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EPIDEMIOLOGY

Inflammatory breast cancer in the Netherlands; improved survival over the last decades

D. J. P. van Uden[1] · R. Bretveld[2] · S. Siesling[2,3] · J. H. W. de Wilt[1] · C. F. J. M. Blanken-Peeters[4]

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Abstract
Purpose Locally advanced breast cancer (LABC) includes inflammatory breast cancer (IBC) as well as non-inflammatory LABC (NI-LABC). The aim of this population-based study was to compare the tumour characteristics, treatment and relative survival of IBC and NI-LABC patients.
Methods Patients with either IBC (cT4d) or NI-LABC (cT4a–c) were identified from the nationwide Netherlands Cancer Registry from the period 1989–2015. In each group, patients are divided into three time periods in order to perform a trend analysis: 1989–1997, 1998–2006, and 2007–2015.
Results IBC comprised 1.1% and NI-LABC 4.6% of all diagnosed breast cancer patients. IBC patients showed more nodal metastases (77.8 vs. 69.7%, $P < 0.001$) and distant metastases (39.7 vs. 34.1%, $P < 0.001$). IBC tumours were more often triple negative (23.2 vs. 12.8%, $P < 0.001$) and poorly differentiated (69.8 vs. 53.8%, $P < 0.001$). Trimodality therapy (neoadjuvant chemotherapy, surgery and adjuvant radiotherapy) was more often applied over time in both groups (IBC: 23.7%–56.0%–68.6%; NI-LABC: 3.7%–25.9%–43.6%; $P_{trend} < 0.001$). In IBC patients, relative 5-year survival was significantly shorter than in patients with NI-LABC (30.2 vs. 45.1%, $P < 0.001$). The relative survival significantly improved for IBC from 17.2% (1989–1997) to 30.0 and 38.9% for the last two time periods (1998–2006: $P < 0.001$; 2007–2015: $P < 0.001$). In contrast, survival did not significantly improve in NI-LABC breast cancer: from 44.7% (1989–1997) to 44.0 and 48.4% (1998–2006: $P = 0.483$; 2007–2015: $P = 0.091$).
Conclusions IBC has tumour characteristics that determine its aggressive biology compared to NI-LABC. Trimodality therapy was increasingly applied in both groups, but did not improve survival in NI-LABC. Although relative survival in IBC patients has improved during the last decades, it remains a disease with a dismal prognosis.

Keywords Locally advanced breast cancer · Inflammatory breast cancer · Epidemiology · Treatment · Survival · The Netherlands

✉ D. J. P. van Uden
djpvanuden@gmail.com

[1] Department of Surgical Oncology, Radboud University Medical Center Nijmegen, Geert Grootplein Zuid 10, 6525 GA Nijmegen, The Netherlands

[2] Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, Hoog Catharijne, Godebaldkwartier 419, 3511 DT Utrecht, The Netherlands

[3] Department of Health Technology and Services Research, MIRA Institute for Biomedical Technology and Technical Medicine, Drienerlolaan 5, 7522 NB Enschede, The Netherlands

[4] Department of Surgery, Rijnstate Hospital, Arnhem, Wagnerlaan 55, 6815 AD Arnhem, The Netherlands

Introduction

Inflammatory breast cancer (IBC, cT4d) is rare and represents less than 3% of breast cancer diagnoses annually, as found in the SEER database [1]. Even though IBC can be confused with non-inflammatory locally advanced breast cancer (NI-LABC, cT4a–c), it is a distinct form of locally advanced breast cancer (LABC) with unique clinico-pathophysiological features and a worse prognosis [1]. IBC is clinically characterized by diffuse induration of the skin with an erysipeloid edge, which should be present for the diagnosis [2]. Although detection of tumour emboli in

dermal lymphatic vessels is supportive of the diagnosis, it is not required. Furthermore, dermal lymphatic invasion without typical clinical findings is not sufficient for a diagnosis of IBC [3].

At first presentation, the majority of IBC patients have lymph node involvement and 30% already have metastases, of which lungs, liver, brain and skeleton are most frequent [4]. The current management of non-metastatic IBC cases include neoadjuvant chemotherapy, complete mastectomy with axillary lymph node dissection and locoregional adjuvant radiotherapy (trimodality therapy). Neoadjuvant and adjuvant trastuzumab, and adjuvant antihormonal therapy are applied in patients with Human Epidermal growth factor Receptor 2 (HER2) and/or estrogen/progesterone (ER/PR)-positive tumours, respectively [4]. Although this multidisciplinary therapeutic approach has improved the survival in these subgroups in recent years, IBC remains a disease with a poor prognosis [5].

To date, epidemiological research has been limited by variety in case definition and the relatively small number of patients, leading to contradicting data concerning incidence of IBC within one country [6].

We aimed to examine characteristics, treatment and survival of patients with inflammatory breast cancer in a nationwide population-based study in which the definition for IBC has not changed over time. This cohort was compared to patients with NI-LABC.

Materials and methods

Data source

The most important statistics on cancer in the Netherlands are registered in the nationwide population-based Netherlands Cancer Registry (NCR), which is hosted by the Netherlands Comprehensive Cancer Centre Organisation (IKNL). The NCR is a nationwide prospective population-based cancer registry in which all newly pathologically confirmed malignancies in the Netherlands are recorded. New malignancies are notified through the national Pathology Archive, which collects all pathology reports of Dutch hospitals. Trained registrars from the NCR collect directly from the patient's medical records the patient and tumour characteristics, as well as the treatment type for the primary tumour. Data completeness is estimated to be at least 95% [7]. Morphology and differentiation are graded according to the international classification of diseases for oncology (ICD-O) [8]. Staging is performed according to the TNM classification. The specific edition depended on the year of incidence [9–13]. With respect to T4 breast cancer, the criteria used in the TNM system have not changed over time.

The municipal administration is used to verify the patient's vital status and, if applicable, date of death. Follow-up has been completed until December 31, 2015, except for patients who emigrated out of the Netherlands. The privacy committee of the Netherlands Cancer Registry has approved the study.

Patients and study variables

Patients clinically diagnosed from 1989 to 2015 with T4 breast cancer were identified: cT4 not further specified; cT4a; cT4b; cT4c; and cT4d. Patients with all stages (including stage IV) were included. Patients diagnosed based on autopsy were excluded. The NCR database does not contain data on symptoms or interval between complaints and diagnosis.

Patient and tumour characteristics, as well as treatment types, have been selected. Estrogen and progesterone receptors are registered from 2005 onwards. HER-2 (Human Epidermal Growth Factor Receptor 2) is registered from 2006 onwards. Lymph node involvement pertains to residual disease, as was found at postoperative pathologic evaluation (pN), even after neoadjuvant systemic therapy (ypN).

Data of completeness of resection is reported from 2009 onwards. Chemotherapy and hormonal therapy are reported as administered or not administered, since the specific agents are not registered in the period under study. Specific treatments initiated at a later time are not registered.

Statistical analysis

In order to perform a trend analysis for treatments of IBC and NI-LABC, patients are divided into three time periods: 1989–1997, 1998–2006, and 2007–2015. Data is compared between the different groups using X^2 tests for categorical variables and non-parametric approaches (Student's t test) for continuous variables.

The overall survival is calculated for all patients based on the date of diagnosis to the date of death from any cause, or the follow-up cutoff. The relative 5-year survival rates are estimated using the Ederer II method and stratified by period. Dutch national life tables of the Central Bureau of Statistics (CBS) are used to estimate the expected survival of the general population. For 2007–2015, survival of IBC patients receiving trimodality therapy was compared to patients solely undergoing a surgical procedure. All statistical analyses are performed in the software package STATA version 13.1 (StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP; 2013). A non-parametric test of trends is prepared. To determine significance, the alpha value is set to ≤ 0.05.

Results

General patient characteristics

From 1989 to 2015, a total of 313,466 patients with breast cancer have been collected in the Dutch nationwide cancer registry. A total of 17,869 patients (5.7%) have been diagnosed with LABC, of which 3481 patients (1.1% of the total population) have IBC (cT4d). Within the total group, 1363 male patients (0.5%) were diagnosed with breast cancer. Of the 177 men (1.0%) who are diagnosed with T4-carcinoma, six were diagnosed with IBC (0.2%).

The mean age at diagnosis (years ± standard deviation) was lower for IBC patients (61.6 ± 15.4) compared to cT4a–c (69.1 ± 15.0, $P < 0.001$). The general clinicopathological characteristics of all patients with locally advanced breast cancer are listed in Table 1.

Distribution over time of locally advanced (T4) breast cancer subtypes

The incidence rates of IBC increase during all years of the study (Fig. 1). In contrast, T4 non-specified and T4b breast cancer both decrease during the covered time period.

Histopathologic features of primary tumours

Ductal cancer was the most common type of breast cancer in both groups. Patients with IBC were less likely to present with lobular cancer ($P = 0.001$). Compared to NI-LABC, poorly differentiated tumours were more commonly observed in IBC ($P < 0.001$). With respect to hormone and HER2 status, IBC tumours were more often estrogen receptor and progesteron receptor negative ($P < 0.001$). IBC tumours were more often HER2 positive ($P < 0.001$). In case of HER2 negativity, IBC cases were more often (23.3% of the cases, 2005–2015) triple negative ($P < 0.001$).

Locoregional and distant metastases

Postoperative pathologic evaluation revealed more lymph node involvement in IBC (77.8 vs. 69.7%, $P < 0.001$,), with also an observed difference in number of involved lymph nodes (LNs): 4–9 LNs (15.1 vs 10.9%, $P < 0.001$); ≥10 LNs (14.5 vs. 6.0%, $P < 0.003$). At first presentation, 1276 patients with IBC (39.7%) and 4301 (34.1%) patients with NI-LABC have distant metastases ($P < 0.001$).

Table 1 Clinicopathological characteristics of all patients with T4a–c versus T4d breast cancer

	T4a–c $N = 14.388$	T4d $N = 3.481$	P value[a]
Mean age (years)	69.1	61.6	<0.001
Age groups (years)			
≥70	7.833 (54.4)	1.161 (33.4)	0.001
Tumor subtype			
Intraductal	8.890 (61.8)	2.209 (63.5)	Reference
Lobular	1.878 (13.0)	379 (10.9)	0.001
Other	3.620 (25.2)	893 (25.6)	0.870
Grade			
1	514 (8.59)	57 (4.7)	Reference
2	2.251 (37.6)	310 (25.5)	0.155
3	3.219 (53.8)	849 (69.8)	<0.001
ER status[#]			
Positive	3706 (80.4)	1.079 (58.8)	Reference
Negative	905 (19.6)	769 (41.2)	<0.001
PgR status[#]			
Positive	2.752 (61.1)	750 (41.1)	Reference
Negative	1751 (38.9)	1076 (58.9)	<0.001
HER2 status[#]			
Positive	703 (18.5)	565 (34.0)	Reference
Negative	3.106 (81.5)	1098 (66.0)	<0.001
Triple negative[#]	357(12.8)	288 (23.3)	<0.001
No. Positive LNs[¥]			
0	3.973 (30.3)	721 (22.2)	Reference
1–3 positive LNs	6.929 (52.8)	1.567 (48.2)	<0.001
4–9 positive LNs	1.424 (10.9)	489 (15.1)	<0.001
≥10 positive LNs	787 (6.0)	472 (14.5)	0.003
Residual tumour			
None	3.530 (86.7)	998 (84.7)	Reference
Microscopic	361 (8.9)	94 (7.9)	0.497
Macroscopic	181 (4.4)	87 (7.4)	<0.001
Distant metastases			
Yes	4.301 (34.1)	1.275 (39.7)	<0.001

T4 histologic proven malignancy, locally advanced breast cancer not further specified; *T4a* Extension to chest wall, not including only pectoralis muscle adherence/invasion; *T4b* Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma; *T4c* Both T4a and T4b. T4d (IBC) Inflammatory carcinoma, diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass

ER estrogen receptor, *PgR* progesteron receptor, *HER2* human epithelial growth factor receptor 2, *LNs* lymph nodes, *RR* rate ratio, *CI* confidence interval

[#] From 2005 onwards

[¥] Lymph nodes found at postoperative pathologic evaluation

[a] Two-sided P value for difference between two cohorts

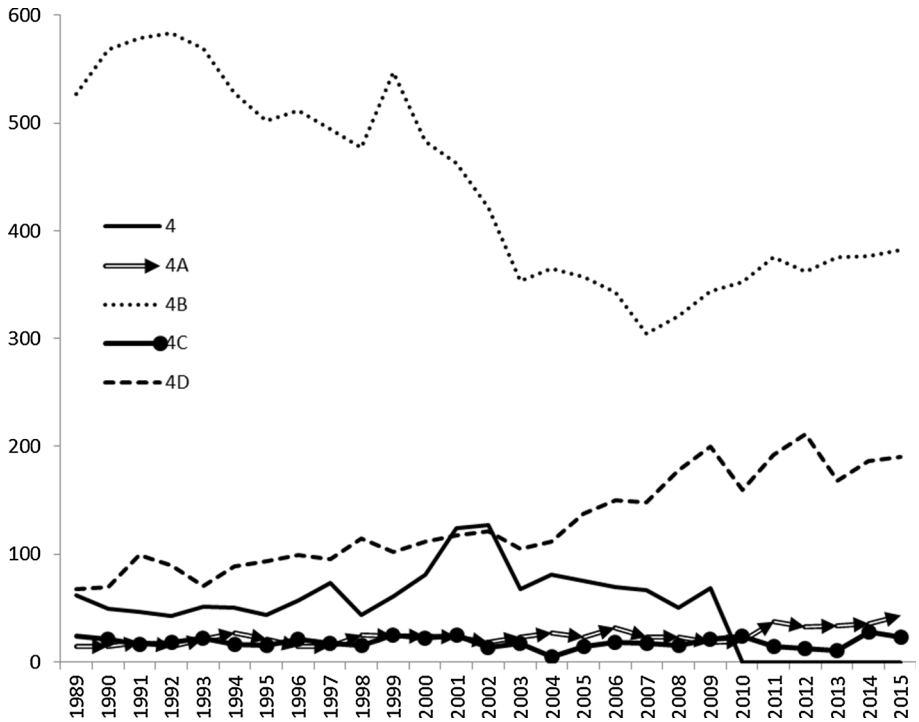


Fig. 1 Distribution by T4 breast cancer subtypes in the Netherlands, from 1989 to 2015. T4 represents the group of "not further specified" tumours

Table 2 Treatment characteristics of T4d breast cancer

	1989–1997 $N = 775$	1998–2006 $N = 1073$	2007–2015 $N = 1633$	P_{trend}
No Surgery	513 (66.2)	557 (51.9)	792 (48.5)	<0.001
Type of other treatment				0.386
No treatment	16 (3.1)	46 (8.3)	61 (7.7)	
RT	29 (5.6)	15 (2.7)	24 (3.0)	
CT	113 (22.0)	120 (21.5)	118 (14.9)	
HT	113 (22.0)	154 (27.7)	265 (33.5)	
RT and CT	201 (39.2)	184 (33.0)	237 (29.9)	
NFS	41 (8.0)	38 (6.8)	87 (11.0)	
Surgery	262 (33.8)	516 (48.1)	841 (51.5)	<0.001
Type of surgery				0.218
BCT−ALND	5 (2.2)	7 (1.4)	13 (1.6)	
BCT+ALND	1 (0.4)	12 (2.3)	20 (2.4)	
UM+ALND	192 (83.1)	420 (82.0)	658 (80.0)	
UM−ALND	33 (14.3)	73 (14.3)	131 (15.9)	
Neoadjuvant CT	93 (35.5)	361 (70.0)	699 (83.1)	<0.001
Adjuvant CT	59 (22.5)	95 (18.4)	62 (3.7)	<0.001
Adjuvant RT	158 (60.3)	385 (74.6)	656 (78.0)	<0.001
Triple therapy	62 (23.7)	289 (56.0)	577 (68.6)	<0.001

BCT breast conserving therapy, *UM* unilateral mastectomy, *ALND* axillary lymph node dissection, *CT* chemotherapy, *RT* radiation therapy, *HT* hormone therapy, *NFS* not further specified

Treatment

Treatment characteristics are presented in Table 2, subdivided by tumour type (Table 2 for IBC, Table 3 for NI-LABC and Table 4 for a comparison between both groups). A total of 672 patients (3.8%) have not received any treatment, which is similar for both groups.

Table 3 Treatment characteristics of T4a–c breast cancer

	1989–1997 $N = 5670$	1998–2006 $N = 4905$	2007–2015 $N = 3813$	P_{trend}
No Surgery	2338 (41.2)	2280 (46.5)	2129 (55.8)	
Type of other treatment				0.048
No treatment	134 (5.7)	202 (8.9)	213 (10.0)	
RT	119 (5.1)	46 (2.0)	35 (1.6)	
CT	291 (12.5)	249 (10.9)	123 (5.8)	
HT	963 (41.2)	1088 (47.7)	1205 (56.6)	
RT and CT	609 (26.1)	447 (19.6)	311 (14.6)	
NFS	222 (9.5)	248 (10.9)	242 (11.4)	
Surgery	3332 (58.8)	2625 (53.5)	1684 (44.2)	<0.001
Type of surgery				0.001
BCT−ALND	63 (2.4)	113 (4.3)	104 (6.3)	
BCT+ALND	227 (8.6)	121 (4.6)	67 (4.1)	
UM+ALND	2003 (75.5)	2,004 (76.6)	1155 (70.0)	
UM−ALND	359 (13.5)	378 (14.5)	323 (19.6)	
Neoadjuvant CT	201 (6.0)	828 (31.5)	870 (51.7)	<0.001
Adjuvant CT	348 (10.4)	390 (14.8)	155 (9.2)	0.986
Adjuvant RT	1705 (51.2)	1600 (61.0)	1163 (69.0)	<0.001
Triple therapy	123 (3.7)	680 (25.9)	734 (43.6)	<0.001

BCT breast conserving therapy, *UM* unilateral mastectomy, *ALND* axillary lymph node dissection, *CT* chemotherapy, *RT* radiation therapy, *HT* hormone therapy, *NFS* not further specified

Table 4 Treatment differences between T4a–c and T4d breast cancer

	T4a–c $N = 14.388$	T4d $N = 3.481$	P value[a]
No surgery	6747 (46.9)	1862 (53.5)	
Other treatment			
No treatment	549 (8.1)	123 (6.6)	Reference
RT	200 (3.0)	68 (3.7)	0.015
CT	663 (9.8)	351 (18.9)	<0.001
HT	3256 (48.3)	532 (28.6)	0.004
RT and CT	1367 (20.3)	622 (33.4)	<0.001
NFS	712 (10.6)	166 (8.9)	0.763
Surgery	7641 (53.1)	1619 (46.5)	<0.001
Type of surgery			
BCT−ALND	280 (4.1)	25 (1.6)	<0.001
BCT+ALND	415 (6.0)	33 (2.1)	<0.001
UM+ALND	5162 (74.6)	1270 (81.2)	Reference
UM−ALND	1060 (15.3)	237 (15.1)	0.222
Neoadjuvant CT	1899 (24.9)	1153 (71.2)	<0.001
Adjuvant CT	755 (9.9)	139 (8.6)	0.063
Adjuvant RT	4468 (58.5)	1.199 (74.1)	<0.001
Triple therapy	1537 (20.1)	928 (57.3)	<0.001

BCT breast conserving therapy, *UM* unilateral mastectomy, *ALND* axillary lymph node dissection, *CT* chemotherapy, *RT* radiation therapy, *HT* hormone therapy, *NFS* not further specified

[a] Two-sided P value for difference between two cohorts

Chemotherapy

Chemotherapy, neoadjuvant as well as adjuvant, was administered more often in case of IBC than in case of NI-LABC. A larger percentage of IBC patients underwent chemotherapy as monotherapeutical treatment (18.9 vs. 9.8%, $P < 0.001$), and neoadjuvant chemotherapy was more frequently administered in IBC (71.2 vs. 24.9%, $P < 0.001$). The administration of neoadjuvant chemotherapy significantly increases over time in both groups.

Surgery

Surgical intervention was less often performed on IBC patients (46.5%) compared to NI-LABC (53.1%) ($P < 0.001$). A significant increase in surgical procedures is observed for IBC ($P_{trend} < 0.001$) over time, with a simultaneous significant decrease in the NI-LABC group ($P_{trend} < 0.001$).

Mastectomy with axillary lymph node dissection (ALND) was the most frequently performed surgical intervention in both groups. In IBC, 1507 patients (93.0% of operated patients) underwent mastectomy compared to 81.4% of operated patients with NI-LABC, which did not differ significantly.

Patients with IBC were less likely to undergo breast conserving therapy. A total of 58 IBC patients (3.6%)

underwent breast conserving therapy, of which 33 patients were operated in the interval 2007–2015.

In both groups, 17.2% of stage IV patients underwent a surgical procedure (IBC: 219 (/1275); NIBC: 737 (/4301). Mastectomy is performed in 15.1% of patients with metastatic IBC and 14.1% in NIBC.

With respect to surgical completeness of resection, macroscopic tumour residue occured most often for IBC ($P < 0.001$). Microscopic tumour residue was however similar in both groups ($P = 0.497$). In patients with complete surgery (either without neoadjuvant therapy or after neoadjuvant therapy), no residual tumour tissue was left.

Hormone therapy

Antihormonal therapy was less frequently administered in IBC. Of all IBC patients, 1718 (49.3%) received antihormonal therapy. Only in recent years (2007–2015), receptor status was registered, and of the 936 ER-positive patients, 84.4% received antihormonal therapy. Monotherapeutical antihormonal therapy was less often administered in IBC compared to NI-LABC ($P = 0.004$). Since estrogen/progesterone and HER-2 receptors are registered from 2005, and 2006, respectively, the actual change over time of antihormonal treatment therefore could not be assessed.

Radiation therapy

Radiation therapy was applied as monotherapy in 268 patients and more often in patients with IBC ($P = 0.015$). Patients with IBC more often received chemotherapy and radiation therapy as the sole treatment modalities ($P < 0.001$). As an adjuvant to surgery, postoperative radiation therapy was performed in 74.1% of IBC patients who underwent a surgical procedure. Postoperative radiation therapy was given significantly more often in both groups over time ($P_{trend} < 0.001$).

Trends in multidisciplinary treatment between 1989 and 2015

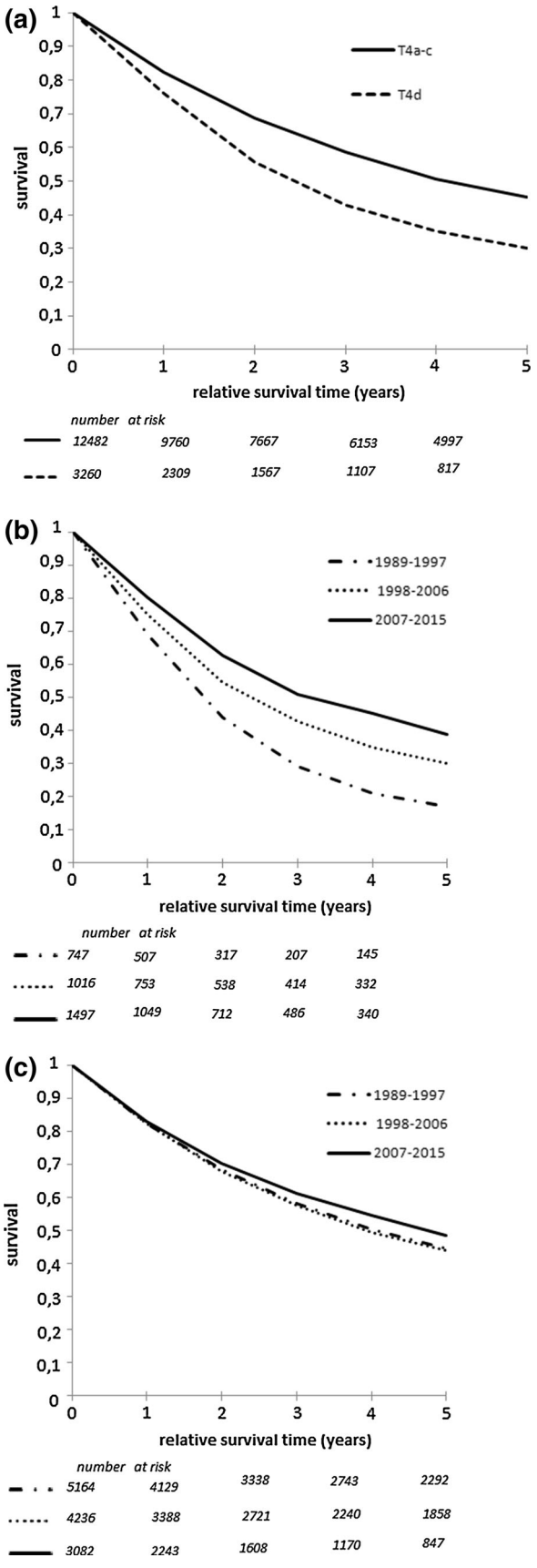
Of all operated patients with T4 breast cancer, 2465 patients (26.6%) have received trimodalilty therapy. With respect to the entire cohort of IBC, 26.7% received trimodality therapy. Of the patients operated on, 57.3% underwent this treatment regimen. Patients with IBC were more likely to receive trimodality therapy ($P < 0.001$). Over time, the use of trimodality therapy has significantly increased for both groups of locally advanced breast cancer ($P_{trend} < 0.001$).

Survival outcomes

The relative overall survival was significantly shorter for patients with IBC compared to NI-LABC (Fig. 2a). In IBC, relative 5-year survival was significantly shorter than in patients with NI-LABC (30.2 vs. 45.1%, $P < 0.001$). The relative survival of IBC patients significantly improved from 17.2% (1989–1997) to 30.0 and 38.9% during the last two time periods (1998–2006: $P < 0.001$; 2007–2015: $P < 0.001$) (Fig. 2b). In contrast, the survival did not significantly improve in cT4a–c breast cancer, from 44.7% (1989–1997) to 44.0 and 48.4% (1998–2006: $P = 0.483$; 2007–2015: $P = 0.091$) (Fig. 2c). Patients with metastatic disease were included in this analysis (IBC: 1.275(39.7%); NI-LABC: (4.301) 34.1%). The relative survival of IBC patients receiving trimodality therapy is significantly better than the survival of IBC patients treated with a surgical procedure without (neo)adjuvant therapy (Fig. 3). This was only analysed for 2007–2015.

Discussion

The results of this study accentuate the more aggressive biology and unfavourable outcome of IBC compared to NI-LABC. IBC comprises 1.1% of the total incidence of breast cancer, and we demonstrated a lower incidence of IBC in men compared to women (0.2 vs. 1.1%), which is also displayed in other population-based studies [14].The incidence of IBC seems to increase which might be the result of improved registration and not an actual rise in incidence as reflected by the simultaneous decrease of the T4 not further specified (NFS) group (Fig. 1). Furthermore, increased awareness among physicians concerning the clinical symptoms of IBC may have contributed to an improved registration. However, the major difficulties in collecting data on IBC properly are due to its definition and its partial similarity with T4b breast cancer with respect to clinical appearance. The data of this study suggest a shift in T4 substages, with a decrease in T4b and an increase in IBC over the last two decades (without a change of criteria according to TNM-staging) [9–13].The non-specificity of the clinical criteria has resulted in variability of case definition, which has limited the possibility to compare the results of studies focusing on the prognostic outcomes patients with IBC [15]. Other prognostic factors in breast cancer are accurate staging of both the primary tumour and the axillary lymph nodes (LNs). In case of pathologic nodal involvement, the overall survival is decreased and the locoregional recurrence risk increased with a growing number of involved LNs [16]. In our study, over 77% of IBC patients had nodal metastases compared to and 69.7%



◀**Fig. 2** **a** Relative survival curves for T4a–c and T4d breast cancer. **b** Relative survival curves for T4d breast cancer per time interval. **c** Relative survival curves for T4a–c breast cancer per time interval

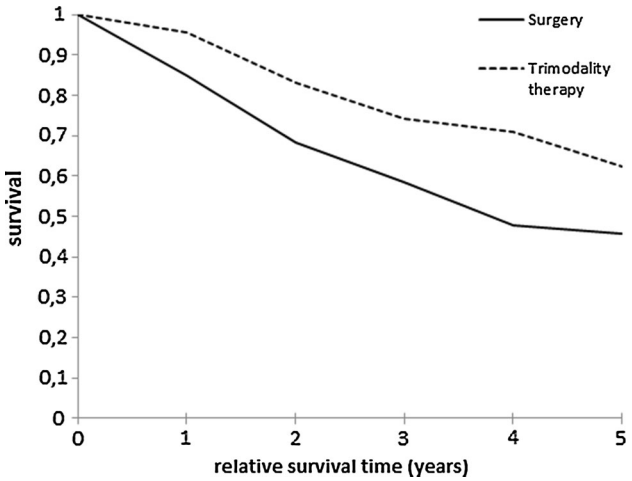


Fig. 3 Relative survival curves for patients in 2007–2015 with T4d breast cancer, solely treated with a surgical procedure, compared to patients withT4d breast cancer treated with trimodality therapy

in NI-LABC 39.6% of T1–3 patients in the same period (unpublished data NCR). Positive nodal status is found to be an adverse prognostic factor in other retrospective studies [17].

In the literature, contradictory data exist with respect to the mean age at diagnosis of IBC. Some reported that IBC is a disease of younger women, whereas others found that IBC more often affects older women [1, 6]. In the present study, the mean age at diagnosis is 61.6 years for IBC patients, which was significantly younger than NI-LABC (69.1 years) but comparable to patients with T1-3 breast cancer (60.7 years) during the same period (unpublished data, NCR). This is also observed in another population-based study [1].

Compared to NI-LABC tumours, IBC tumour more frequently lacks hormone receptor expression, restricting therapeutic possibilities which results in a more aggressive clinical course and decreased survival [18]. Comparable to other population-based studies, approximately one-third of IBC patients display HER2-positive cancers. This is notably higher than non-T4 patients and NI-LABC [19]. Overexpression of HER2 in breast cancer is associated with higher recurrence rates and higher mortality [20]. In this study, 23.3% of IBC tumours are triple negative. Primary IBC has a poor prognosis regardless of the ER/PR/HER2 subtype, with the worst outcome in patients with triple-negative IBC [21].

The neoadjuvant approach to breast cancer is established as a therapeutic strategy for selected high-risk breast cancers: tumours ≥2 cm and for locally advanced (including initially ineligible for resection) disease. Achieving complete pathological response is associated with better outcomes [22]. We demonstrated that the use of trimodality therapy (neoadjuvant chemotherapy, surgery and radiation therapy) positively influenced the survival of IBC patients, as found in other population-based studies [5]. Application of trimodality therapy increases over time, although improvements are still very much possible and needed. Only 57% of operated patients underwent this comprehensive treatment schedule and neoadjuvant chemotherapy is administered in only 71.2% of operated patients. Improvement in locoregional control makes radiation therapy an important modality in the treatment protocol [4]. In the adjuvant setting, around 75% of IBC patients receive adjuvant radiation therapy. Administration of both chemotherapy and radiation therapy should occur more often in patients clinically eligible of receiving these modalities. LABC, and IBC in particular, has a poor prognosis. We therefore need to ensure that patients who are fit for surgery are also reviewed for eligibility for aggressive multimodality oncological treatments. After all, trimodality therapy improves survival [5, 23]. Unfortunately, we were not able to identify patient or physician factors associated with the differences in administration of trimodality therapy.

Nearly 4% of IBC patients operated on were treated with substandard breast conserving therapy. Despite a clinical response to treatment, residual disease may still be present in the affected skin of the involved breast [24]. Therefore, breast conserving therapy in IBC is associated with unacceptably high incomplete tumour margins and local recurrence rates and a mastectomy is recommended for IBC patients, followed by adjuvant radiation therapy (RT) [4].

Dutch breast cancer patients are treated according to nationally implemented treatment guidelines. This population therefore is suitable to be investigated. However, several limitations of our study have to be noted. Firstly, several clinicopathological characteristics are not available for the entire period, resulting in missing data. Estrogen, progesterone and HER2 receptor status are well-known predictors of survival and could not be accounted for in the first two periods. Hormonal receptor status potentially differs between periods as shown in a prior study, but may also be the result of improved registration (as reflected by the simultaneous decrease of patients with unknown receptor status) [25]. Furthermore, the registration of trastuzumab was not accurately registered in the NCR database. Knowledge of this is important, since neoadjuvant trastuzumab in combination with chemotherapy demonstrated a significantly improved event-free survival in patients with HER2-positive LABC and IBC [26]. Secondly, ethnicity of the population was not considered. Four large population-based studies report a higher incidence in young African-American and Hispanic women, and they have a worse survival compared to Caucasian women. The cause of racial disparities has not yet been elucidated [27].

Thirdly, NCR does not register the cause of death, breast cancer specific survival could not be determined. In addition, the T4-NFS group could possibly bias some results, since the composition of the group is not clear. A bias might also be present due to our choice to only analyse clinical T4d breast cancers, instead of analysing both clinical and pathological T4d breast cancers. However, since IBC is typically diagnosed clinically (dermal lymphatic invasion without typical clinical findings is not sufficient for a diagnosis of inflammatory breast cancer), analysis of clinical T4d breast cancers (with pathological confirmed malignancy) seems to be the most accurate approach [14].

Furthermore, neither the presence of erythema, nor the time from onset of symptoms to diagnosis could be evaluated in the NCR database. Therefore, a differentiation between primary and secondary IBC is difficult to be made. By primary IBC, we refer to the development of breast cancer in a previously normal breast. The term secondary IBC cancer is given to the development of inflammatory skin changes associated with invasive breast cancer in a breast that already had cancer (neglected LABC). This also might potentially influence our results. Moreover, metastatic disease was included in the survival analysis, which might be a potential confounding factor.

We show that IBC has several different characteristics that underline the aggressive biology compared to NI-LABC. This is amongst others reflected by the high rate of positive lymph node involvement, poor differentiation and triple-negative status, resulting in poor survival rates. A multimodal therapeutic approach has significantly improved patient survival. Locoregional therapies (surgery and radiation therapy) combined with a systemic treatment (neoadjuvant chemotherapy) improve the overall survival for patients with IBC [28].

Our analysis shows that IBC treatments vary and that improvement is necessary, despite the increase in multimodal therapy over time. Even though we did not analyse this, known factors associated with receipt of care that is not guideline concordant are among others age, race, hospital size and year of graduation of the treating physician [29]. Moreover, the use of trimodality therapy was associated with younger age, type of treating facility, geographic location, year of diagnosis, race, insurance status, educational status, income, and the presence of comorbid conditions [5].

It is essential that eligible patients with non-metastatic IBC receive trimodality treatment, since this currently is

the most effective regimen. Therefore, prompt referral for neoadjuvant chemotherapy and postoperative radiation therapy is crucial.

Furthermore, new and additional agents are necessary to improve the standard treatment. Breast cancer treatment will be increasingly based on molecular profiling of tumours rather than on histology alone. Molecular subtyping has identified several specific characteristics of IBC compared to non-inflammatory breast cancer and has enabled the identification of new therapeutic targets to regulate the aggressive nature of IBC. So far, however, none of the tested agents has been incorporated in multimodal treatment for IBC [4].

There is a paucity of data from large-scale, prospective, multicenter, randomized trials due to the low incidence of IBC, and the optimal chemotherapeutic regimens, in combination with targeted treatments, are yet to be defined. Future trials to evaluate targeted agents are necessary to improve the survival for patients with this aggressive form of breast cancer.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. The privacy committee of the Netherlands Cancer Registry has approved the study. All patients are anonymous. The authors declare that the study complies with the current laws of Netherlands.

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