Recurrence analysis in T4 breast cancer in the Netherlands

A POPULATION-BASED STUDY

Student:
I. Bouwen

Supervisors:
Dr. M.C. van Maaren
Prof. Dr. S. Siesling
Dr. D.J.P. van Uden

UNIVERSITY OF TWENTE
MSC HEALTH SCIENCES – OPTIMIZATION OF HEALTHCARE PROCESSES
FACULTY OF SCIENCE AND TECHNOLOGY (TWN)

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integraal kankercentrum Nederland

UNIVERSITY OF TWENTE.

Abstract

Background Tumors of any size with direct extension to chest wall and/or to skin are classified as T4 breast cancer. Currently, there is limited information available on the occurrence of recurrences in T4 breast cancer. This population-based study aimed to analyze trends and risks of recurrence over time in patients with nonmetastatic T4 breast cancer in the Netherlands.

Methods All patients with nonmetastatic cT4 breast cancer between 2005-2008 and 2012-2016 in the Netherlands were selected. Patient-, tumor-, and treatment related characteristics were compared over time and between T4 subcategories. Locoregional recurrences were analyzed over a 5-year follow-up using Kaplan-Meier curves and Cox proportional hazard regression to estimate hazard ratios, accounting for confounders and considering competing risks.

Results 3,659 patients were diagnosed with cT4 breast cancer between 2005-2008 and 2012-2016: 1,654 (45.2%) in 2005-2008, and 2,005 (54.8%) in 2012-2016. Among the total population at risk of a recurrence (2,339 patients), 7.4% (155 patients) experienced a locoregional recurrence (LRR) within 5 years after their last surgery. The LRR rate decreased from 9.9% in 2005-2008 to 5.7% in 2012-2016. T4d shows the highest LRR rate of 11.4%, compared to 3.8% in T4ns, T4a, and T4c, and 5.9% in T4b. Clinical tumor stage, differentiation grade, multifocality, receptor subtype, and trimodal therapy were showed to be significant prognostic factors for the five-year RFS.

Conclusion These findings provide valuable insights into the trends and risks of locoregional recurrence in nonmetastatic T4 breast cancer. Understanding these trends and risk factors can support patient-tailored treatments and individualized follow-up strategies.

Keywords

Breast cancer – Recurrence risk – 5-year follow-up – Nonmetastatic T4 breast cancer – Hazard Ratio

Abbreviations

CI: Confidence Interval
ER: Estrogen Receptor
HER2: Human Epidermal growth factor Receptor 2
HR+/-: Hormone Receptor positive/negative
HR: Hazard Ratio
IBC: Inflammatory Breast Cancer
MICE: Multivariate imputation by chained equations
KM: Kaplan-Meier
LLR: Locoregional Recurrence
NCR: Netherlands Cancer Registry
pCR: Pathologic Complete Response
PH: Proportional Hazard
PR: Progesterone Receptor
RFS: Recurrence-free Survival
SD: Standard Deviation

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1 Introduction

Breast cancer is the most common cancer in women worldwide (1). In the Netherlands, approximately one in seven women will develop breast cancer at some point in their lifetime (2). According to the Netherlands Cancer Registry (NCR) about 15.500 women are diagnosed with breast cancer yearly (2). Survival chances are highly determined by the stage of the tumor at diagnosis. The relative overall survival rate of breast cancer five years after diagnosis is 88% (2). This is an approximation of the cancer-specific survival, meaning that there is an 88% chance of surviving breast cancer within the five-year period after diagnosis in a hypothetical world where no other causes of death exist (3). For patients diagnosed with a stage I tumor this rate is 98%, however, for patients diagnosed with a stage IV tumor, this rate drops to 23% (2).

Tumors are classified according to the TNM system by the American Joint Committee on Cancer (AJCC). This system provides information about the primary tumor (T), involved regional lymph nodes (N), and distant metastasis (M). A specific and rare subtype of breast cancer is T4 breast cancer, defined as a "tumor of any size with direct extension to chest wall and/or to skin" (4).

T4 breast cancer is a broad heterogeneous group (5). Within T4 there are four subcategories distinguishing between non-inflammatory (T4a, T4b, T4c) and inflammatory (T4d) breast cancer. T4a comprises tumors that are extended to the chest wall. In T4b breast cancers, the majority of T4 breast cancers, the tumor has direct extension to the skin. This is characterized by ulceration, ipsilateral satellite skin nodules, or skin oedema (4). T4b tumors without metastasis at diagnosis are categorized under anatomic stage group IIIB and treated accordingly (4). T4c is a combination of both T4a and T4b (4). Inflammatory breast cancer (IBC), classified as T4d, is a specific, rare, and aggressive subtype of T4, accounting for less than 5% of all diagnosed breast cancer, but causing 7-10% of breast cancer-related deaths (6). IBC is characterized by its aggressive nature, poor prognosis, and distinct clinical presentation. The typical clinical presentation includes symptoms like erythema (redness of the skin), swelling of the breast, nipple retraction, a dimpling appearance known as 'peau d'orange', and a rapid progression (7).

Treatment of T4 breast cancer varies. In case of metastasis (stage IV), the main goals of treatment include improving or maintaining quality of life, alleviating symptoms, and extending survival (8). In contrast, patients with nonmetastatic T4 breast cancer undergo treatment with the purpose to cure, aiming to improve survival and minimize the risk of recurrence (9). This approach involves trimodal therapy, which includes neoadjuvant chemotherapy, surgery, and adjuvant radiation. For Human Epidermal growth factor Receptor 2 (HER2) and/or estrogen/progesterone (ER/PR)-positive tumors trastuzumab and/or antihormone therapy can be added (10).

Currently, the Dutch guideline advises to treat all nonmetastatic T4 breast cancer patients the same, despite the possibility that this invasive treatment might not be necessary for all subcategories. Another aspect that can influence treatment, is the receptor status of the tumor. There are four different subtypes based on hormone receptor (HR) and HER2 status: HR+/HER2-, HR+/HER2+, HR-/HER2-, and HR-/HER2+ (11). Pathologic complete response (pCR), defined as the disappearance of all invasive cancer in the breast post-neoadjuvant chemotherapy, has demonstrated increased overall survival and disease-free survival (12). However, the incidence and prognostic impact of pCR vary across breast cancer subtypes (13).

One of the primary objectives in treating nonmetastatic T4 breast cancer is to minimize the risk of recurrence. However, there is currently limited information available on the occurrence of recurrences in T4 breast cancer. Among women diagnosed with invasive non-metastatic breast cancer in 2005, 4.7% experienced local recurrences within 10 years, 3.0% were diagnosed with a regional recurrence, and 15% developed a distant metastasis (14). While these rates are relatively low, they do not specifically address the risks associated with T4 breast cancer. Gaining more insight in potential recurrence patterns can give T4 breast cancer patients a realistic understanding of their prognosis, and can help care providers and patients in making informed treatment choices. Therefore, the objective of this study is to analyze trends and risks of recurrence over time in patients with nonmetastatic T4 breast cancer in the Netherlands.

1.1 Research questions

Following the objective of this research, the following main question needs to be answered: *What are the recurrence trends and risk factors in patients with nonmetastatic T4 breast cancer in the Netherlands?*. To answer this question, the following sub-questions have been formulated:

- What is the proportion of locoregional recurrence among patients with nonmetastatic T4 breast cancer in the Netherlands and how does this compare over time?
- How do recurrence trends vary among subcategories of nonmetastatic T4 breast cancer considering incidence rates?
- How does the time to recurrence vary among patients with nonmetastatic T4 breast cancer?
- Which factors influence the risk of recurrence in nonmetastatic T4 breast cancer?

2 Context

2.1 Anatomy of the breast

The breasts (Latin: *mammae*) stand out as the most prominent superficial structures on the anterior thoracic wall, particularly in women. They typically extend from the second till the sixth rib and are positioned above the pectoralis major and minor muscles. The breasts primarily consist of glandular, adipose (fat), and connective tissue. At the center of the breast lies the nipple, surrounded by a circular pigmented area of skin called the areola (15).

The glandular tissue includes mammary glands, which lie in the subcutaneous tissue and are responsible for the production of milk. These mammary glands consist of approximately 15 to 20 lobes, containing lobules. Each of these lobules is connected to lactiferous ducts, facilitating the passage of fluids within the breast. The lactiferous sinus is a dilated portion of the duct within the areola where milk accumulates. The firm attachment of mammary glands to the skin is facilitated by the suspensory ligaments of Cooper. Constructed from fibrous connective tissue, these ligaments provide structural support, contributing to the overall form and stability of the breasts (15). An overview of the anatomy of the breast is shown in Figure 1.

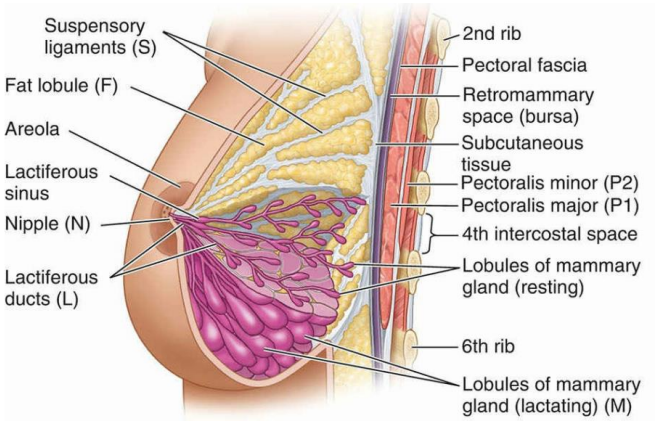

Figure 1 *Medial view of the breast (15)*

The lymphatic drainage of the breast is plays an important role in the metastasis of cancer. Lymphatic fluid passes from the nipple, areola, and lobules of the mammary glands to the subareolar lymphatic plexus. From this plexus, 75% of this lymphatic flow is directed towards the axillary lymph nodes, leading to drainage into the clavicular lymph nodes and further connecting to the subclavian lymphatic trunk. Most of the remaining lymph drains to the parasternal lymph nodes, entering the broncho mediastinal lymphatics trunks (15).

To delineate the anatomical location and description of breast tumors, the breast surface is divided into four quadrants: superolateral, inferolateral, superomedial, and inferomedial (16). Different probabilities of developing a malignant tumor exist in the different quadrants. Figure 2 illustrates the quadrants and also shows that the superolateral quadrant has the highest likelihood of developing a malignant tumor, approximately 60% (16).

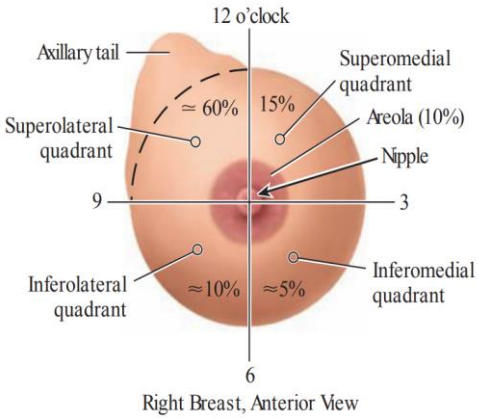

Figure 2 *Quadrants of the breast. The percentages show the proportion of malignant tumors (16).*

2.2 Staging and classification of breast cancer

Tumors are classified according to the TNM system by the American Joint Committee on Cancer (AJCC). This system provides information about the primary tumor (T), involved regional lymph nodes (N), and distant metastasis (M). The T-category is determined by the largest mass and ranges from Tis to T4, the N-category ranges from N0 to N3, and the M-category distinguishes between M0 (no distant metastasis) and M1 (distant metastasis) (4). The TNM categories are combined to determine the overall anatomic stage, ranging from stage 0 to stage IV (17). Table 1 provides the overall anatomic stage corresponding to TNM classification. This overall anatomic stage is arguably the most powerful in predicting how cancer will progress and can help physicians plan treatments tailored to each patient (18).

Table 1 *Anatomic stage group according to TNM staging. T: tumor, N: lymph node, M: metastasis, Tis: tumor in situ (4)*

	T category	N category	M category
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0, T1	N1mi	M0
Stage IIA	T0, T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1,N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

To determine the stage of the tumor, the National Comprehensive Cancer Network (NCCN) recommends to perform history and physical examination, bilateral mammography, pathology evaluation, and assessment of hormone receptors (19). The staging system contains four categories designated by prefixes: clinical staging “c”, pathologic staging “p”, post-neoadjuvant chemotherapy staging “yp”, and restaging in event of recurrence “r” (17). For T4 breast cancer, the staging is mainly done based on clinical examination, since clinically visible features of T4 tumors, like edema and peau d’orange, are often not confirmed by histological evaluation (5).

2.3 T4 breast cancer

T4 breast cancer is a specific and rare subtype of breast cancer, but it is a broad heterogenous group (5). It is defined as a “tumor of any size with direct extension to chest wall and/or to skin” (4). Within T4 there are four subcategories distinguishing between non-inflammatory (T4a, T4b, T4c) and inflammatory (T4d) breast cancer. The definitions of the subcategories can be found in Table 2. However, it is argued whether T4a, T4b, and T4c should be eliminated from the T4 category and rather be classified according to their T and N status (20). Güth et al. have shown that considerable numbers of patients are overclassified in stage IIIB, because they only show limited disease extent. By removing them from category T4, the heterogeneity in this group could decrease (20).

Table 2 *Current definitions of T4 breast cancers according to the AJCC TNM classification (4)*

Tumor classification	Definition
T4	Tumor of any size with direct extension to chest wall and/or to skin
T4a	Extension to chest wall
T4b	Ulceration, ipsilateral satellite skin nodules, or skin oedema (including peau d’orange)
T4c	Both 4a and 4b
T4d	Inflammatory carcinoma

2.3.1 Receptor subtypes

A potential limitation of the staging system described in section 2.2 is that the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status, which have been proved to be of predictive and prognostic value, have not been integrated (18). Cancer cells with receptors for estrogen and/or progesterone use these hormones to grow. ER and PR are often grouped together as hormone receptors (HR) positive or negative. HER2, part of the HER family, plays a role in regulating cell growth, survival, and differentiation. In 15-30% of invasive breast cancer, there is an overexpression of HER2, which holds both prognostic and predictive implications (21). Press et al. have shown that in breast cancer patients with overexpression of HER2 the risk of developing a recurrence is 3.0 times as high as patients without overexpression (22).

Four breast cancer subtypes have been identified based on these receptors: HR+/HER2- (luminal A), HR+/HER2+ (luminal B), HR-/HER2 (triple negative), HR-/HER2+ (HER2-enriched) (11). These subtypes are associated with different time to and patterns of recurrence (23).

2.3.2 Treatment of T4 breast cancer

Cancer treatment can be divided into local and systemic therapy. Local therapy includes surgical resection of the tumor and sampling or removal of axillary lymph nodes, and postoperative radiation (9). Standard approaches of surgery are either a total mastectomy or breast-conserving surgery (lumpectomy) (9). To prevent the tumor from spreading through the lymphatic system, a sentinel lymph node (SLN) biopsy or an axillary lymph node dissection could be added (24). Postoperative radiation is performed to eliminate any remaining cancer cells (24).

Systemic therapy includes neoadjuvant (preoperative) and/or adjuvant (postoperative) chemotherapy, endocrine therapy, and immunotherapy (24). Which form of systemic therapy is administered is determined based on breast cancer subtype, see section 2.3.1 (9). Neoadjuvant chemotherapy is aimed at downsizing the tumor, rendering unresectable tumors operable, and allowing sentinel lymph nodes biopsy instead of axillary lymph node dissection (24).

Treatment of T4 breast cancer depends on whether or not the cancer is metastasized at diagnosis. For patients with metastatic breast cancer (stage IV), the goals of treatment are prolonging life, symptom palliation, and preserving quality of life (8). Unfortunately, metastatic breast cancer remains incurable in virtually all affected patients (9). For these patients the recommended treatment is systemic therapy and local therapy is only used as palliation (25). On the other hand, patients with nonmetastatic breast cancer undergo treatment with the purpose to cure, aiming to minimize the risk of recurrence and improve survival (9).

Treatment of nonmetastatic T4 breast cancer involves a combination of therapies, known as trimodal therapy. This includes neoadjuvant chemotherapy, surgery, and adjuvant radiation. In cases of Human Epidermal growth factor Receptor 2 (HER2) and/or estrogen/progesterone (ER/PR)-positive tumors trastuzumab and/or antihormone therapy can be included as additional therapies (10).

2.3.3 Recurrences

If there are residual cancer cells after treatment, a recurrence can occur. Recurrences can be divided into three categories: local, regional, and distant. Moossdorff et al. conducted a study addressing the consensus on the definitions for classification of recurrences in breast cancer. Local recurrences occur in the ipsilateral breast tissue, in the surgical scar, or in the biopsy tract. Regional recurrences emerge in the ipsilateral lymph nodes in the axilla, around the clavicula, or at the sternum. Distant recurrences occur in any other organ or tissue than the breast in the body. There is also a chance for a second primary breast cancer, meaning breast cancer occurs in the contralateral breast (26). This study focuses on locoregional recurrences (LRR), which include both local and regional recurrences.

2.4 Survival analysis

Survival analysis is a statistical technique widely used in medical research to investigate the time until an event of interest occurs, commonly referred to as survival time. It is essential to clearly define what the event of interest exactly is and when the observation period starts and finishes (27). In many studies, overall survival (OS) is the outcome, where the event of interest is time till death. Another outcome can be the disease free survival (DFS), where the event of interest is any form of recurrent disease, including distant metastases. This study focuses on recurrence free survival (RFS), meaning time till locoregional recurrences is the event of interest.

According to Clark et al., challenges arise in survival analysis due to censoring, where a subset of the study group has unknown survival times. Specialized methods such as Kaplan-Meier and Cox regression have been developed to address this issue. Censoring can occur in three forms: a patient has not (yet) experienced the relevant outcome by the time of the end of the study, a patient is lost to follow-up, or a patient experiences a different event that makes further follow-up impossible. However, the survival time is partially known, representing the duration between the beginning of observation and the occurrence preventing continued follow-up. These patients are recorded as no event happening till that point in time. This leads to an underestimation of the true survival time, necessitating those special methods for analysis (27).

Clark et al. state that survival data are commonly described and modelled in terms of two probabilities: survival and hazard. The survival probability, denoted as *S(t)*, signifies the likelihood of an individual surviving from the time origin to a certain point in time. These probabilities for different points in time provide valuable insights into the chances of individuals surviving up to or beyond a specified duration, describing the survival experience of a cohort. On the other hand, the hazard, denoted as *h(t)*, is the immediate event rate for an individual who has already survived up to a certain point in time. In conclusion, the survival probability focuses on not having an event, while the hazard focuses on the incident event rate when the event has occurred (27).

2.4.1 Kaplan-Meier curve

In 1958 Edward L. Kaplan and Paul Meier wrote an article about nonparametrically estimating the survival probability from observed censored and uncensored survival times, the Kaplan-Meier (KM) method (28). The Kaplan-Meier survival method allows to analyze the time to the first event. There are three assumptions that should be considered: first, censoring should be unrelated to the study outcome; second, survival probabilities should remain consistent for individuals recruited early and late in a study; and third, accurate survival estimates require the availability of the specific event's occurrence date, encompassing day, month, and year (29). The Kaplan-Meier curve is a plot of the KM survival probability against time, providing a visual summary of the data used for estimating measures like the median survival time (27).

The essential information to create a Kaplan-Meier survival curve consists of the time until the event of interest and the binary variable indicating the patients status, distinguishing between the presence or absence of the event (29). The equation to calculate the survival probability at time t_j is as following (27):

$$S(t_j) = S(t_{j-1})\left(1 - \frac{d_j}{n_j}\right)$$

Where $S(t_j)$ is the probability of being alive at time t_j, $S(t_{j-1})$ the probability of being alive at t_{j-1}, d_j the number of events at t_j, and n_j the number of patients at risk just before t_j. The estimated probability is a step function that changes value only at the time of each event, because the value of S(t) is constant between times of events (27). The curve starts from 1 and decreases over time, depending on the number of events and patients at risk (29).

To compare the KM-curves of two or more groups to each other, for example between the subtypes as explained in section 2.3.1, the log-rank test is used (30). This method involves comparing the number of observed events (O_i) and the number of expected events (E_i) for group *i* (29). The number of expected events is calculated under the assumption of the null hypothesis, where the two groups have no difference in the occurrence of events. This null hypothesis is then tested against the alternative hypothesis of suggesting that there is a significant difference between the two groups. The log-rank statistic is calculated by the following formula (27):

$$\chi^2 = \sum_{i=1}^{g} \frac{(O_i - E_i)^2}{E_i}$$

This value is approximately distributed as a Chi-squared test statistic with degrees of freedom equal to the number of comparison groups (g) minus 1 (29). Using the outcome of this formula and the degrees of freedom, a p-value can be derived from the Chi-squared table, to calculate the statistical significance of the differences between the survival curves of the different groups (27).

2.4.2 Cox proportional hazard regression

Multivariable regression models are an important tool in statistical analysis, used to explore relationships between multiple independent variables and one dependent variable (31). Given the frequent discussion about the terminology of regression models, Tim Peters has provided an overview, which is summarized in Table 3 (32).

Table 3 *Current definitions of terminology of regression models (32)*

Name of the regression model	Outcome	Explanatory variables
Univariate	One	Regardless how many
Multivariate	More than one	Regardless how many
Univariable	Regardless how many	One
Multivariable	Regardless how many	More than one

The standard form of a linear multivariable regression model looks like the following, where Y is the dependent variable, β_0 the model intercept, β_1 , β_2 etc. the parameters for the covariates, X_1, X_2 etc. the covariates, and ε the random error (31):

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p + \varepsilon$$

Grant et al. describe that the 3 most common types of multivariable regression are linear regression, logistic regression and Cox proportional hazard regression. These models are designed for distinct purposes, aiming to assess the association between specific covariates and different outcomes. Linear regression assesses this association to a continuous outcome, logistic regression to a binary outcome without longitudinal aspect, and Cox proportional hazards regression to a time to event outcome. In a logistic regression model, the effect size of a covariate is usually expressed as an odds ratio (OR) along with 95% confidence intervals (CIs). In Cox proportional hazards models, the effect size is presented as a hazard ratio (HR) with 95% CIs. Both the OR and HR are determined by exponentiating the β term (31).

The cox proportional hazard regression model is the most commonly used approach to estimate the relative hazard of an event in survival analysis (33). The model is based on the hazard function, denoted as *h(t)*, showing the instantaneous risk of an event occurring at time t. Mathematically, the Cox model can be expressed as (33):

$$h(t) = h_0 * \exp\left(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p\right)$$

In this function, h_0 represents the baseline hazard, X_1, X_2, etc. the covariates, and β_1 , β_2, etc. the parameters of the covariates. The baseline hazard is the value of the hazard if all covariates (x) are zero, meaning it is the hazard for a patient who has the reference values for all covariates. The key assumption in this model is that the hazard ratios (HRs) are proportional, meaning that the relative effect of a covariate on the hazard function remains constant over time with different covariate levels (34). This assumption allows for comparison of hazard ratios between different groups. The other assumption of the model is that the relationship between the log hazard and a covariate is linear (35).

The HR in the Cox model is calculated by taking the exponent of the parameters of the covariates, so $\exp(\beta_p)$. It represents the relative rate of the occurrence of an event between two groups defined by a particular covariate. If the HR for a covariate is higher than 1, it means that the covariate is positively associated with the probability of the event occurring (33). However, in terms of recurrence analysis, this positive association means that the covariate is a bad prognostic factor, because the event is more likely to occur. In contrast, a HR smaller than 1 indicates a decrease in the event probability and is thus a good prognostic factor. A HR of 1 indicates no association.

When the effect of a covariate on the HR varies with time, it violates the proportional hazard (PH) assumption, which can lead to biased coefficient estimates (36). To test the PH assumption, there are both graphical methods and statistical tests (35). Common graphical methods include Kaplan-Meier curve assessment, log(−log) plots, and examination of scaled Schoenfeld residuals (34). The Schoenfeld residual is defined by the difference between the observed and expected covariate values at each event time (37). Plotting Schoenfeld residuals over time reveals patterns; non-random patterns indicate PH assumption violation (37). If the assumption is violated, further investigation or model adjustments may be necessary.

2.4.3 Competing risk analysis

In section 2.4.1, three assumptions for the Kaplan Meier method were described. However, when studying recurrences in breast cancer patients, the first assumption – that censoring is unrelated to the study outcome – may be violated, especially when patients die before a recurrence occurs. Treating these patients as censored observations can lead to bias and overestimation in the Kaplan-Meier estimate, as it assumes the event could still happen, which is not possible (38). Therefore, other methods are needed.

A solution for this is using Fine and Gray's proportional sub hazards model (FG model), which is a type of competing risk analysis. This model can be applied to evaluate the effects of covariates on the cumulative incidence function directly, which indicates the probability of the event of interest happening before a given time (39). The FG model focuses on the sub distribution hazard function or the cause-specific hazard function, which estimates the probability of experiencing a specific type of event (k) at a given time (t), accounting for the presence of competing risks.

However, the sub distribution hazard function of the Fine and Gray's model can be difficult to interpret. Another method for competing risk analysis, described by Putter et al., involves a competing risks analogue of the Cox proportional hazard (38). In this method, the cause-specific hazard function for the event of interest (in this study, recurrences) is estimated by censoring patients who experience a competing event. Next, regression is possible on the cause-specific hazard, providing hazard ratios for covariates included in the model (38).

2.5 Multiple imputation

Missing data is a common challenge in medical studies. Little and Rubin classified missing data into three categories: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) (40). Data are classified as MAR if the probability of data being missing depends only on observed data and not on unobserved data. In such cases, statistical techniques like multiple imputation can be used for handling missing data.

Multiple imputation (MI) involves estimating a range of possible values for missing data based on the distribution of observed data (41). This estimation is based on the observed values for an individual and the observed relationships among other individuals in the dataset. In contrast to single imputation, MI accounts for the uncertainty in imputations by incorporating random components into the estimated values (42).

Multivariate imputation by chained equations (MICE) is a specific technique of multiple imputation, which operates under the assumption that the missing values are MAR. Applying MICE to data not meeting this assumption could result in biased estimates (42). MICE models each variable with missing data based on its distribution: binary variables are imputed using binary logistic regression, nominal variables using multinomial logistic regression, and ordinal variables using ordered logistic regression.

The MICE process follows a series of steps. Each variable with missing data is treated as the dependent variable in a regression model, with the other variables serving as predictors. The missing variables are then replaced with predictions (imputations) from the regression model. This process iterates for each variable with missing data until convergence. Subsequently, the entire procedure can be repeated m times to generate multiple imputed datasets (42). The rule of thumb is that m should be at least equal to the percentage of incomplete cases (41).

Before analyzing the imputed dataset, it is important to check the convergence and fit of the imputation. Convergence can be assessed using trace plots, which monitor the stability of parameter estimates across iterations by the mean and standard deviation of the imputed values (43). A trace plot indicating convergence should display consistent and stable behavior without visible patterns. The fit of the model can be evaluated by comparing the distributions of the imputed variables with those in the observed dataset. A good fit is indicated by minimal differences between the distribution percentages.

3 Methods

3.1 Data source

The Netherlands Comprehensive Cancer Organization (IKNL) hosts the Netherlands Cancer Registry (NCR), a nationwide population-based cancer registry. All newly pathologically confirmed malignancies in the Netherlands, notified through the Dutch Nationwide Pathology Databank (PALGA), are recorded since 1989. Trained registrars collect data directly from the electronic patient files. Per type of cancer, there is a NCR-itemset, which defines the registered items. This is divided into general data, like patient and tumor characteristics, and tumor-specific data. Tumor topography and morphology are graded according to the International Classification of Disease for Oncology (ICD-O). Staging of the tumor is performed according to the corresponding edition of the TNM classification, depending on the year of incidence. Regarding T4 breast cancer, the criteria used in the TNM system have not changed over time. Data on recurrences were collected using two methods: for data between 2005-2008 it was retrospectively gathered from patient files and defined based on existing consensus-based definitions for classifying recurrence. For the period between 2012-2016, the NCR was linked to the PALGA database. Subsequently, only patients suspected of locoregional recurrence were selected. This suspicion was based on an algorithm based on diagnostic codes within the database and dates of occurrence. Consequently, NCR data managers manually reviewed patient files for these selected patients to collect additional data on recurrences, if applicable. Patients not suspected of having a recurrence were not subjected to file reviews, assuming they were free from recurrence.

This study was approved by the privacy committee of the NCR and the NABON-BOOG scientific evaluation committee (reference number: K23.336).

3.2 Study population

The study population included Dutch breast cancer patients with the diagnosis nonmetastatic primary cT4 breast cancer between 2005-2008 and between 2012-2016. These specific time periods were chosen because there is information available on recurrences for these years. However, there were still some patients without follow-up data. These patients were excluded for the recurrence analyses, as well as patients who did not have surgery. Characteristics of both the patient and the tumor, along with treatment types were obtained from the NCR.

3.3 Definitions

Based on the available treatment data, a new variable was created to indicate whether patients received trimodal therapy. Treatment was classified as trimodal if a patient underwent surgery (either mastectomy or breast conserving surgery) and also received both neoadjuvant chemotherapy and adjuvant radiotherapy. Hormone therapy for HR+ tumors or targeted therapy for HER2+ tumors was not taken into account in determining whether a patient received trimodal therapy.

Recurrences were registered in the NCR based on the consensus definitions for classification by Moossdorff et al. Local recurrences were defined as those occurring in the ipsilateral breast tissue, in the surgical scar, or in the biopsy tract. Regional recurrences were defined as those occurring in the ipsilateral lymph nodes in the axilla, around the clavicula, or at the sternum (26). For this study, local and regional recurrences were grouped together as locoregional recurrences (LRR). A recurrence was also considered locoregional in cases where distant metastases were diagnosed within a 30-day timeframe before or after the diagnosis of the locoregional recurrence.

For the calculation of the locoregional recurrence-free survival (RFS) probability, the observation period started from the date of the last surgery date and ended at the date of recurrence diagnosis, end of follow-up, date of death, or the date of occurrence of a second primary tumor.

3.4 Statistical analysis

The dataset was divided into two time periods: 2005-2008 and 2012-2016. Basic descriptive statistics were performed to characterize the study population regarding patient-, tumor-, and treatment related characteristics. This was summarized in a baseline characteristics table. The characteristics were compared between the two time periods using a Pearson's Chi-squared test. Recurrence incidence rates were explored by visualizing the number of T4 breast cancer diagnoses per year in a graph, distinguishing between the four subcategories (T4a-d). The same methodology was applied to analyze incidence rates and characteristics of recurrences among the T4 subcategories, summarized in a

baseline characteristics table and graph over time. To analyze the T4 subcategories, a group was created containing T4ns (not further specified), T4a, and T4c, due to the limited events in these individual groups.

For all analyses of recurrences, the 5 year follow-up time was used and only the first event was used. To analyze time till recurrence occurs, survival analysis was performed. The crude (unadjusted) locoregional recurrence-free survival (RFS) probability was estimated using Kaplan-Meier curves. The Kaplan-Meier curves of the cohorts and T4 subcategories were compared to each other using the log-rank test. Multivariable Cox proportional hazard regression was used to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) to analyze the influence of covariates on recurrence. The variables were selected based on clinical foreknowledge and availability. Variables that did not significantly contribute to the model ($p < 0.1$) were manually removed afterwards. Competing risk analysis was used to estimate the probability of recurrence, while considering the competing risk of mortality or diagnosis of a second primary tumor before a recurrence could occur. The proportional hazard assumption was tested by plotting the scaled Schoenfeld residual of all covariates over time and inspecting them for consistency.

Missing values were imputed using multivariate imputation by chained equations (MICE), assuming the missing data in this study were missing at random. A total of 20 imputed datasets were generated. Convergence of the imputation model was assessed graphically using trace plots. The distributions of the imputed variables in the generated dataset were compared with those in the observed dataset. If the distribution percentages approximately matched, the imputed model was assumed to represent the observed model correctly.

A p-value of ≤0.05 was considered statistically significant. All statistical analyses were performed in the software package STATA version 17.0 (44).

4 Results

4.1 Baseline characteristics

In the Netherlands, 3,659 patients were diagnosed with cT4 breast cancer between 2005-2008 and 2012-2016: 1,654 (45.2%) in 2005-2008, and 2,005 (54.8%) in 2012-2016. Within the total group, 51 (1.39%) male patients were diagnosed with T4 breast cancer. The mean age at diagnosis was 69.6 (±16.5) and ranged from 25 to 100 years. Table 4 summarizes the baseline characteristics.

Table 4 *Baseline characteristics of T4 breast cancer patients in the Netherlands diagnosed between 2005-2008 and 2012-2016 by time cohort categorized by year of diagnosis*

		Time cohort		
Characteristics	**Total**	**2005-2008**	**2012-2016**	**p-value[1]**
Sample size	3,659 (100)	1,654 (45.2)	2,005 (54.8)	
Age at diagnosis, years [mean (SD)]	69.6 (±16.5)	68.3 (±16.9)	70.7 (±16.0)	<0.001
Gender				0.086
Female	3,608 (98.6)	1,637 (99.0)	1,971 (98.3)	
Male	51 (1.4)	17 (1.0)	34 (1.7)	
Age at diagnosis, years				<0.001
<40	123 (3.4)	74 (4.5)	49 (2.4)	
40-49	447 (12.2)	238 (14.4)	209 (10.4)	
50-59	507 (13.9)	237 (14.3)	270 (13.5)	
60-69	603 (16.5)	231 (14.0)	372 (18.6)	
70-79	626 (17.1)	291 (17.6)	335 (16.7)	
80-89	1,017 (27.8)	463 (28.0)	554 (27.6)	
90+	336 (9.2)	120 (7.3)	216 (10.8)	
Clinical T stage				<0.001
4ns	183 (5.0)	183 (11.1)	0 (0.0)	
4A	228 (6.2)	80 (4.8)	148 (7.4)	
4B	2,156 (58.9)	917 (55.4)	1,239 (61.8)	
4C	72 (2.0)	38 (2.3)	34 (1.7)	
4D	1,020 (27.9)	436 (26.4)	584 (29.1)	
Clinical N stage				<0.001
N0	1,170 (32.0)	557 (33.7)	613 (30.6)	
N1	1,807 (49.4)	811 (49.0)	996 (49.7)	
N2	132 (3.6)	57 (3.4)	75 (3.7)	
N3	298 (8.1)	72 (4.4)	226 (11.3)	
Unknown	252 (6.9)	157 (9.5)	95 (4.7)	
Clinical stage				<0.001
IIIB	3,361 (91.9)	1,582 (95.6)	1,779 (88.7)	
IIIC	298 (8.1)	72 (4.4)	226 (11.3)	
Morphology				0.006
Ductal	3,019 (82.5)	1,351 (81.7)	1,668 (83.2)	
Lobular	410 (11.2)	193 (11.7)	217 (10.8)	
Mixed	72 (2.0)	46 (2.8)	26 (1.3)	
Other	158 (4.3)	64 (3.9)	94 (4.7)	
Differentiation grade				<0.001
Grade 1, well differentiated	215 (5.9)	98 (5.9)	117 (5.8)	
Grade 2, moderately differentiated	733 (20.0)	277 (16.7)	456 (22.7)	
Grade 3, poorly differentiated	817 (22.3)	402 (24.3)	415 (20.7)	
Unknown	1,894 (51.8)	877 (53.0)	1,017 (50.7)	
Lateralization				0.948
Left	1,818 (49.7)	823 (49.8)	995 (49.6)	
Right	1,840 (50.3)	831 (50.2)	1,009 (50.3)	
Unknown	1 (0.0)	0 (0.0)	1 (0.0)	

***Table 4** Continued*

Sublocalisation				<0.001
Lateral quadrants	1,012 (27.7)	472 (28.5)	540 (26.9)	
Medial quadrant	355 (9.7)	145 (8.8)	210 (10.5)	
Central parts	521 (14.2)	189 (11.4)	332 (16.6)	
Overlapping lesions	1,539 (42.1)	725 (43.8)	814 (40.6)	
Unknown	232 (6.3)	123 (7.4)	109 (5.4)	
Multifocality				0.461
Yes	637 (17.4)	270 (16.3)	367 (18.3)	
No	2,698 (73.7)	1,187 (71.8)	1,511 (75.4)	
Unknown	324 (8.9)	197 (11.9)	127 (6.3)	
Receptor subtype				0.006
HR+/HER2-	1,854 (50.7)	740 (44.7)	1,114 (55.6)	
HR+/HER2+	368 (10.1)	168 (10.2)	200 (10.0)	
HR-/HER2-	503 (13.7)	219 (13.2)	284 (14.2)	
HR-/HER2+	332 (9.1)	163 (9.9)	169 (8.4)	
Unknown	602 (16.5)	364 (22.0)	238 (11.9)	
Type of surgery				0.034
Breast conserving surgery	243 (6.6)	97 (5.9)	146 (7.3)	
Mastectomy	2,096 (57.3)	983 (59.4)	1,113 (55.5)	
No surgery	1,320 (36.1)	574 (34.7)	746 (37.2)	
Axillary lymph node dissection				<0.001
Yes	1,782 (48.7)	950 (57.4)	832 (41.5)	
No	1,877 (51.3)	704 (42.6)	1,173 (58.5)	
Trimodal therapy				0.181
Yes	1,268 (34.7)	554 (33.5)	714 (35.6)	
No	2,391 (65.3)	1,100 (66.5)	1,291 (64.4)	
Second primary tumor				0.061
Yes	260 (7.1)	132 (8.0)	128 (6.4)	
No	3,399 (92.9)	1,522 (92.0)	1,877 (93.6)	

[1]Pearson's chi-squared test was used for comparison between time periods. The p-value is calculated on known values only.
Abbreviations: SD: standard deviation, ns: not further specified, HR: hormone receptor, HER: human epidermal growth factor.

The mean age at diagnosis increased from 68 to 71 years across the two time cohorts. In the period of 2005-2008, for 11.1% of all diagnoses, the clinical T stage is not further specified than T4. However, in the second cohort, all tumors had a specified clinical T stage. Over time, there was a rise in the incidence of T4a and T4b breast cancer, while T4c and T4d incidences remained relatively stable (Figure 3).The majority of T4 breast cancer cases were clinically diagnosed as T4b (58.9%), N1 (49.4%), and staged as IIIB (91.9%). In the 2012-2016 cohort, there was an increase in the diagnosis of clinical N3 stage, resulting in an increase of clinical stage IIIC (4.4% in 2005-2008 versus 11.3% in 2012-2016).

In both cohorts, most patients presented with ductal carcinoma, a tumor located in overlapping breast lesions, without multifocality, or second primary tumors. The most commonly diagnosed receptor subtype in the total population was HR+/HER2- (50.7%). The proportion of cases with unknown receptor subtype decreased over the two cohorts (from 22.0% to 11.9%). The majority of patients underwent a mastectomy (57.3%), but this rate decreased over time (from 59.4% to 55.5%), with an increase in breast conserving surgery and no surgical treatment. There was a significant decrease in the performance of an axillary lymph node dissection (from 57.4% to 41.5%). Overall, 34.7% of all patients received trimodal therapy, with no significant increase observed over the two cohorts.

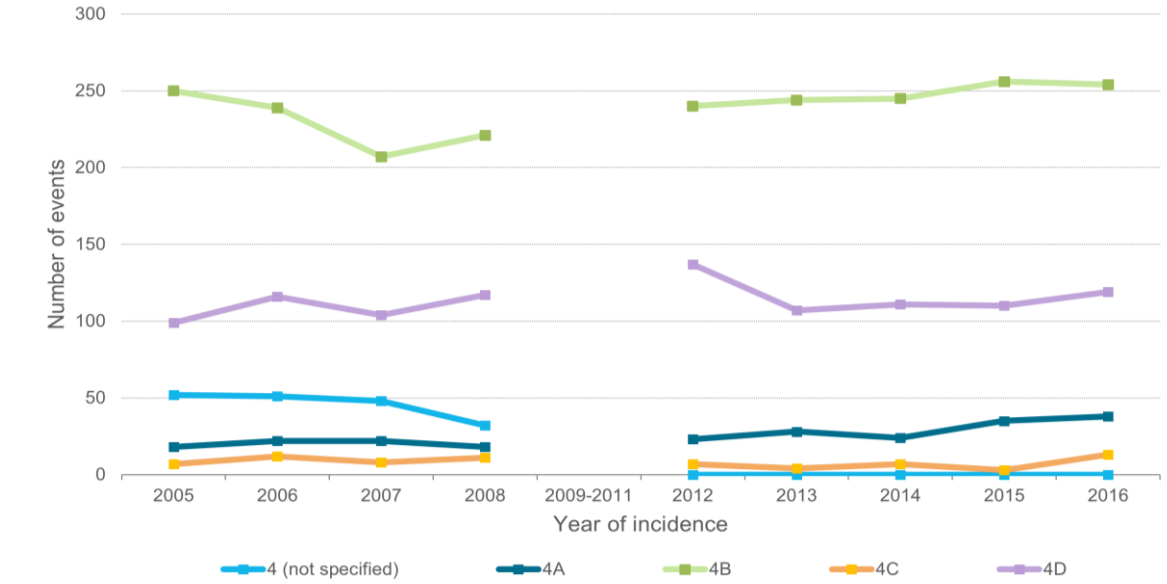

Figure 3 *Distribution of T4 breast cancer subcategories in the Netherlands, from 2005 to 2016. For the period of 2009-2011 there was no data available*

4.2 Locoregional recurrences

The total population at risk of a recurrence consists of 2,339 patients. Of this population, 239 patients had unknown follow-up, leading them to be excluded from the analyses. Among this population, 7.4% (155 patients) experienced a locoregional recurrence (LRR) within 5 years after their last surgery. Across the two cohorts, the LRR rate decreased from 9.9% in 2005-2008 to 5.7% in 2012-2016 (Table 5). Figure 4 illustrates a decrease in the LRR rate starting from 2008. This decrease is also evident in the absolute numbers, becoming noticeable from 2007 onwards.

Table 5 *Incidence of locoregional recurrences by cohort*

Characteristics	Total	Time cohort 2005-2008	Time cohort 2012-2016	p-value
Sample size, [N (%)]	2,100 (100)	841 (40.0)	1,259 (60.0)	-
Locoregional recurrence				<0.001
Yes	155 (7.4)	83 (9.9)	72 (5.7)	
No	1,945 (92.6)	758 (90.1)	1,187 (94.3)	

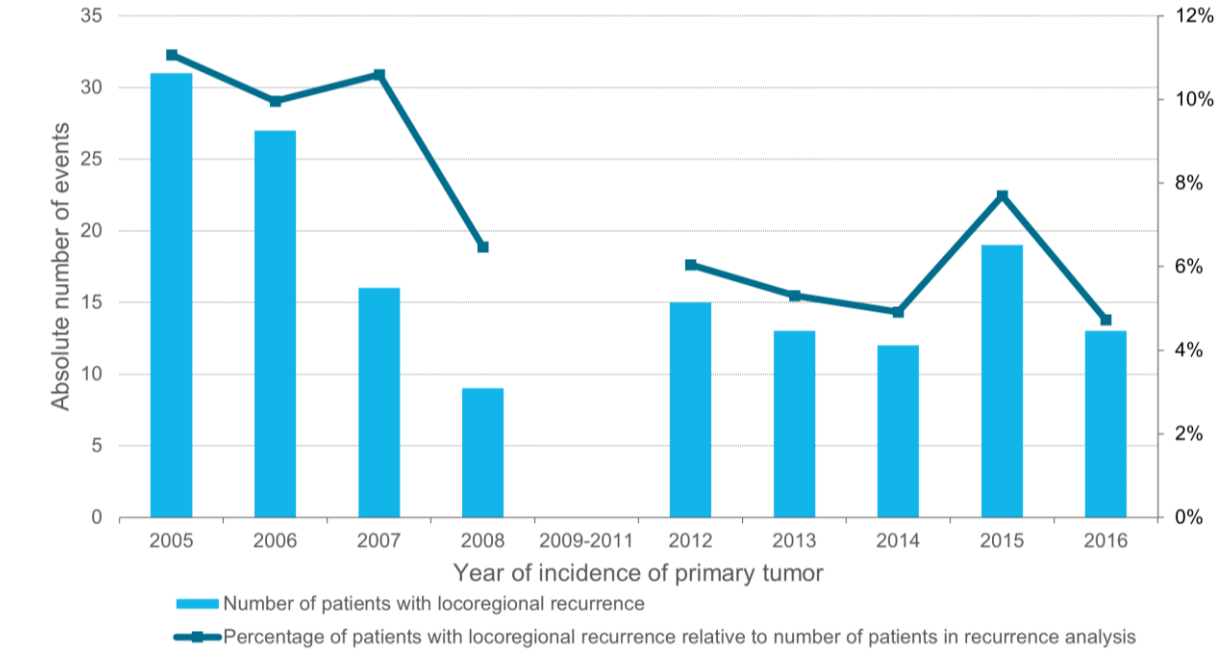

Figure 4 *Absolute and relative incidence of locoregional recurrences. For the period of 2009-2011 there was no data available*

4.3 T4 breast cancer subcategories

In the two cohorts from 2005 to 2008 and 2012 to 2016, 483 (13.2%) patients were diagnosed with T4a, T4c or T4 not further specified, 2,156 (58.9%) with T4b, and 1,020 (27.9%) with T4d breast cancer. Table 6 displays the characteristics of the T4 breast cancer subcategories. The incidence of T4b and T4d breast cancer has increased over the two cohorts, while the incidence of T4ns, T4a, and T4c has decreased. Patients with T4d breast cancer were diagnosed at a significantly younger age than patients with T4b breast cancer (62.8 years versus 72.6 years). In the entire population, no males were diagnosed with T4d breast cancer.

T4d tumors more often have a higher clinical nodal stage than non-inflammatory T4 tumors: 16.1% had N3 stage in T4d compared to 4.1% and 5.3% in the non-inflammatory categories. This also results in a higher clinical stage of the tumor for T4d breast cancer. In all subcategories, most patients presented with ductal carcinoma, a tumor located in overlapping breast lesions, without multifocality or second primary tumors, and receptor subtype HR+/HER2-. In patients with T4d, HR+/HER2- was less common than in T4b (56.1% in T4b compared to 37.2% in T4d), but all the other receptor subtypes had a larger proportion.

An increase can be seen in the performance of a mastectomy across the subcategories: from 11.4% in the group of T4ns, T4a, and T4c, to 55.4% in T4b, reaching the highest at 66.8% in T4d. There is also a more frequent performance of axillary lymph node dissection in T4d (57.9%) compared to T4ns, T4a, and T4c (42.7%), and T4b (45.7%). Patients with T4d breast cancer were more often treated with trimodal therapy than the other subcategories (27.2% for T4b versus 53.4% for T4d).

Table 6 *Baseline characteristics of T4 breast cancer patients in the Netherlands diagnosed between 2005-2008 and 2012-2016 by T4 breast cancer subcategory*

Characteristics	T4ns, T4a, T4c	T4b	T4d	p-value[1]
Sample size, [N (%)]	483 (13.2)	2,156 (58.9)	1,020 (27.9)	
Age at diagnosis, years [mean (SD)]	70.6 (±16.4)	72.6 (±15.5)	62.8 (±16.3)	<0.001
Cohort				<0.001
2005-2008	301 (62.3)	917 (42.5)	436 (42.7)	
2012-2016	182 (37.7)	1,239 (57.5)	584 (57.3)	
Gender				<0.001
Female	474 (98.1)	2,114 (98.1)	1,020 (100.0)	
Male	9 (1.9)	42 (1.9)	0 (0.0)	
Age at diagnosis, years				<0.001
<40	15 (3.1)	35 (1.6)	73 (7.2)	
40-49	52 (10.8)	204 (9.5)	191 (18.7)	
50-59	65 (13.5)	247 (11.5)	195 (19.1)	
60-69	74 (15.3)	336 (15.6)	193 (18.9)	
70-79	81 (16.8)	390 (18.1)	155 (15.2)	
80-89	148 (30.6)	697 (32.3)	172 (16.9)	
90+	48 (9.9)	247 (11.5)	41 (4.0)	
Clinical N stage				<0.001
N0	205 (42.4)	773 (35.9)	192 (18.8)	
N1	205 (42.4)	1,030 (47.8)	572 (56.1)	
N2	14 (2.9)	77 (3.6)	41 (4.0)	
N3	20 (4.1)	114 (5.3)	164 (16.1)	
Unknown	39 (8.1)	162 (7.5)	51 (5.0)	
Clinical stage				<0.001
IIIB	463 (95.9)	2,042 (94.7)	856 (83.9)	
IIIC	20 (4.1)	114 (5.3)	164 (16.1)	
Morphology				0.015
Ductal	378 (78.3)	1,778 (82.5)	863 (84.6)	
Lobular	74 (15.3)	246 (11.4)	90 (8.8)	
Mixed	7 (1.4)	42 (1.9)	23 (2.3)	
Other	24 (5.0)	90 (4.2)	44 (4.3)	

Differentiation grade				<0.001
Grade 1, well differentiated	33 (6.8)	151 (7.0)	31 (3.0)	
Grade 2, moderately differentiated	88 (18.2)	493 (22.9)	152 (14.9)	
Grade 3, poorly differentiated	88 (18.2)	470 (21.8)	259 (25.4)	
Unknown	274 (56.7)	1,042 (48.3)	578 (56.7)	
Lateralization				0.225
Left	257 (53.2)	1,066 (49.4)	495 (48.5)	
Right	226 (46.8)	1,089 (50.5)	525 (51.5)	
Unknown	0 (0.0)	1 (0.1)	0 (0.0)	
Sublocalisation				<0.001
Lateral quadrants	150 (31.1)	619 (28.7)	243 (23.8)	
Medial quadrants	85 (17.6)	206 (9.6)	64 (6.3)	
Central parts	40 (8.3)	379 (17.6)	102 (10.0)	
Overlapping lesions	173 (35.8)	828 (38.4)	538 (52.7)	
Unknown	35 (7.2)	124 (5.8)	73 (7.2)	
Multifocality				0.001
Yes	67 (13.9)	361 (16.7)	209 (20.5)	
No	366 (75.8)	1,628 (75.5)	704 (69.0)	
Unknown	50 (10.4)	167 (7.7)	107 (10.5)	
Receptor subtype				<0.001
HR+/HER2-	265 (54.9)	1,210 (56.1)	379 (37.2)	
HR+/HER2+	34 (7.0)	190 (8.8)	144 (14.1)	
HR-/HER2-	49 (10.1)	236 (10.9)	218 (21.4)	
HR-/HER2+	23 (4.8)	145 (6.7)	164 (16.1)	
Unknown	112 (23.2)	375 (17.4)	115 (11.3)	
Type of surgery				<0.001
Breast conserving surgery	55 (11.4)	157 (7.3)	31 (3.0)	
Mastectomy	221 (45.8)	1,194 (55.4)	681 (66.8)	
No surgery	207 (42.9)	805 (37.3)	308 (30.2)	
Axillary lymph node dissection				<0.001
Yes	206 (42.7)	985 (45.7)	591 (57.9)	
No	277 (57.3)	1,171 (54.3)	429 (42.1)	
Trimodal therapy				<0.001
Yes	136 (28.2)	587 (27.2)	545 (53.4)	
No	347 (71.8)	1,569 (72.8)	475 (46.6)	
Second primary tumor				0.002
Yes	38 (7.9)	127 (5.9)	95 (9.3)	
No	445 (92.1)	2,029 (94.1)	925 (90.7)	

[1]Pearson's chi-squared test was used for comparison between subcategories. The p-value is calculated on known values only.
Abbreviations: SD: standard deviation, ns: not further specified, HR: hormone receptor, HER: human epidermal growth factor.

Within the total population at risk of recurrence (2,100 patients), 7.4% (155 patients) experienced a LRR within 5 years after their last surgery (Table 5). Table 7 shows an increase in the LRR rate across the T4 breast cancer subcategories: from 3.8% in T4ns, T4a, and T4c, to 5.9% in T4b, and further to 11.5% in T4d. Figure 5 displays the LRR rate per T4 subcategory over time, revealing that patients with T4d breast cancer show the highest incidence rate across both cohorts. There were no events of locoregional recurrence in patients with T4c breast cancer.

Table 7 *Incidence of locoregional recurrences by T4 breast cancer subcategory*

Characteristics	T4ns, T4a, T4c	T4b	T4d	p-value
Sample size, [N (%)]	238 (11.3)	1,216 (57.9)	646 (30.8)	
Locoregional recurrence				<0.001
Yes	9 (3.8)	72 (5.9)	74 (11.5)	
No	229 (96.2)	1,144 (94.1)	572 (88.5)	

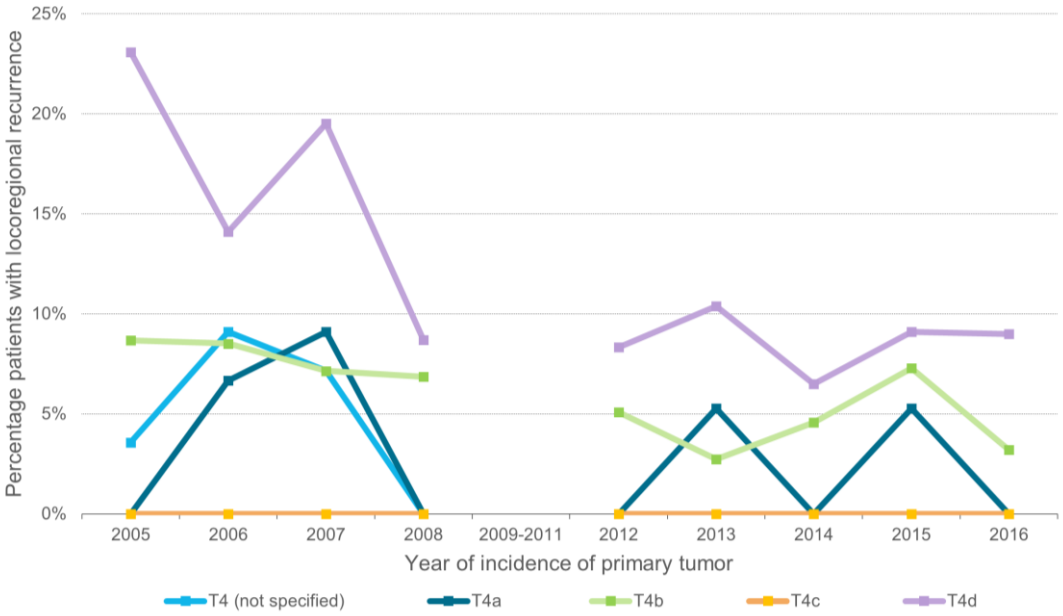

Figure 5 *Percentage of patients with a locoregional recurrence per T4 subcategory relative to the total number of patients at risk for a recurrence*

4.4 Time to recurrence

The median time to recurrence was 14.7 months (446 days) with a interquartile range of 11.0-26.1 months. Figure 6 is a graphical representation of the time to recurrence in boxplots. It shows an increase of two months in median time to recurrence over the cohorts: from 14.2 months (interquartile range 9.8-22.3) in 2005-2008 to 16.2 months (interquartile range 11.9-34.3) in 2012-2016. Among the T4 subcategories, there were also differences in median time to recurrence observed. For the group consisting of T4 not further specified, T4a, and T4c the median time to recurrence is 16.8 months (interquartile range 13.3-46.1). The median time to recurrence is slightly lower for T4b (15.6 months), and for T4d the time to recurrence decreases to 13.8 months (interquartile range 10.2-22.2).

A graphical representation of the five-year locoregional recurrence-free survival (RFS) is presented in Figure 7. Figure 7a shows that the five-year RFS has increased over time, with a significantly higher survival probability for the 2012-2016 cohort (93.0%) compared to the 2005-2008 cohort (88.0%). Figure 7b illustrates a significantly lower five-year RFS for patients with T4d breast cancer (86.1%) than for patients with T4b breast cancer (92.7%), as well as the combined group consisting of T4 not further specified, T4a, and T4c (95.4%).

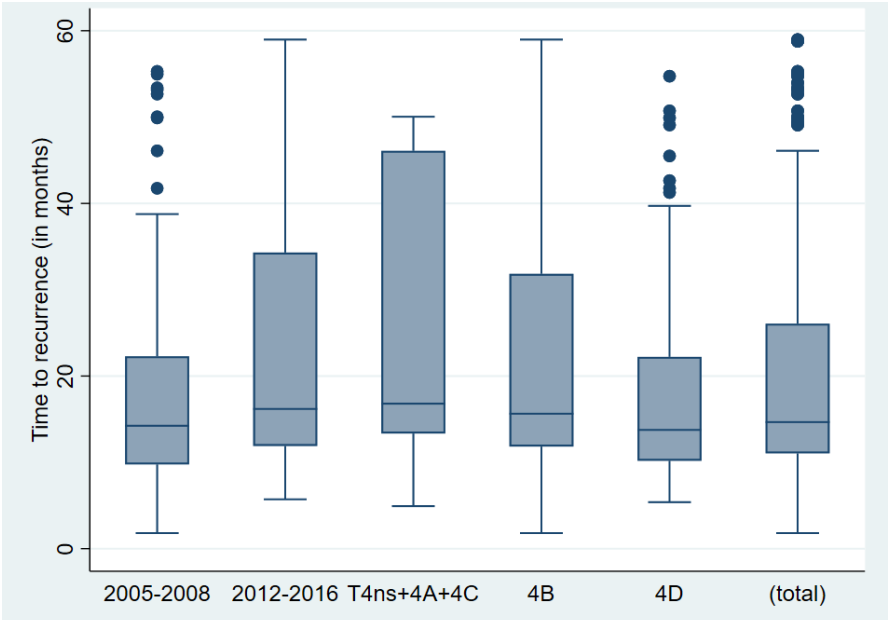

Figure 6 *Boxplots of the time to locoregional recurrence for per time cohort, per T4 breast cancer subcategory, and for the total group*

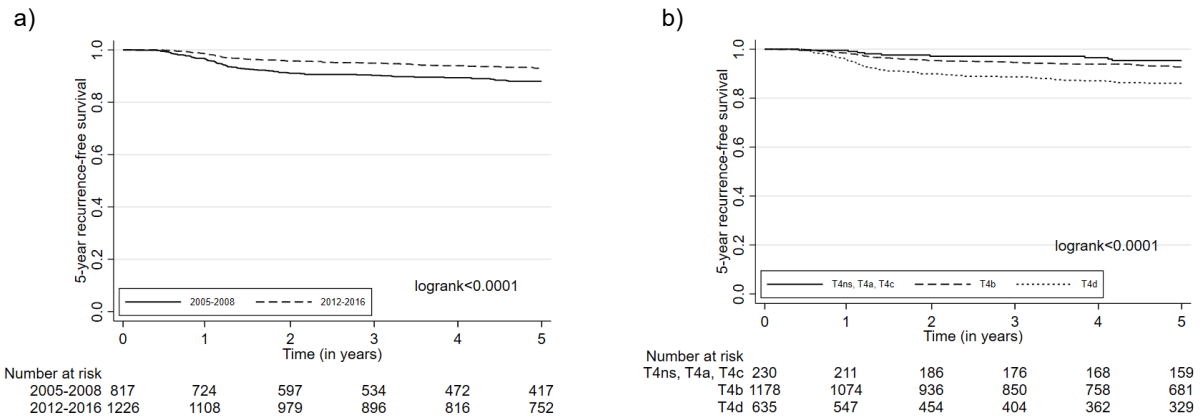

Figure 7 *Unadjusted five-year locoregional recurrence-free survival probability for T4 breast cancer, a) per time cohort, b) per T4 subcategory*

4.5 Risk factors

Before the multivariable Cox proportional hazard regression, missing values were imputed. In total, 252 missing values were present in the variable clinical nodal stage, 1,894 in differentiation grade, 232 in sublocalisation, 324 in multifocality, 179 in hormone receptor status, 527 in HER2 status, and 1 in lateralization (see Table 4). The variable subtype (602 missing values) was imputed afterwards based on the imputed variables of hormone receptor status and HER2 status. After imputation, the distribution percentages closely matched the complete cases.

Table 8 *Adjusted hazard ratios of variables on the five-year recurrence-free survival in T4 breast cancer*

Variables	Hazard Ratio (95% CI)	p-value
Cohort		
2005-2008	1 (ref)	-
2012-2016	0.55 (0.39-0.76)	<0.001
Age at diagnosis, years		
<40	0.79 (0.41-1.53)	0.477
40-49	1 (ref)	-
50-59	0.74 (0.46-1.20)	0.226
60-69	0.52 (0.30-0.89)	0.017
70-79	0.60 (0.34-1.05)	0.072
80-89	0.73 (0.40-1.49)	0.310
90+	2.31 (0.95-5.61)	0.065
Clinical T stage		
4ns, 4A, 4C	0.58 (0.29-1.18)	0.131
4B	1 (ref)	-
4D	1.96 (1.36-2.82)	<0.001
Differentiation grade		
Grade 1, well differentiated	0.15 (0.05-0.49)	0.002
Grade 2, moderately differentiated	0.36 (0.22-0.58)	<0.001
Grade 3, poorly differentiated	1 (ref)	-
Multifocality		
No	1 (ref)	-
Yes	1.95 (1.36-2.82)	<0.001
Receptor subtype		
HR-/HER2-	1 (ref)	-
HR+/HER2-	0.38 (0.25-0.57)	<0.001
HR+/HER2+	0.29 (0.16-0.55)	<0.001
HR-/HER2+	0.39 (0.23-0.64)	<0.001
Trimodal therapy		
No	1 (ref)	-
Yes	0.60 (0.39-0.91)	0.016

Abbreviations: CI: confidence interval, ref: reference category, ns: not further specified, HR: hormone receptor, HER: human epidermal growth factor.

In the first model, the hazard ratios on the five-year recurrence-free survival were corrected for cohort, age group, clinical tumor stage, clinical nodal stage, lateralization, sublocalisation within the breast, multifocality, trimodal therapy, type of surgery, receptor subtype, morphology, axillary lymph node dissection, differentiation grade, hormone therapy and targeted therapy. Manual backwards selection was performed on variables that were not statistically significant ($p < 0.1$), remaining with the seven final variables: cohort, age group, clinical tumor stage, differentiation grade, multifocality, receptor subtype, and trimodal therapy. The adjusted hazard ratios are shown in Table 8. The proportional hazards assumption was tested by plotting the scaled Schoenfeld residuals for each covariate, which showed no trends over time, indicating that the assumption holds.

A decline in locoregional recurrences over time can be seen in Table 8, with a HR of 0.55 (95% CI: 0.39-0.76) for the 2012-2016 cohort. An age above 90 at the time of primary tumor diagnosis appears to be a bad prognostic factor for the five-year recurrence-free survival, indicated by an HR of 2.31 (95% CI: 0.95-5.61), although this is not significant ($p = 0.065$). The HR for T4d breast cancer was 1.96 (95% CI: 1.36-2.82), indicating a significantly higher chance of a locoregional recurrence ($p < 0.001$). Table 8 also shows that multifocality is a significant bad prognostic factor for the five-year recurrence-free survival (HR 1.95 (95% CI: 1.36-2.82).

Regarding differentiation grade, compared to the reference category of grade 3, grade 1 (HR 0.15) and grade 2 (HR 0.36) are identified as good prognostic factors for the recurrence-free survival. Furthermore, any other receptor subtype than the reference category of HR-/HER2- is associated with improved five-year recurrence-free survival. The HR of 0.60 (95% CI: 0.39-0.91) indicates that trimodal therapy is also significantly associated with an increased five-year recurrence-free survival.

The adjusted hazard ratios on the five-year recurrence-free survival were also calculated on the complete cases, which consisted of 1,093 patients. These results are presented in Table 9 in the Supplementary Material. The obtained hazard ratios are mostly consistent with the imputed model, but less accurate.

5 Discussion

This study aimed to analyze trends and risks of recurrence over time in patients with nonmetastatic T4 breast cancer in the Netherlands. To the best of our knowledge, this is the first population-based study to describe recurrence patterns in nonmetastatic T4 breast cancer. Although no direct comparisons are available due to the lack of prior studies in this field, some parallels can be drawn with similar research.

First of all, the T4 breast cancer population in the Netherlands was observed. Over the time of the two cohorts, there were some noticeable changes. In 2005-2008, there were 183 patients (11.1%) without specification of their clinical tumor stage. In the second cohort, this number declined to zero, which can be attributed to either better registration or improved diagnostics. There were also significantly more clinical nodal stage 3 and thus clinical stage IIIC tumors over time, which might be due to advancements in imaging techniques and dissemination research. These changes highlight improvements in diagnostic accuracy and staging over the years. Another notable finding is that only 34.7% of the total population received trimodal therapy, despite it being the guideline for T4 breast cancer patients. This might be due to patients preferences or indicate an area for potential improvement in adherence to treatment guidelines.

5.1 Locoregional recurrences

One of the main findings of this study is the five-year LRR rate of 7.4% among patients with nonmetastatic T4 breast cancer in the Netherlands. This rate is notably higher than the five-year LRR rate of 1.9–4.2% reported by van Hezewijk et al., that included relatively low-risk patients from various countries (45). The difference in LRR rate can be explained by the aggressive nature of T4 breast cancer. However, this comparison is limited due to differences between inclusion criteria of both studies. Another Dutch study on nonmetastatic all-T breast cancer reported five-year LLR rates of 2.7% for local recurrences and 1.5% for regional recurrences (46). Both these differences suggest that the likelihood of locoregional recurrence is higher for T4 breast cancer compared to all-T breast cancer.

Across the two cohorts, a significant decrease in five-year LRR rate was observed from 9.9% in 2005-2008 to 5.7% in 2012-2016. The Kaplan-Meier curve indicated a significant increase in the RFS probability over time. These results are consistent with a previous Dutch study on non-metastatic all-T breast cancer recurrences, which also showed a continuing decrease in LRR rate (46). The improvement occurred despite no significant increase in the use of trimodal therapy, hormone therapy, or targeted therapy over the years, suggesting overall advancements in treatment quality and cancer care. Additionally, the median time to recurrence increased from 14.2 months in 2005-2008 to 16.2 months in 2012-2016. This might be due to the different way of registry of the recurrences, as for the second cohort only pathological confirmed recurrences were collected.

Furthermore, significant differences in five-year LRR rate across T4 breast cancer subcategories were observed. The LRR rate for T4d was the highest at 11.5% compared to 5.9% for T4b and 3.8% for the combined group of T4ns, T4a, and T4c. Patients with T4d breast cancer also had a significantly lower five-year RFS probability of 86.1% compared to 92.7% for T4b, and locoregional recurrences occurred faster than in the other subcategories. These findings align with the understanding that T4d has a worse prognosis than the other subcategories (6). Moreover, significant differences were found in characteristics between the subcategories, especially in clinical nodal stage, differentiation grade, receptor subtype, multifocality, and treatment. These findings highlight the heterogeneity within the T4 classification. Güth et al. proposed to eliminate T4a-c and classify it according to tumor size, rather than invasion of the chest wall or skin, since smaller tumors often have a better prognosis (5, 20). However, given that the LRR rate for T4b remains higher than for all-T breast cancers, it is questionable whether removing T4b from the T4 classification is appropriate.

5.2 Risk factors

To find the effects of different covariates on the five-year RFS, multivariable Cox proportional hazard regression was performed. Clinical tumor stage, differentiation grade, multifocality, receptor subtype, and trimodal therapy were significant prognostic factors for the five-year RFS. This partially agrees with previous Dutch studies on breast cancer recurrences, although it is notable that nodal involvement was not a significant variable in our study and multifocality was, in contrast to these previous studies (46, 47). Clinical nodal stage was expected to be a prognostic variable, it might be due to limited number of patients and recurrences with clinical N2 and N3 stage that these results were not significant.

The good prognostic value of trimodal therapy confirms previous findings that this approach reduces the LRR rates, however, this study was only conducted for patients with T4d breast cancer (48). Given that one of the primary objectives in treating nonmetastatic T4 breast cancer is to minimize the risk of recurrence, these results indicate that trimodal therapy is an effective treatment for these patients. Nonetheless, as previously mentioned, only about a third of all T4 breast cancer patients received trimodal therapy, which is noteworthy and highlights the potential for increased implementation of this treatment approach.

For the receptor subtype, it was shown that HR+/HER2-, HR+/HER2+, and HR-/HER2+ had significantly better five-year RFS compared to reference category HR-/HER2-. This indicates that HR-/HER2- is a bad prognostic factor for five-year RFS in T4 breast cancer patients. T4d patients were much more likely to have the HR-/HER2- subtype than the other subcategories, which may be associated with the higher LRR rate observed in T4d patients. Regular follow-up for breast cancer patients is aimed at detecting locoregional recurrences in an early stage to improve survival (49). The observed risk factors provide valuable insights for clinicians and patients, helping in personalized follow-up decisions.

Variables in the multivariable Cox proportional hazard regression model were selected based on foreknowledge and data availability. However, some potentially influential variables on the 5-year RFS for T4 breast cancer could not be included to the model because the NCR does not register them. For instance, pathologic complete response, which has been shown to increase disease-free survival, might be a prognostic factor in this study (12). Additionally, the NCR does not provide information on comorbidities or actual tumor size, both of which would be valuable factors to consider.

5.3 Strengths

An important strength of this study is the use of nationwide data from the NCR. Data were retrospectively gathered from all hospitals in the Netherlands, making it generalizable results. The largest possible number of T4 breast cancer patients were included in the study, so the sample size is large, creating great statistical power. Furthermore, the population-based nature of this study ensures representativeness and minimizes selection bias (50). Additionally, missing data was imputed by MICE. Since recurrence rates are generally low, the number of events in this study was also low. Due to missing values in the data, some events were excluded from the recurrence analyses. This was dealt with by using MICE, where missing values were replaced by predictions of a regression model, leading to no reduction in sample size for the analyses. The imputed data closely matched the complete cases, but the accuracy of the results was improved.

5.4 Limitations

However, there are some limitations to this study. First, there is a difference in follow-up data collection methods between the time cohorts. For the 2005-2008 cohort, every patient was manually reviewed for recurrence data, whereas for the 2012-2016 cohort, only patients suspected of recurrence were manually reviewed. The patients not suspected of a recurrence were therefore assumed to not have one, which can lead to an underestimation of the total number of recurrences. However, this method of data collection has been validated, demonstrating approximately 90% completeness in identifying all diagnosed locoregional recurrences (results not yet published). Moreover, for the 2012-2016 cohort follow-up was only available for pathologically confirmed recurrences and not for clinical diagnoses, while for 2005-2008 both were available. As locoregional recurrences with also distant metastases diagnosed within the 30-day timeframe, are often only clinically confirmed, there might have been an underestimation of the number of recurrences.

Additionally, for the first cohort of 2005-2008, within the group at risk of recurrence, there were 239 patients (10.2%) with unknown follow-up. For 2005 and 2006, there were 25 patients with unknown follow-up. These were patients with another synchronous not-T4 carcinoma, or a previous tumor diagnosed before of the included years, for which follow-up was not gathered. The largest part of missing follow-up was from 2007 and 2008 (214 patients), during which only 56% of the hospitals provided follow-up data. Patients with unknown follow-up were excluded for the recurrence analyses, potentially affecting the results. However, in comparing the characteristics of the unknown and known follow-up groups, no significant differences were found (unpublished results).

Furthermore, for the recurrence analyses the 5-year follow-up time was used, due to availability of the data. Only for the year 2005 there was data on 10-year follow-up. To be able to compare the results data has been cut off at five

years. Also for the follow-up of the second cohort only recurrences within five years after last surgery have been taken into account. Previous research has shown that it is important to at least have 10 years of follow-up when studying recurrences (14, 47). However, as the median time to recurrence was 14.7 months (interquartile range: 11.0-26.1 months), it seems recurrences occur faster in T4 breast cancer and therefore 5-year follow-up is most probably long enough for this group. Lastly, some groups had low number of patients and events, especially in the T4 subcategories. There were only 228 patients with T4a breast cancer and 72 with T4c, resulting in a low number of recurrences in these groups. These subcategories were grouped together with the not further specified clinical tumor stage. Therefore this study cannot provide any conclusions on recurrences for T4a and T4c.

5.5 Future research

As this research is one of the first in the field to explore recurrences within T4 breast cancer, there are numerous possibilities for further studies. This study focused solely on recurrence-free survival. Given that locoregional recurrences negatively impact long-term survival, a follow-up study would be to investigate overall, relative, and cause-specific survival of T4 breast cancer patients with and without recurrences (51). This would provide more insights into the effect of recurrences on survival of T4 breast cancer patients, contributing to more realistic prognosis for these patients.

Another potential area of research would be to study subsequent recurrences and distant metastases in patients with T4 breast cancer, as this study only focused on the first event of a locoregional recurrence. Previous studies have shown a high risk of subsequent recurrences in breast cancer (47). Since the incidence rates of locoregional recurrences are higher for T4 breast cancer compared to general breast cancer, subsequent recurrences might also occur more often. Understanding these trends could help in developing more individualized follow-up plans.

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6 Conclusion

This study provided important insights into the trends and risks of recurrence in nonmetastatic T4 breast cancer patients in the Netherlands. The overall five-year locoregional recurrence rate was found to be 7.4%, which, while relatively low, is higher compared to breast cancer in general, indicating a higher chance of recurrences in T4 breast cancer. Furthermore, a decreasing trend in the LRR rate and an improvement in the recurrence-free survival probability over time was found.

Among the different T4 subcategories, T4d breast cancer showed the highest LRR rate and a faster occurrence of recurrences. Patients with T4d also had a poorer RFS probability compared to other T4 subcategories, highlighting the particularly aggressive nature of T4d breast cancer. Significant prognostic factors for the five-year RFS of nonmetastatic T4 breast cancer included clinical tumor stage, differentiation grade, multifocality, receptor subtype, and trimodal therapy.

The knowledge gained from this study on locoregional recurrence trends and risk factors in nonmetastatic T4 breast cancer can help in developing patient-tailored treatments and individualized follow-up strategies, potentially improving patient outcomes and quality of care.

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B2 Supplementary Material

Table 9 *Adjusted hazard ratios of variables on the five-year risk on recurrence in T4 breast cancer with complete cases*

Variables	Hazard Ratio (95% CI)	p-value
Cohort		
2005-2008	1 (ref)	-
2012-2016	0.54 (0.33-0.87)	0.011
Age at diagnosis, years		
<40	1.18 (0.46-3.03)	0.735
40-49	1 (ref)	-
50-59	0.88 (0.40-1.93)	0.748
60-69	0.85 (0.39-1.90)	0.700
70-79	0.92 (0.41-2.05)	0.842
80-89	0.79 (0.31-2.01)	0.626
90+	2.48 (0.65-9.53)	0.185
Clinical T stage		
4ns, 4A, 4C	0.61 (0.21-1.75)	0.359
4B	1 (ref)	-
4D	2.10 (1.23-3.58)	0.007
Differentiation grade		
Grade 1, well differentiated	0.26 (0.08-0.86)	0.027
Grade 2, moderately differentiated	0.37 (0.20-0.67)	0.001
Grade 3, poorly differentiated	1 (ref)	-
Multifocality		
No	1 (ref)	-
Yes	2.07 (1.24-3.47)	0.005
Receptor subtype		
HR-/HER2-	1 (ref)	-
HR+/HER2-	0.33 (0.18-0.59)	<0.001
HR+/HER2+	0.27 (0.12-0.67)	0.004
HR-/HER2+	0.38 (0.18-0.84)	0.016
Trimodal therapy		
No	1 (ref)	-
Yes	0.79 (0.44-1.42)	0.424

Abbreviations: CI: confidence interval, ns: not further specified, HR: hormone receptor, HER: human epidermal growth factor.