5-year adherence to adjuvant endocrine treatment in Dutch women with early stage breast cancer: a population-based database study (2006-2016).

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Research Article

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Abstract

Purpose

Hormonal receptor (HR) positive breast tumors are common. Adjuvant hormonal therapy (AHT) with Tamoxifen or Aromatase Inhibitors (AIs) is beneficial depending on the stage of the tumor. Despite the fact that AHT has been shown to improve survival and recurrence, Dutch adherence rates, which were mostly dependent on Tamoxifen prescriptions until 2006, plummeted from 80% after one year to 50% after five years. Nonadherence with AHT reduces its effectiveness. This research presents more recent adherence statistics (from 2006 to 2016) as well as factors that influence AHT adherence. In addition to Tamoxifen data, AIs are now included in prescriptions.

Methods

The Netherlands Cancer Registry (NCR) was used to find women with early-stage breast cancer who started AHT within a year of surgery and were linked to the PHARMO Database Network. The Kaplan-Meier approach was used to measure AHT adherence five years after treatment was started, with a 60-day gap between refills as our primary outcome. Furthermore, the Medication Possession Rate (MPR) was determined using a cutoff of 50%. Subgroup analysis was performed on influential factors of adherence.

Results

The 5-year adherence rate was 46.6% when gaps of 60 days between refills were allowed. Based on MPR 80 %, the five-year adherence rate was 53.3%. Age, ≥ 70 years (HR (95% CI) 1.20 (1.10 – 1.30), 50-69 years (HR (95 % CI) 1.09 (1.02 – 1.17) vs < 49 years), and year of diagnosis, 2011-2016 (HR (95 percent CI) 2.39 (2.24-2.56) vs 2006-2010) were also linked with adherence continuance.

Conclusion

Dutch 5-year AHT adherence has remained poor.

Introduction

Roughly eighty-five percent of all carcinomas of the breast in women are hormone receptor (HR) positive (HR). [1] Adjuvant hormonal therapy (AHT) has been shown to be an effective treatment for HR-positive breast cancer, with reported decrease in recurrence of 13.2 percent and a reduction in mortality of 9.3 percent after 15 years [2, 3]. AHT is split into two groups: selective estrogen receptor modulators such as tamoxifen which block estrogen receptors directly [4], and aromatase inhibitors (AIs), which are a newer class of AHT. AIs prevents the enzyme aromatase from converting androgens to estrogen, resulting in estrogen depletion [5].

Patients with HR + carcinomas who are premenopausal should be treated with tamoxifen for at least five years, according to the guidelines [6, 7]. If a patient becomes postmenopausal during this time, a switch to AIs can be considered with a 3-monthly status check. Postmenopausal woman should be treated with AIs or tamoxifen for two to three years. Following that, the drug is shifted to the other group, for another two to three years. However, certain high-risk premenopausal women, are given extended Tamoxifen for ten years, while high-risk postmenopausal women are given extended AI medication for 8 to 10 years following diagnosis [8].

Despite its demonstrated effectiveness, AHT adherence rates have been found to be far from ideal. Non-adherence rates have been reported to range from a quarter to more than 50 percent over the world [9, 10]. Low adherence has been linked to an increased risk of recurrence and mortality [11]. Van Herk-Sukel et al. published the most recent adherence estimates in the Netherlands in 2010, covering the years 1998–2006 and based on data from the southern portion of the country. In this study, adherence was observed to be as low as 49 percent [12].

This study is a follow-up to the 1998–2006 study. The goal of this study is to determine the current adherence rates in the Netherlands (2006–2016). Apart from the fact that our data come from a bigger sample and we now include information on AIs besides Tamoxifen, which may make our study more newsworthy. We also look at characteristics including age, tumor size, lymph node status, TNM-classification and year of diagnosis to see if they have an impact on adherence. Such knowledge could aid in identifying patients who are at high risk of quitting AHT intake early and developing and testing interventions for these subgroups.

Methods

Study population

Women diagnosed with early-stage invasive breast cancer (stage I - IIIA according the TNM 6th and later the 7th edition guidelines) between 2006–2014 made up the study population. Because this study focusses on adjuvant therapy, women that did not get surgery were eliminated from the final study group. The selecting procedure is depicted in Fig. 1. At the time of death or the end of the trial period on December 31, 2016, patients were censored.

Data

First, eligible women were retrieved from the Netherlands Cancer Registry (NCR) (https://iknl.nl/en.) The NCR provides basic information about all newly diagnosed breast cancer patients in the Netherlands, such as age, tumor stage (TNM-classification) and primary (and possible secondary) treatment [11][13]. Second, the NCR was linked to the PHARMO Database Network, a Dutch population-based network of electronic healthcare databases that contains anonymized data from various healthcare settings. The Out-patient Pharmacy Database, which comprises both GP and specialist prescribed healthcare products

supplied by the out-patient pharmacy, was used for this study. Data from out-patient pharmacies span a catchment area of 4.2 million people (about 25% of the Dutch population)[14].

Dispensing records include information on the type of product, date, dosage, quantity and prescriber specialty. Drug dispensing is coded according to the WHO ATC classification system [12].

We were able to identify 8,679 women with a dispensing for hormonal (endocrine) treatment by integrating these databases. With this information, we were able to describe whether women succeed to continue their treatment as prescribed by their specialist or GP. More method details can be found elsewhere [11].

Definitions on treatment adherence

Women who successfully sustained their renewals during the follow-up period were defined as adherent to their therapeutic participants. The method we utilized to determine whether patients were complying was based on Catalan and Lelorier's study, which was also employed in van Herk-Sukel et al.'s prior study. [13, 15]. A treatment episode was determined by the number of pills dispensed in one renewal, divided by the number of pills taken daily. The number of pills taken daily being predetermined by the women's pharmacy. A gap of 60 days was acceptable when the time of a renewal period was longer than the treatment episode. As there is no way to know when a patient stopped taking their medication, the date of non-adherence was set at half of the time from the last dispensing.

We also used another definition of medication (non-)adherence, which was the proportion of total dispensed medication or medication possession rate (MPR) at 1, 2, 3, 4 and 5 years.

We chose an MPR of 80 percent or above as this is the most commonly used cut-off for adherence studies. [16–18] MPR was calculated by dividing the duration of a prescription divided by the length of a dispensing. The total length of all prescriptions was determined by dividing the amount of all prescriptions by the number of pills taken daily as indicated by the patient's pharmacy [17].

In current study, switching therapies was not considered an endpoint or as medication non-adherence since women continue to take endocrine medication. A switch is advised in the (inter-(national) guidelines after two to three years, or results from switching for other reasons, such as patient's preference or adverse effects.

Analysis

Kaplan-Meier survival analysis was used to calculate the amount of adherence over time, in which stopping AHT was considered as elimination and censoring patients who were lost to follow-up. Patients were censored at the time of death or the end of study period at the 31st of December 2016. Rates of usage of any endocrine therapy were determined at 1, 2, 3, 4, and 5 years after initiation. Additionally, sensitivity analysis of gaps of 90 and 180 days were performed [13, 19]. Stratified analysis for age, tumor

stage, tumor size, lymph node status and year of diagnosis were performed. We used the log-rank test to determine whether the stratification used made a statistically significant difference.

Cox proportional hazards analysis was used to identify independent determinants of discontinuation, within five years after starting endocrine therapy.

Statistical significance was defined as an alpha level of 0.05. Data was organized and analyzed using SAS programs that are available in the SAS version 9.4.

Results

The selection procedure is depicted in Fig. 1. A total of 8,679 women were included in the study who received endocrine treatment (Tamoxifen or AIs) within a year of their diagnosis. A total of 683 women were excluded from the study because they had not had surgery prior to their treatment. Table 1 shows the baseline characteristics of the final study population, which included 7,996.

Table 1
– Characteristics at diagnosis of early-stage breast cancer patients surgically treated between 2006–2014 (N = 7,996)

Characteristics at time of diagnosis		
Age	*n*	*(%)*
≤ 35 years	185	(2.3)
36–49 years	1 808	(22.6)
50–59 years	1 920	(24.0)
60–69 years	2 121	(26.5)
≥ 70 years	1 962	(24.5)
Period of diagnosis		
2006–2009	608	(7.6)
2010–2013	3 590	(44.9)
2014–2016	3 798	(47.5)
Hormone receptor status		
ER + and / or PR+	7 949	(99.4)
ER - and PR -	20	(0.3)
Unknown	21	(0.3)
Tumor size		
≤ 1.0 cm	493	(6.2)
1.1–2.0 cm	3 453	(43.2)
2.1–3.0 cm	2 105	(26.3)
3.1–4.0 cm	575	(7.2)
> 5.0 cm	371	(4.6)
Unknown	998	(12.5)

Characteristics at time of diagnosis		
Lymph node status		
Positive	3 827	(47.9)
Negative	4 072	(50.9)
Unknown	97	(1.2)
TNM-classification		
Stage 1	2 593	(32.4)
Stage 2a	2 943	(36.8)
Stage 2b	1 575	(19.7)
Stage 3a	885	(11.1)
Histologic grade		
Well differentiated	1 139	(14.2)
Moderately differentiated	4 185	(52.3)
Poorly differentiated	1 889	(23.6)
Unknown	783	(9.8)
Other therapies		
Chemotherapy	4 191	(52.4)
Radiotherapy	5 400	(67.5)
Comorbidities at diagnosis		
None	1 603	(20.1)
1	876	(11.0)
≥ 2	712	(8.9)
Unknown	4 805	(60.1)

The median age (± SD) was 61 years (± 14.4). The youngest group (under 35 years old) was also the smallest group, accounting for 2.3% of all patients. The remaining age groups (36 to 49, 50 to 59, 60 to 69 and older than 70) were fairly evenly split (22.6%, 24.0%, 26.5%, 24.5% respectively). Roughly one-third of the tumors were stage I (32.4%). Most of the included tumors were stage II, which were further split into stage IIa (36.8%) and IIb (19.7%). The stage III tumors made up the smallest group, counting for 11.0% of all tumors. Of all patients, 52.4% had chemotherapy, and 67.5% received radiotherapy.

Medication adherence by using medication gaps

After diagnosis, the average follow-up time was 4.2 (SD ± 2.5) years. Allowing a gap of 60 days, the percentage of continuous users of any endocrine treatment for 1, 2, 3, 4 and 5 years was 83.4%, 72.1%, 63.1%, 56.2% and 46.6%, respectively (Fig. 2). Sensitivity analysis using a permissible gap op 90 and 180 days, showed a 5-year persistence rate of 55.4% and 66.6%, respectively.

Medication possession rate (MPR)

Looking at the MPR, we can see that endocrine therapy adherence is gradually declining. After one year, 6,830 (84.4%) patients were still on endocrine therapy. After 2, 3, 4 and 5 years, the percentages fell to 8,832 (72.9%), 5,227 (65.4%), 4,680 (58.5%) and 4,261 (53.3%), respectively.

Determinants of endocrine treatment analysis

Figures 3 and 4 depict stratification based on age and tumor stage, respectively. Univariate analysis revealed that increasing age and later period of diagnosis (≥ 2011) both enhance the likelihood of continuation and may thus be determinants of endocrine treatment adherence (Table 2). Adherence seemed unaffected by tumor size, lymph node status, and tumor stage.

Table 2
– Multivariate analysis of determinants of discontinuation of endocrine treatment during follow-up

Characteristics	HR univariate (95% CI)	HR multivariate* (95% CI)
Age at diagnosis		
≤ 49	1	1
50–69	1.13 (1.05–1.21)	1.09 (1.02–1.17)
≥ 70	1.25 (1.15–1.35)	1.20 (1.10–1.30)
Tumor size		
≤ 1 cm	1	1
1,1–2,0 cm	0.94 (0.83–1.07)	0.90 (0.79–1.03)
2,1–5,0 cm	0.87 (0.76–0.99)	0.87 (0.76-1.00)
≥ 5,0 cm	1.14 (0.92–1.41)	1.11 (0.89–1.38)
Lymph node status		
Negative	1	1
Positive	0.95 (0.88–1.02)	0.98 (0.91–1.06)
Tumor stage		
Low	1	1
High	0.87 (0.82–0.93)	0.95 (0.89–1.01)
Year of diagnosis		
2006–2010	1	1
2011–2016	2.42 (2.27–2.59)	2.39 (2.24–2.56)
*adjusted for age at diagnosis, tumor stage and year of diagnosis		

We additionally performed a multivariate analysis to determine what factors that would impact endocrine treatment cessation, using the 60- day permissible gap as a criterion (Table 2). Patients who continue endocrine treatment are also more likely to be over 70 years old (HR (95% CI) 1.20 (1.10–1.30)) or 50–69 years, HR (95% CI) 1.09 (1.02–1.17) vs ≤ 49) (Table 2). Patients diagnosed between 2006–2010 were less likely to be adherent than those diagnosed after 2010; HR (95% CI) = 2.39 (2.24–2.5).

Discussion

When employing a reasonable gap between refills of 60 days, this study found that adherence to any endocrine medication until five years from the commencement of the treatment is less than half.

According to the MPR criterion of ≥ 80%, the five-year endocrine treatment adherence in everyday practice appeared to be slightly higher (about half). Looking at the multivariate analysis, both advanced age (≥ 50 years) and a more recent diagnosis (period 2011–2016) were identified as independent variables that may favorably influence five-year adherence to endocrine treatment in the multivariate analysis.

Based on the definition of gaps, the adherence rates observed in this study are in accord with previously reported adherence rates, but at the lower end of the range [13, 20, 21] As other studies have shown, there is a minor extra reduction in endocrine treatment adherence approximately 2–3 months before five-year milestone. This could be due to the adherence definition utilized, which sets the date of non-adherence to be half from the last dispensing. Furthermore, this could also indicate either that the patient or the clinician is less strict in completing the entire five-year period (especially for low-risk patients [22]) and instead complete as much of this period as the patient can tolerate (especially when nearing the treatment end), as found and reported by another study [23]. When comparing data from other studies using the alternative definition of adherence, MPR ≥ 80%, we see similar results. These studies' adherence rates appear to be slightly higher than the MPR rates discovered in our study [11, 24, 19].

In line with another studie [25], we found that being younger than 50 years old is an independent determinant of stopping endocrine medication before the recommended five years. Because the burden of side effects is greater in these younger patients, they may be less committed to adjuvant endocrine therapy. Non-menopausal women experience menopausal symptoms more abruptly than postmenopausal women, thus they notice more changes. For all endocrine treatments, the most common side effects include hot flushes, depression, and vaginal dryness. For AIs specifically, musculoskeletal symptoms are significant [26].

Another factor that showed to be an independent variable of early treatment discontinuation was tumor stage. Patients that had a higher stage tumor (II-IIIa) at diagnosis were more likely to continue their endocrine treatment for the recommended five years. This finding is in line with studies that suggest that patients with a higher stage tumor or lymph node involvement are more likely to remain adherent. [27, 28] Though, others show that the contrary might be true [13, 19].

There is a scarcity of research into strategies that could increase endocrine therapy adherence in breast cancer patients [29]. Although adequate knowledge (behavioral capability) is still required, more routinely monitoring and ongoing support for adherence maintenance in follow-up sessions appear to be necessary [30]. Women require opportunities to discuss the (dis-) advantages of ATH (which may alter over time) and support in dealing with or coping with side effects, which is individualized to the particular patient [31, 32].

Higher adherence rates will result in health benefit (such as the prevention of breast cancer cell growth) and total cost savings since the risk of relapse will be reduced [33].

The study's strengths include its scope, both in terms of numbers and in terms of how it reflects a large portion of the Netherlands. Furthermore, data was collected by professional workers, ensuring the accuracy of the information. Another strength is the use of multiple adherence definitions. This makes it easy to compare this article to other relevant material and provides a comparison of the two meanings that are used in international literature.

This study has some shortcomings as well. First, we only provide information on refills and not on actual medication intake. It's possible that adherence percentages defined as 'really taken' are worse. Second, in the database used, we had no information on potential medical justified reasons for non-adherence. Patients treated with endocrine treatment still have a 1 to 2 percent chance of recurrence yearly in the first five years after surgery. This might even be slightly higher when patients are treated with tamoxifen only [34]. As ATH therapy is then halted by the treating specialist recurrence leads to an overestimation of patients' non-adherence.

It is also worth noting that although age and tumor stage were independent variables of early treatment continuation, their effects were not large. This means that these variables are statistically significant but might not be clinically relevant for daily practice.

Finally, comparing the results of current study to the study by Van Herk-Sukel et al. [13], it seems that although initiatives have been taken to address ATH adherence since the earlier publication, it might be too early yet to see a beneficial impact since the implementation of, for instance new guidelines, take years.

Conclusion

Accepting a gap of 60 days between refills, we found that the five-year adherence rate to adjuvant endocrine therapy in daily practice lies around 32.3 percent. This means that adherence to adjuvant endocrine treatment has not improved in the Netherlands despite the increased awareness of the low adherence rate. A planned approach may be needed, based on well-defined determinants of adherence behavior and environmental conditions.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yannick van den Biggelaar and Josephina Kuiper. The first draft of the manuscript was written by Yannick van den Biggelaar, Adri Voogd and Ilse Mesters and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to the connection between two datasets of two organizations but are available from the corresponding author on reasonable request.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the internal ethical committees of both organization, Pharmo Database Network and NCR respectively.

Consent to participate

The study involves anonymous data of national registries.

Consent to publish

Not applicable

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Figures

Figure 1 – Flowchart of patient selection

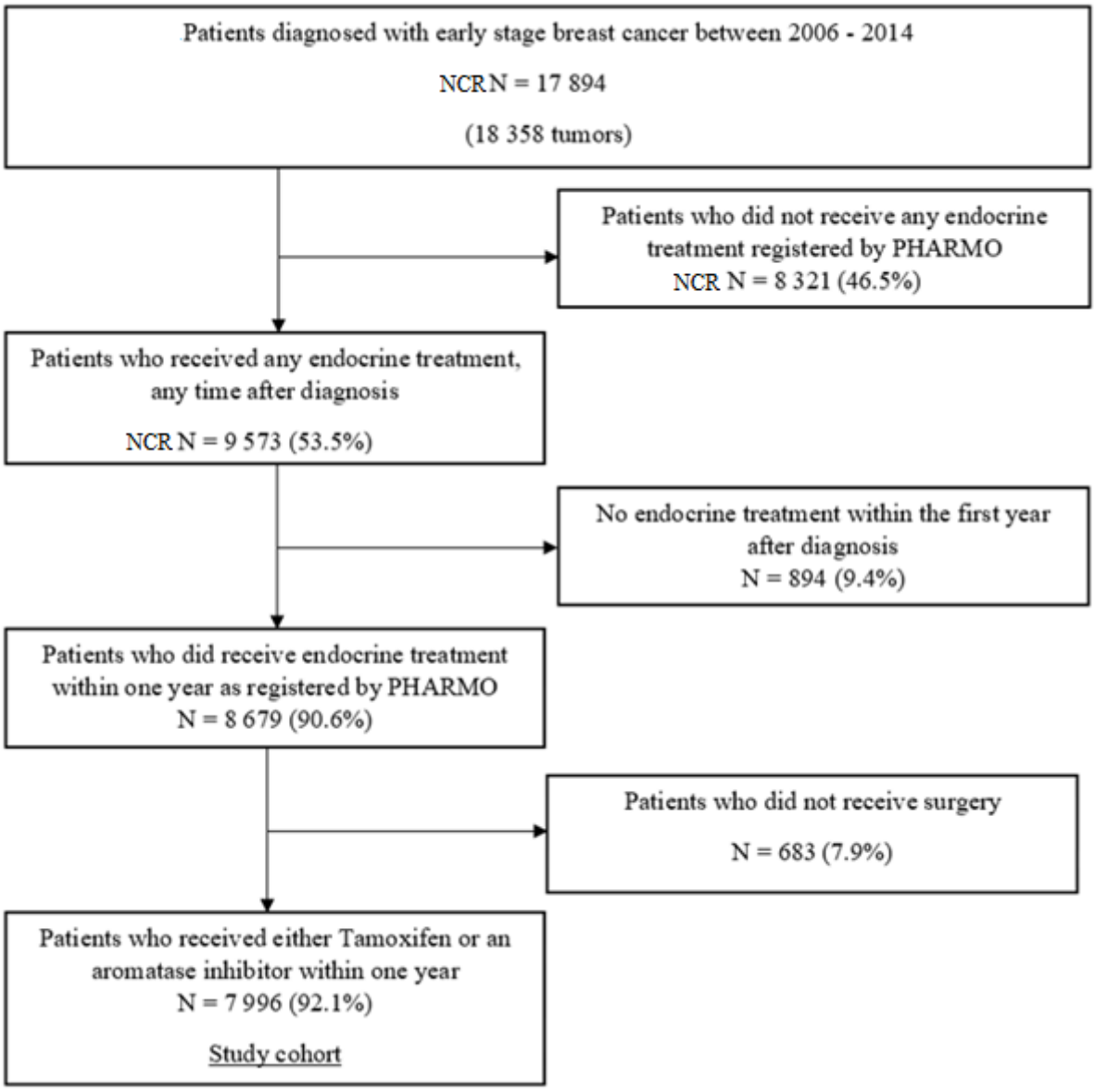

Figure 1

Flowchart of patient selection.

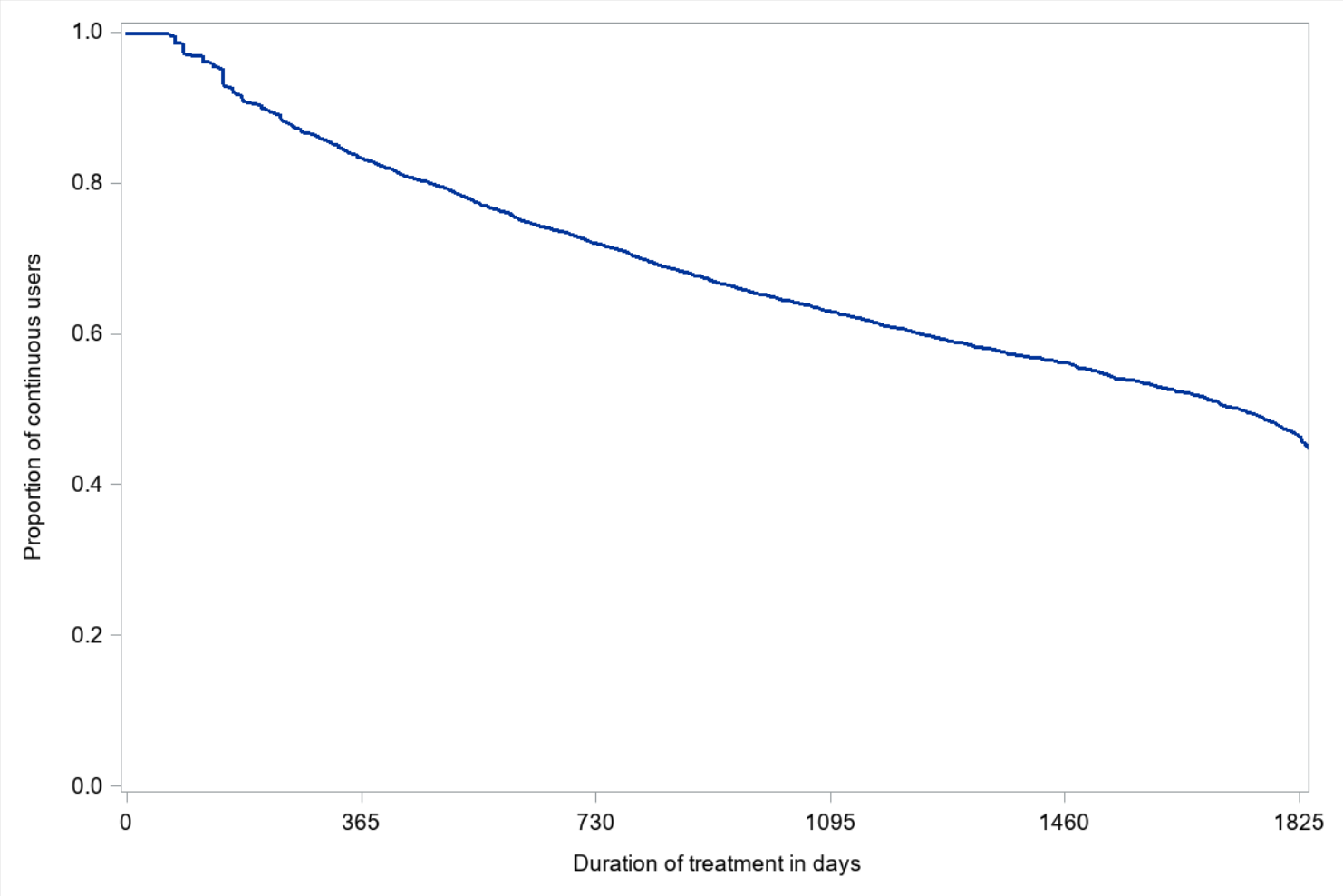

Figure 2

Proportion of patients that uses endocrine treatment continuously, allowing a gap of 60 days

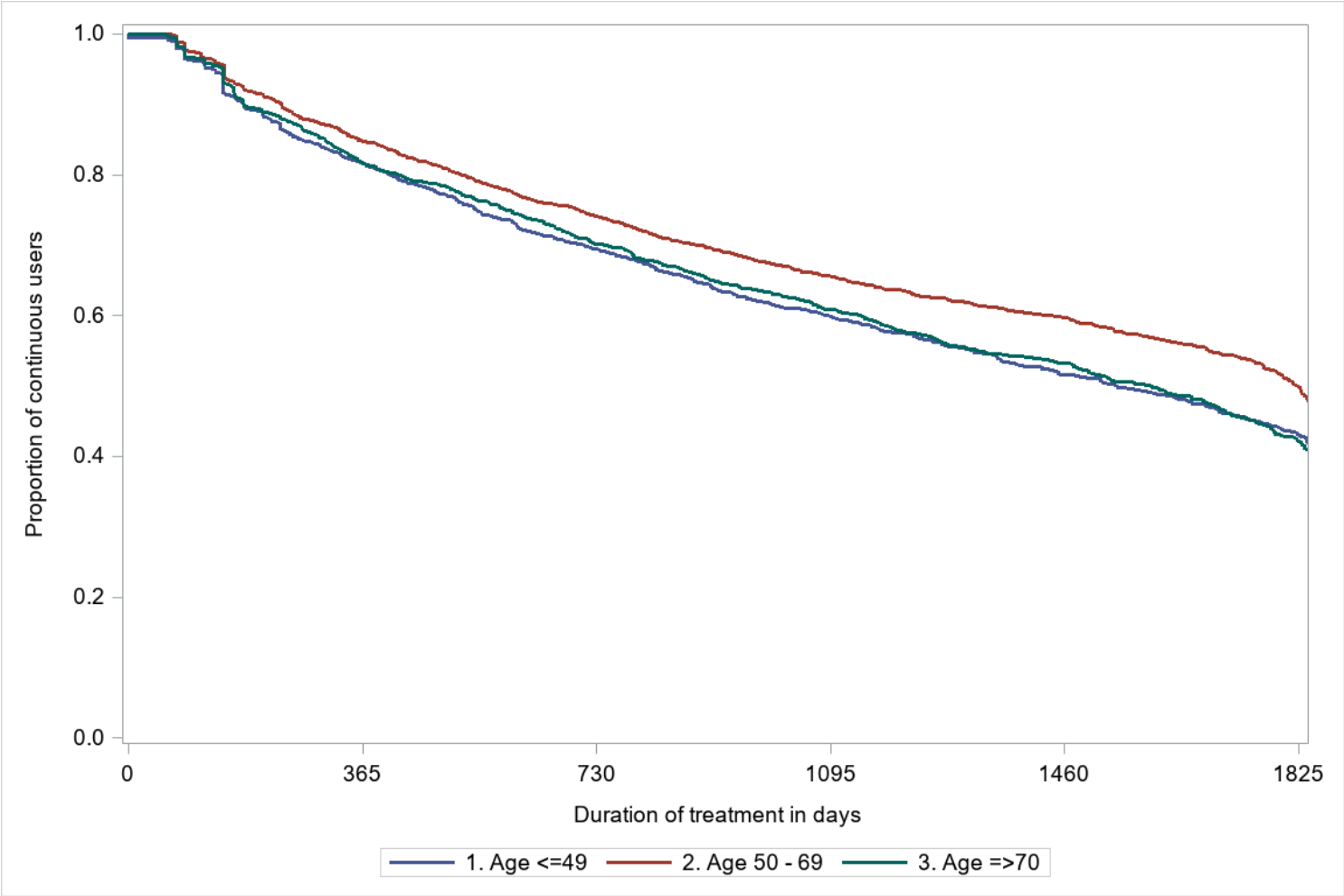

Figure 3

Proportion of patients that uses endocrine treatment continuously, allowing a gap of 60 days, stratified by age category

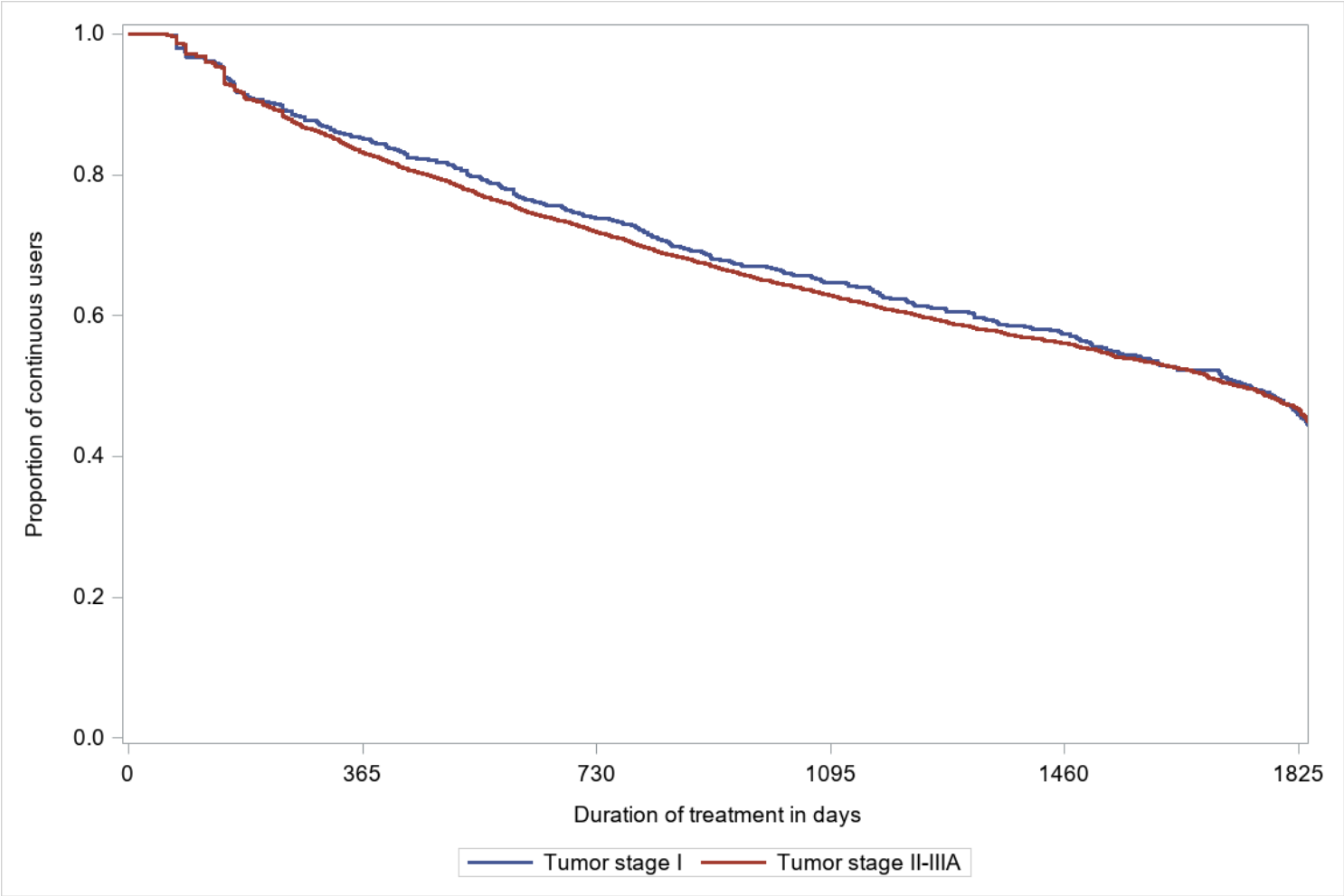

Figure 4

Proportion of patients that uses endocrine treatment continuously, allowing a gap of 60 days, stratified by tumour stage