherence, since the test calculates difference at the end of the curves. All patients discontinue after 60 months and the curves converge, thus, this might lead to an underestimation of the significance. To correct this, the cut-off could have been corrected to four and a half years when calculating, excluding the last section where the curves start to converge.
Conclusion

Adherence to hormonal therapy over five years was 82.5%, which demonstrates an increase when compared with previous studies. Factors found significantly increasing adherence was small tumour size and young age, with tumour size contradicting earlier research, and age indicating the same as previously shown.

ET was prescribed to 44% of patients with high-risk tumours, and treatment was discussed with 71%.

Even though the adherence in this study seems to be greater than previously shown, it still needs improving to enable increased medication effect, and thus, decreased risk of recurrence and mortality. This can be achieved through better understanding of reasons for discontinuation giving the opportunity to prevent them and to target sub-groups at higher risk of low adherence. It would be prescient to investigate further factors associated with adherence to understand what leads to successful treatment.
References


Appendix

Appendix 1

<table>
<thead>
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<th>Cox regression*‡</th>
<th>HR (CI 95%)</th>
<th>( P ) value#</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
<td>1.03(1.008-1.05)</td>
<td>0.008</td>
</tr>
<tr>
<td>Tumour size</td>
<td></td>
<td>1.03(1.01-1.04)</td>
<td>&lt;0.001</td>
</tr>
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<td>Elston grade</td>
<td></td>
<td>1.002(0.58-1.72)</td>
<td>0.99</td>
</tr>
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</table>

*Adjusted for age, tumour size, Elston grade
‡2-tailed
§Elston grade categorical

Appendix 2

Patients >55 years old included

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<tr>
<th></th>
<th>Cox regression*§</th>
<th>HR (CI 95%)</th>
<th>( P ) value#</th>
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<tr>
<td>Tam vs AI</td>
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<td>2.13(0.89-5.09)</td>
<td>0.09</td>
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<td>Elston grade</td>
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<td>1.17(0.63-2.18)</td>
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</table>

*Adjusted for first type of hormonal therapy, tumour size, Elston grade
‡2-tailed
§Elston grade categorical

Appendix 3

<table>
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<tr>
<th></th>
<th></th>
<th>Age</th>
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<td></td>
<td></td>
<td>( \leq 50 )</td>
<td>( &gt;50 )</td>
<td></td>
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<tr>
<td>Tumour</td>
<td>≤20</td>
<td>12(43%)</td>
<td>74(70%)</td>
<td>86(64%)</td>
</tr>
<tr>
<td>size</td>
<td>&gt;20</td>
<td>16(57%)</td>
<td>32(30%)</td>
<td>48(36%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>28(100%)</td>
<td>106(100%)</td>
<td>134(100%)</td>
</tr>
</tbody>
</table>

\( P=0.008 \)
(Chi-square test)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Age</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( \leq 50 )</td>
<td>( &gt;50 )</td>
<td></td>
</tr>
<tr>
<td>Tumour</td>
<td>≤20</td>
<td>2(50%)</td>
<td>12(57%)</td>
<td>14(56%)</td>
</tr>
<tr>
<td>size</td>
<td>&gt;20</td>
<td>2(50%)</td>
<td>9(43%)</td>
<td>11(44%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>4(100%)</td>
<td>21(100%)</td>
<td>25(100%)</td>
</tr>
</tbody>
</table>

\( P=1.0 \)
(Fisher’s exact test)
Cover letter

January 5th 2017

Corresponding author: Sofia Axén, Bachelor of Medicine, Örebro University

Dear Editor,

Adherence to adjuvant hormonal therapy in patients with invasive oestrogen receptor positive breast cancer without distant metastasis

In this study new results regarding adherence to hormonal therapy in patients with breast cancer are presented. A previous study concerning adherence in a Swedish setting has shown 69%, however, in this study an adherence of 82.5% was found, suggesting that an increase in adherence has occurred. Factors associated with adherence were also determined and significance in increasing adherence was found for small tumour size and young age. The results found for tumour size contradict earlier research, while those found for age are in keeping with what has previously been shown. This data suggests that correlations between factors and adherence are complex, and therefore contribute to the understanding of what leads to successful treatment.

We also investigated what proportion of patients with high-risk tumours was prescribed extended therapy, as guidelines recommend, showing 44%. Studies concerning this subject are scarce, and therefore, this study contributes important information for improvements pertaining to daily practice at oncology departments.

Best Regards,

Sofia Axén
Ethical considerations

One consideration is for a student, without any professional relation to the patients, to access the medical records and document personal information, to be used in studies. It is important for this to be done in a suitable manner, meaning to remove all personal identification numbers as soon as this is possible, and for this information to be stored securely. Something that could be considered unethical is for them not to be aware of the fact that this is happening. On the other hand, it is also important to consider enabling the greatest benefit for the greatest number of patients possible.

One of the main issues considered here is quality registers in general. The issue is regarding inclusion, since patient approval is needed once, but then the information may be used several times in different studies without further approval, if the aim of the study is to improve the practice at the clinic. This leads to patients possibly being included in studies they have not given their consent on.

An upside to being included in these types of studies is to contribute to the development of the practice for the better, and thus hopefully also improving their own treatment. No intervention was performed, but results on what affects adherence were collected. Therefore, the patients will almost only experience benefits from this study, whereas one might argue that no real ethical dilemma is present. Although, if the aim was to publish the results, which would lead to a chance for the patients to possibility read it, an approval would be both suitable and necessary.
Populärvetenskaplig sammanfattning


Biverkningar är den vanligaste orsaken till att många patienter inte tar sitt läkemedel som ordinerat, vilket då ger en ökad risk för att sjukdomen återkommer. Att ta reda på orsakerna till avbruten läkemedelsbehandling är viktigt för att kunna vara beredd och behandla dessa när de uppstår, så att man kan få så många patienter som möjligt att ta sina läkemedel som det är tänkt.

Normalt tar man hormonell behandling i 5 år, men kvinnor med spridning till lymfkörtlar rekommenderas att fortsätta behandlas i ytterligare 5 år, för att ytterligare minska risken för återfall.

Vi har i denna studie undersökt hur stor andel av patienter som tar sitt hormonella behandling som det är ordinerat och orsakerna till att patienter slutar. Även undersökt faktorer som påverkar följsamheten, till exempel om någon patientgrupp är bättre på att ta sin behandling. Vi har granskat hur många av patienterna som fick vara med i en diskussion kring förlängd behandling och om de fick behandling förskrivet.

Det vi kom fram till var att 82.5% av patienterna var följsamma till sin behandling. Vanligaste orsaken till att de slutade var biverkningar. Vi fann också att unga patienter och de med små tumörer var bättre på att ta sin behandling. 44% av patienter med spridning till lymfkörtlarna fick förlängd behandling och 71% var inkluderade i en diskussion kring behandlingen.