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Original Research

Differences in treatment and survival of older patients with operable breast cancer between the United Kingdom and the Netherlands – A comparison of two national prospective longitudinal multi-centre cohort studies

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KEYWORDS
Breast cancer;

Abstract ***Background:*** Previous studies have shown that survival outcomes for older patients with breast cancer vary substantially across Europe, with worse survival reported in the

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Older patients;
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United Kingdom. It has been hypothesised that these differences in survival outcomes could be related to treatment variation.

Objectives: We aimed to compare patient and tumour characteristics, treatment selection and survival outcomes between two large prospective cohorts of older patients with operable breast cancer from the United Kingdom (UK) and The Netherlands.

Methods: Women diagnosed with operable breast cancer aged ≥70 years were included. A baseline comprehensive geriatric assessment was performed in both cohorts, with data collected on age, comorbidities, cognition, nutritional and functional status. Baseline tumour characteristics and treatment type were collected. Univariable and multivariable Cox regression models were used to compare overall survival between the cohorts.

Results: 3262 patients from the UK Age Gap cohort and 618 patients from the Dutch Climb cohort were included, with median ages of 77.0 (IQR: 72.0–81.0) and 75.0 (IQR: 72.0–81.0) years, respectively. The cohorts were generally comparable, with slight differences in rates of comorbidity and frailty. Median follow-up for overall survival was 4.1 years (IQR 2.9–5.4) in Age Gap and 4.3 years (IQR 2.9–5.5) in Climb. In Age Gap, both the rates of primary endocrine therapy and adjuvant hormonal therapy after surgery were approximately twice those in Climb (16.6% versus 7.3%, $p < 0.001$ for primary endocrine therapy, and 62.2% versus 38.8%, $p < 0.001$ for adjuvant hormonal therapy). There was no evidence of a difference in overall survival between the cohorts (adjusted HR 0.94, 95% CI 0.74–1.17, $p = 0.568$).

Conclusions: In contrast to previous studies, this comparison of two large national prospective longitudinal multi-centre cohort studies demonstrated comparable survival outcomes between older patients with breast cancer treated in the UK and The Netherlands, despite differences in treatment allocation.

1. Introduction

Cancer is predominantly a disease of the older population and the number of older patients with breast cancer is increasing due to ageing of Western societies, with a third of all cases occurring in women over 70 years [1].

With increasing age, levels of comorbidity and frailty increase, and deaths from other causes exceed those from breast cancer [2,3]. Consequently, frailer, older women with operable breast cancer may be offered alternative treatment strategies compared to their younger counterparts [4,5] as disease control may be achieved by the use of anti-estrogens only (primary endocrine therapy, PET). However, within this population, there is great heterogeneity in terms of general health and fitness, but also in terms of preferences on specific treatment options.

On the contrary, several studies have identified worse survival outcomes in older patients treated with PET compared to those treated with surgery, especially in those with a life expectancy of more than 2–5 years [6,7]. However, it is also important to avoid unnecessary harm in the very frail with a limited life expectancy by over-treating what may be an indolent disease [8]. Whilst international guidelines recommend that PET should only be considered in patients with a life expectancy of 2–3 years and who are unfit for or refuse surgery [9,10], some older women place a higher value on maintenance of independence and quality of life compared to younger women [11,12] and may prefer to avoid surgical treatment [11].

A number of studies have demonstrated that the outcomes of older women with breast cancer vary substantially across Europe in terms of both treatment strategies and survival [13]. The management of this heterogeneous group of patients has become a research priority [14,15], with the establishment of several large nationwide cohort studies being run simultaneously to try and identify areas for improvement in practice [16,17].

The aim of this study was to compare the patient and tumour characteristics, treatment selection and survival outcomes between two large prospective cohorts of older patients with operable breast cancer from the United Kingdom and The Netherlands.

2. Methods

2.1. Design and study population

2.1.1. UK Age Gap cohort

British patients were included from the Bridging the Age Gap in Breast Cancer study (previously described elsewhere) [16,18–23]. In short, this prospective, multicentre, observational cohort study comprised women aged 70 years and older with primary operable invasive

breast cancer, recruited from 56 sites in England and Wales between 2013 and 2018. Women were recruited at the time of breast cancer diagnosis and before their initial treatment.

A baseline comprehensive geriatric assessment was performed using validated tools with data collected on age, comorbidities, medication use, physical function (as indicated by activities of daily living (ADL) [24] and instrumental activities of daily living (IADL) scores) [25], cognitive function (using the Mini-Mental State Examination, MMSE) [26] and nutritional status (using the abridged Patient-Generated Subjective Global Assessment, aPG-SGA) [27]. Baseline tumour characteristics were collected, including tumour size, biological subtype, grade and nodal status. Treatment types were recorded, i.e. type of breast and axillary surgery, receipt of endocrine therapy (whether primary or adjuvant), radiotherapy, chemotherapy and trastuzumab.

2.1.2. Dutch Climb cohort

Dutch patients were included from the Climb Every Mountain study (CLIMB), a prospective, multicentre longitudinal cohort study of women aged 70 years and older who were diagnosed with primary operable breast cancer between 2013 and 2018 and recruited from 9 sites in the western part of the Netherlands.

A baseline comprehensive geriatric assessment was performed before primary treatment initiation, with data collected on age, comorbidities and medication use, nutritional status (using the Malnutrition Universal Screening Tool, MUST [28]), cognition (using the MMSE [26]), physical function (using the Timed Up and Go test, TUG [29]) and functional status assessment using the Groningen Activity Restriction Scale (GARS), which consists of eleven items on ADL and seven items on IADL [30]. Baseline tumour characteristics and treatment type were collected, similar to the Age Gap cohort.

2.2. Procedures

2.2.1. Inclusion criteria for this comparative study

For this comparative study, we included women aged 70 years or older with primary operable invasive breast cancer (TNM stages: T1-3, N0-2, M0). Multifocal and bilateral cancers were eligible. Patients with previous breast cancer within five years were excluded. Patients with advanced dementia and the incapability to fill in questionnaires were excluded.

2.2.2. Comparison of baseline tumour and geriatric characteristics

The following tumour characteristics were available in both cohorts and compared at baseline: biological tumour type, grade, lateralisation (either unilateral or bilateral), focality (either unifocal or multifocal), primary tumour size and nodal status, oestrogen, progesterone, and HER2 receptor status.

With respect to the comparable geriatric measures, comorbidity was registered in both cohorts according to the Charlson Comorbidity Index (CCI), but without age adjustment [31–33]. Polypharmacy was defined as five or more daily medications [34]. For nutritional status, aPG-SGA data from the Age Gap cohort were recalculated into the MUST score, as used in the Climb cohort, together with BMI. The calculated MUST score is categorised into three groups according to the risk of malnutrition: low, medium or high risk [28]. For comparing the data on functional status (ADL) the GARS questionnaire used in Climb was mapped onto the Barthel score, as used in the Age Gap cohort [24]. Due to the unavailability of data on controlling bladder and bowel function in the Climb cohort, these two items from the Barthel were excluded. Interpretation of the Barthel sum score was categorised into three groups (0–31 points: very/fully dependent, 32–63 points: partially/minimally dependent, 64–80 points: independent, or unknown if data was missing [35]. For cognitive status, the MMSE scores collected in both cohorts were compared. If less than 10% of the total score was missing, the maximum score was given for the missing question. If more than 10% was missing, the total MMSE score was defined as unknown.

2.2.3. Comparison of treatment modalities

For each patient, the most extensive surgical procedure was recorded, both for the type of breast surgery (no surgery, breast-conserving surgery, mastectomy, unknown) and for the type of axillary surgery (no surgery, sentinel lymph node procedure, axillary lymph node dissection, unknown). Primary endocrine therapy (PET) was defined as endocrine therapy as primary treatment without receiving surgery, or endocrine therapy as primary treatment with surgery received more than one year post-diagnosis; the latter was considered as failed PET. For the specific PET versus surgery analysis, patients were classified in the surgery group when they had received primary surgery, either with or without neoadjuvant systemic therapy, adjuvant systemic therapy, radiotherapy and/or trastuzumab. For this specific analysis, patients with ER-negative tumours were excluded, as well as patients who received no treatment or any treatment that did not include either PET or surgery (i.e. radiotherapy alone).

2.2.4. Outcomes

The main outcomes were the frequencies of a particular treatment (PET versus surgery) and overall survival (OS). For the Age Gap cohort, survival outcomes were obtained via direct follow up to 2 years and beyond 2 years via the UK cancer registry. For the Climb cohort, survival outcomes were obtained through direct follow-up data collection up to 2 years and beyond via the

Personal Records Database (BRP) or obtained from the medical charts up to February 2021. Overall survival was defined as the time in days from the baseline assessment until death or censored at the last date known to be alive. Overall survival was compared between the two complete cohorts irrespective of treatment and between patients who received PET or surgery within each cohort separately.

2.3. Statistical analysis

All analyses were performed in SPSS version 25. Pearson chi-squared test was used to evaluate differences in the tumour, geriatric and treatment characteristics between the cohorts. Kaplan–Meier analyses and log-rank tests were conducted to evaluate overall survival in both cohorts in total and for the two treatment categories (PET and surgery). Univariate cox regression analysis was performed to compare overall survival between both cohorts in total and between the patients treated with either PET or surgery. For the overall survival comparison between both cohorts in total, an additional multivariable cox regression analysis was performed, taking into account the following potential confounders that were considered as clinically relevant: tumour size, nodal status, grade, hormone receptor status (ER/PR), age, CCI, polypharmacy, BMI, MMSE score and ADL score.

2.4. Ethical approval

For the Age Gap cohort, ethics approval and research governance approval was obtained (IRAS: 115550). The Climb study was approved by the medical ethics committee of the Leiden University Medical Centre (LUMC) (CCMO: NL43463.058.13). Written informed consent was obtained from all participants.

3. Results

3.1. Baseline tumour and patient characteristics

A total of 3262 patients from the Age Gap cohort and 618 patients from the Climb cohort were included, with median ages of 77.0 (IQR: 72.0–81.0) and 75.0 (IQR: 72.0–81.0), respectively. Baseline tumour, patient and treatment characteristics for both cohorts are presented in Table 1. In the Climb cohort, there was a higher percentage of grade III tumours (30.4% in Climb vs 21.4% in Age Gap, $p < 0.001$), and more multifocal tumours (13.6% in Climb vs 9.2% in Age Gap, $p < 0.001$). The percentage of patients with node positive breast cancer was similar in both cohorts. In Age Gap, 2862 patients (88.1%) had ER + tumours, versus 492 patients (85.4%) in Climb ($p = 0.075$).

In Age Gap, a higher proportion of patients had two or more comorbidities at baseline (34.3% in Age Gap versus 23.7% in Climb, $p < 0.001$), and a higher proportion of patients in Age Gap were obese with a BMI >30 (28.9% in Age Gap versus 23.3% in Climb, $p < 0.001$). There was a higher proportion of patients in Age Gap with a high risk of malnutrition (5.4% in Age Gap versus 2.5% in Climb, $p < 0.0001$). The number of patients with impaired mental status, according to the MMSE, was similar in both cohorts (4.8% in Age Gap versus 4.0% in Climb, $p = 0.380$), but in the Climb cohort, there was a higher proportion of functionally dependent patients (11.3% in Climb versus 4.3% in Age Gap, $p < 0.001$).

3.2. Comparison of treatment selection

In the Climb cohort, a higher proportion of the patients that were surgically treated underwent a mastectomy (44.8% in Climb vs 38.6% in Age Gap, $p = 0.002$). Axillary surgery and radiotherapy rates were comparable in both cohorts ($p = 0.022$ and $p = 0.388$, respectively), and the rates of prescribed neo-adjuvant chemotherapy and neo-adjuvant endocrine therapy were low in both Climb and Age Gap (neo-adjuvant chemotherapy 2.3% in Age Gap vs 1.9% in Climb, and neo-adjuvant endocrine therapy 3.1% in Age Gap vs 3.4% in Climb, $p = 0.805$).

In Age Gap, both the rates of adjuvant chemotherapy and adjuvant hormonal treatment were approximately twice those in Climb (4.9% in Age Gap versus 2.6% in Climb, $p < 0.001$ for adjuvant chemotherapy, and 62.2% in Age Gap versus 38.8% in Climb, $p < 0.001$ for adjuvant hormonal therapy) (Table 1).

In Age Gap, 474 out of 2849 (16.6%) patients with ER + tumours, received primary endocrine therapy (PET), and 39 out of 533 (7.3%) patients in Climb received PET ($p < 0.001$) (Fig. 1). Baseline characteristics for PET and surgery patients in both cohorts are presented in Table 2. The patients that received PET in the Age Gap cohort were generally younger compared to the PET patients in the Climb cohort, with a median age of 83.0 (IQR: 78.0–87.3) in Age Gap and 86.0 (IQR: 82.0–90.0) in Climb ($p < 0.001$). Patients receiving PET in the Age Gap cohort had more favourable tumour characteristics (lower grade and smaller tumour size, both $p < 0.001$) and were also generally more fit, with less comorbidity and polypharmacy (both $p < 0.001$), and superior function compared to PET patients in Climb (adjusted Barthel ADL mean score of 72.1 in Age Gap versus 60.8 in Climb, $p < 0.001$) (Table 2). Rates of PET use did not differ significantly over the study period for either cohort.

3.3. Comparison of survival outcomes

Median follow-up for overall survival was 4.1 years (IQR 2.9–5.4) in Age Gap and 4.3 years (IQR 2.9–5.5) in Climb. Of the 3262 patients in the Age Gap cohort,

Table 1
Baseline tumour, patient, and treatment characteristics[a].

	Age Gap (UK)		Climb (NL)		Total		p-value
	N = 3262		N = 618		N = 3880		
	n	(%)	n	(%)	n	(%)	
Age	N = 3261		N = 618		N = 3879		*<0.001*
70-74	1227	(37.6)	288	(46.6)	1515	(39.1)	
75-59	967	(29.7)	135	(21.8)	1102	(28.4)	
80-84	632	(19.4)	115	(18.6)	747	(19.3)	
≥85	435	(13.3)	80	(12.9)	515	(13.3)	
Median (IQR)	77.0	(72.0 −81.0)	75.0	(72.0 −81.0)	76.0	(72.0 −81.0)	*0.009*
Tumour type	N = 3241		N = 599		N = 3840		*<0.001*
Ductal	2294	(70.8)	465	(77.2)	2759	(71.8)	
Lobular	468	(14.4)	100	(16.7)	568	(14.8)	
Other	479	(14.8)	34	(5.7)	513	(13.4)	
Tumour grade	N = 3231		N = 569		N = 3800		*<0.001*
Grade I	515	(15.9)	134	(23.6)	649	(17.1)	
Grade II	2019	(62.5)	247	(43.4)	2266	(59.6)	
Grade III	697	(21.6)	188	(33.0)	885	(23.3)	
Lateralisation	N = 3262		N = 614		N = 3876		*0.918*
Unilateral	3180	(97.5)	599	(97.6)	3779	(97.5)	
Bilateral	82	(2.5)	15	(2.4)	97	(2.5)	
Focality	N = 3090		N = 599		N = 3689		*0.002*
Unifocal	2789	(90.3)	515	(86.0)	3304	(89.6)	
Multifocal	301	(9.7)	84	(14.0)	385	(10.4)	
Tumour size[b]	N = 3250		N = 608		N = 3858		*0.001*
0–2 CM	1897	(58.4)	382	(62.8)	2279	(59.1)	
2–5 CM	1253	(38.6)	195	(32.1)	1448	(37.5)	
>5CM	100	(3.1)	31	(5.1)	131	(3.4)	
Nodal status[b]	N = 3256		N = 582		N = 3838		*0.421*
Node-negative	2729	(83.8)	480	(82.5)	3209	(83.6)	
Node-positive	527	(16.2)	102	(17.5)	629	(16.4)	
ERstatus	N = 3250		N = 576		N = 3826		*0.075*
Negative	388	(11.9)	84	(14.6)	472	(12.3)	
Positive	2862	(88.1)	492	(85.4)	3354	(87.7)	
PR-status	N = 1665		N = 571		N = 2236		*0.013*
Negative	491	(29.5)	200	(35.0)	691	(30.9)	
Positive	1174	(70.5)	371	(65.0)	1545	(69.1)	
HER2-status	N = 2984		N = 486		N = 3470		*0.237*
Negative	2608	(87.4)	434	(89.3)	3042	(87.7)	
Positive	376	(12.6)	52	(10.7)	428	(12.3)	
Charlson Comorbidity Index	N = 3262		N = 618		N = 3880		*<0.001*
0	1605	(49.2)	317	(51.3)	1922	(49.5)	
1	539	(16.5)	155	(25.1)	694	(17.9)	
2	687	(21.1)	90	(14.6)	777	(20.0)	
≥3	431	(13.2)	56	(9.1)	487	(12.6)	
Polypharmacy (5 or more)	N = 3262		N = 594		N = 3856		*0.795*
No	1831	(56.1)	330	(55.6)	2161	(56.0)	
Yes	1431	(43.9)	264	(44.4)	1695	(44.0)	
BMI	N = 2675		N = 614		N = 3289		*0.011*
<18.5	39	(1.5)	4	(0.7)	43	(1.3)	
18.5–25	864	(32.3)	221	(36.0)	1085	(33.0)	
25-30	1000	(37.4)	246	(40.1)	1246	(37.9)	
>30	772	(28.9)	143	(23.3)	915	(27.8)	
Nutritional risk score (MUST)	N = 2579		N = 553		N = 3132		*<0.001*
Low risk	2234	(86.6)	507	(91.7)	2741	(87.5)	
Medium risk	206	(8.0)	32	(5.8)	238	(7.6)	
High risk	139	(4.5)	14	(2.5)	153	(4.9)	
Mental status (MMSE)	N = 2245		N = 582		N = 2872		*0.380*
Normal (≥24)	2137	(95.2)	559	(96.0)	2696	(95.4)	
Impaired (<24)	108	(4.8)	23	(4.0)	131	(4.6)	
Functional status (Barthel)[c]	N = 2942		N = 616		N = 3558		*<0.001*
Independent	2815	(95.7)	546	(88.6)	3361	(94.5)	
Partially or minimally	113	(3.8)	58	(9.4)	171	(4.8)	

(*continued on next page*)

Table 1 (*continued*)

	Age Gap (UK)		Climb (NL)		Total		p-value
	N = 3262		N = 618		N = 3880		
	n	(%)	n	(%)	n	(%)	
dependent							
Very or fully dependent	14	(0.5)	12	(1.9)	26	(0.7)	
Mean	77.7		73.8		77.0		*<0.001*
Most extensive breast surgery[d]	N = 2766		N = 578		N = 3344		*0.002*
No surgery	43	(1.6)	2	(0.3)	45	(1.3)	
Breast conserving	1647	(59.5)	317	(54.8)	1964	(58.7)	
Mastectomy	1076	(38.9)	259	(44.8)	1335	(39.9)	
Most extensive axillary surgery[d]	N = 2754		N = 572		N = 3326		*0.022*
No axillary surgery	115	(4.2)	41	(7.2)	156	(4.7)	
Sentinel lymph node procedure	2130	(77.3)	425	(74.3)	2555	(76.8)	
Axillary lymph node dissection	509	(18.5)	106	(18.5)	615	(18.5)	
Primary Endocrine Therapy (PET)	N = 3200		N = 616		N = 3816		*<0.001*
No	2723	(85.1)	576	(93.5)	3299	(86.4)	
Yes	477	(14.9)	40	(6.5)	517	(13.5)	
Neo-adjuvant systemic treatment	N = 3262		N = 618		N = 3880		*0.805*
None	3088	(94.7)	585	(94.7)	3673	(94.7)	
Neo-adjuvant chemotherapy	74	(2.3)	12	(1.9)	86	(2.2)	
Neo-adjuvant hormonal therapy	100	(3.1)	21	(3.4)	121	(3.1)	
Combination	0	(0.0)	0	(0.0)	0	(0.0)	
Adjuvant systemic treatment	N = 3262		N = 618		N = 3880		*<0.001*
None	828	(25.4)	348	(56.3)	1176	(30.3)	
Adjuvant chemotherapy	161	(4.9)	16	(2.6)	177	(4.6)	
Adjuvant hormonal therapy	2043	(62.6)	237	(38.3)	2280	(58.8)	
Combination	230	(7.1)	17	(2.8)	247	(6.4)	
Radiotherapy	N = 3262		N = 618		N = 3880		*0.388*
No	1464	(44.9)	289	(46.8)	1753	(45.2)	
Yes	1798	(55.1)	329	(53.2)	2127	(54.8)	
Adjuvant trastuzumab	N = 3262		N = 618		N = 3880		*<0.001*
No	3081	(94.5)	605	(97.9)	3686	(95.0)	
Yes	181	(5.5)	13	(2.1)	194	(5.0)	
No treatment received	N = 3262		N = 618		N = 3880		*0.289*
N	15	(0.5)	1	(0.2)	16	(0.4)	

[a]

Missing numbers are not presented in this table.

[b] Clinical tumour size or nodal status, if unavailable, pathological tumour size or nodal status was used.

[c] Barthel: excluding questions on controlling bladder and bowel (absent in climb dataset).

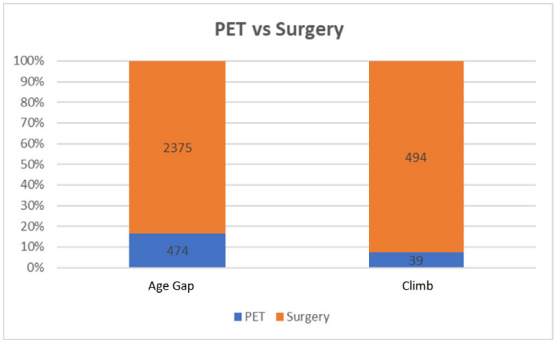
[d] Excluding patients who received PET.

639 (19.6%) died during follow-up, compared to 133 out of 618 (21.5%) patients in the Climb cohort. There was no evidence of a statistical difference between the cohorts for overall survival (adjusted HR 0.94, 95% CI 0.75–1.17, p = 0.568) (Table 3). No statistically significant difference was found for overall survival between the two cohorts according to treatment allocation subgroups, neither for the PET subgroup (for women allocated PET, UK: 181/474, 38.2%, NL: 15/39, 38.5%, unadjusted HR 1.11, 95% CI 0.65–1.88, p = 0.707), nor for the surgery subgroup (for women allocated surgery, UK: 335/2375, 14.1%, NL: 83/494, 16.8%, unadjusted HR 1.11, 95% CI 0.87–1.41, p = 0.403) (Table 3; Fig. 2).

4. Discussion

This is the first study of its kind to compare large, 'real world' prospective cohorts of older patients with operable breast cancer between the UK and Netherlands. We found no evidence of any difference in overall survival outcomes between the two countries in this group of patients, despite differences in treatment selection. This is in contrast with previous comparative European studies using retrospective registry data, which identified substantial variation both in terms of treatment and survival between these two countries [13,36], with the UK having generally worse survival outcomes in this population of patients.

The relative lack of survival gains in recent years for older (>70 years) compared to younger patients remains a problem across Europe and is seen as a research priority, with the European Society of Breast Cancer Specialists (EUSOMA) and International Society of Geriatric Oncology (SIOG) recently publishing their updated recommendations regarding the management of these patients [10]. The Age Gap and Climb studies were both designed to address variations in treatment and outcomes seen in older breast cancer patients, and



*Excluding: ER- tumours, and patients receiving neither PET nor surgery as primary treatment.

Fig. 1. **PET versus primary surgery selection in Age Gap (UK) and Climb (NL) cohort***. **Excluding: ER-tumours, and patients receiving neither PET nor surgery as primary treatment.*

included detailed geriatric assessments that have allowed in-depth age and health stratified comparison of clinical practice and outcomes between the two countries.

The two countries have similar general populations (although the UK is known to have higher rates of obesity [37]), and the predicted life expectancy for a female born in the UK being 83.1 years compared to 83.4 years for those born in the Netherlands [38]. The cohorts were generally comparable in terms of the baseline tumour and patient characteristics. The Climb cohort did, however, have more grade 3 tumours, although it is possible that this is due to the subjective nature of grade assessment, as previous studies have shown grade to be relatively consistent between the two countries [13]. The Age Gap cohort had slightly higher rates of comorbidities and obesity, likely reflecting the baseline differences in the populations between the two countries [37,39,40].

There were several notable differences in treatment patterns between the two countries. Primary Endocrine Therapy was used approximately twice as much within the Age Gap cohort compared to the Climb. Patients treated with PET in the Age Gap cohort tended to be younger and fitter. This has been demonstrated in previous studies and likely reflects that the original trials of PET that were first conducted in the UK; however, the rates shown here for both countries are lower than previously reported [13], showing a reduction in its use. This may be a direct result of clearer European guidance on the use of PET that recommends limiting its use to those with a short predicted life expectancy of 2–5 years [10]. However, it may also reflect that the studies did not recruit large proportions of the oldest and most frail patients, for whom PET may be more appropriate.

There were higher rates of mastectomy compared to breast conservation surgery in the Climb cohort. This may, in part, be attributable to the slightly higher number of T3 tumours within the Climb cohort. Other reasons for differences in rates of mastectomy may be related to patient preference and the wish to avoid the additional burden of radiotherapy [41], although this will be applicable to both cohorts. Rates of axillary surgery and adjuvant radiotherapy were generally comparable, but rates of adjuvant endocrine therapy and chemotherapy were approximately twice as high in Age Gap compared to Climb. Guidelines for the use of adjuvant endocrine therapy differ between the two countries, with NICE in the UK recommending the use of either an aromatase inhibitor or tamoxifen in all postmenopausal women with oestrogen-receptor positive breast cancer [42]. In the Netherlands, hormone therapy is only recommended for those with oestrogen-receptor positive breast cancer who have lymph node-positive disease or otherwise unfavourable tumour characteristics (high grade or $\geq$2 cm) [43]. In both cohorts, there were low rates of adjuvant chemotherapy, however this is comparable to other previous series in this patient population [13].

In contrast to previous retrospective registry-based studies, we did not find a difference in overall survival between the UK and Dutch cohorts, despite a higher rate of patients treated with PET in the UK cohort. This suggests that for a selection of patients, omitting surgery may be safe, at least for a median follow up period of 50–52 months. However, this could also reflect a change in the management of breast cancer patients in the UK, with a reduction of PET being used in recent years. Another factor that may have influenced survival outcome is the difference in adjuvant treatment, with significantly lower rates of prescribed adjuvant hormonal therapy in the Climb cohort. This may have potentially led to smaller differences in survival outcome in favour of the Age Gap cohort. Furthermore, the difference in overall survival between the two cohorts will be influenced by the high probability of competing risk, as the possibility of dying from causes other than the cancer itself increases significantly in older patients, especially when considering a relatively indolent tumour type such as breast cancer [42,43]. In combination with the relatively short follow-up time, this may have resulted in finding smaller differences in overall survival between the cohorts.

This study suggests that, for a select group of frailer, older patients who have ER-positive tumours, PET may allow them to avoid an operation with its associated (albeit low) risk of complications and impact on quality of life [19]. Whilst breast surgery is generally considered safe, with a low risk of complications and can be performed often on a day-case basis, it is not without its risks [8]. There is evidence to suggest that surgery has an impact on quality of life, which is greater if the patient requires a mastectomy and axillary node clearance [19]. Many older patients also place a higher value on independence and quality of life when selecting their treatment [11,12], and so PET remains a valid option to discuss with these patients in the process of shared decision-making. This comparative study emphasises the need for more evidence-based guidelines and consensus

Table 2
Baseline tumour and patient characteristics per primary treatment (PET or surgery)[a].

	PET in Age Gap		PET in Climb		Surgery in Age Gap		Surgery in Climb		p-value
	N = 474		N = 39		N = 2375		N = 494		
	n	(%)	n	(%)	n	(%)	n	(%)	
Age	N = 474		N = 39		N = 2374		N = 494		*<0.001*
70-74	58	(12.2)	1	(2.6)	1009	(42.5)	253	(51.2)	
75-59	90	(19.0)	5	(12.8)	750	(31.6)	111	(22.5)	
0-84	126	(26.6)	11	(28.2)	431	(18.2)	90	(18.2)	
≥85	200	(42.2)	22	(56.4)	184	(7.8)	40	(8.1)	
Median (IQR)	83.0	(78.0–87.3)	86.0	(82.0–90.0)	76.0	(72.0–80.0)	74.0	(72.0–80.0)	*<0.001*
Tumour grade	N = 457		N = 8		N = 2366		N = 479		*<0.001*
Grade I	97	(21.2)	0	(0.0)	409	(17.3)	133	(27.8)	
Grade II	302	(66.1)	3	(37.5)	1557	(65.8)	228	(47.6)	
Grade III	58	(12.7)	5	(62.5)	400	(16.9)	118	(24.6)	
Tumour size[b]	N = 463		N = 36		N = 2374		N = 488		*<0.001*
0–2 CM	222	(47.9)	11	(30.6)	1499	(63.1)	333	(68.2)	
2–5 CM	230	(49.7)	21	(58.3)	809	(34.1)	131	(26.8)	
>5CM	11	(2.4)	4	(11.1)	66	(2.8)	24	(4.9)	
Nodal status[b]	N = 470		N = 31		N = 2374		N = 469		*0.469*
Node-negative	393	(83.6)	25	(80.6)	2039	(85.9)	396	(84.4)	
Node-positive	77	(16.4)	6	(19.4)	335	(14.1)	73	(15.6)	
Charlson Comorbidity Index	N = 474		N = 39		N = 2375		N = 494		*<0.001*
0	171	(36.1)	8	(20.5)	1252	(52.7)	277	(56.1)	
1	81	(17.1)	12	(30.8)	385	(16.2)	116	(23.5)	
2	101	(21.3)	13	(33.3)	483	(20.3)	61	(12.3)	
≥3	121	(25.5)	6	(15.4)	255	(10.7)	40	(8.1)	
Polypharmacy (5 or more)	N = 474		N = 38		N = 2375		N = 476		*<0.001*
No	215	(45.4)	12	(31.6)	1383	(58.2)	283	(59.5)	
Yes	259	(54.6)	26	(68.4)	992	(41.8)	193	(40.5)	
BMI	N = 309		N = 38		N = 2017		N = 493		*<0.001*
<18.5	15	(4.9)	0	(0.0)	19	(0.9)	4	(0.8)	
18.5–25	103	(33.3)	18	(47.4)	624	(30.9)	176	(35.7)	
25-30	113	(36.6)	15	(39.5)	767	(38.0)	197	(40.0)	
>30	78	(25.2)	5	(13.2)	607	(30.1)	116	(23.5)	
Nutritional risk score (MUST)	N = 297		N = 35		N = 1944		N = 447		*<0.001*
Low risk	239	(80.5)	30	(85.7)	1703	(87.6)	413	(92.4)	
Medium risk	28	(9.4)	5	(14.3)	150	(7.7)	23	(5.1)	
High risk	30	(10.1)	0	(0.0)	91	(4.7)	11	(2.5)	
Mental status (MMSE)	N = 286		N = 37		N = 1664		N = 464		*<0.001*
vNormal (≥24)	246	(86.0)	34	(91.9)	1607	(96.6)	449	(96.8)	
Impaired (<24)	40	(14.0)	3	(8.1)	57	(3.4)	15	(3.2)	
Functional status (Barthel)[c]	N = 395		N = 39		N = 2167		N = 492		*<0.001*
Independent	324	(82.0)	25	(64.1)	2123	(98.0)	448	(91.1)	
Partially or minimally dependent	59	(14.9)	12	(30.8)	43	(2.0)	35	(7.1)	
Very or fully dependent	12	(3.0)	2	(5.1)	1	(0.0)	9	(1.8)	
Mean	72.1		60.8		78.6		74.9		*<0.001*

[a] Missing numbers are not presented in this table.
[b] Clinical tumour size or nodal status, if unavailable, pathological tumour size or nodal status was used.
[c] Barthel: excluding questions on controlling bladder and bowel (absent in climb dataset).

on the treatment allocation for the older population with breast cancer.

Limitations of this study include those inherent to all cohort studies, including the fact that patients with dementia were excluded from this study and the very old and frailest patients are under-represented in both cohorts, limiting the generalisability of the results. The survival analysis is also limited by the relatively short follow-up period. However, it is the largest study of its kind to report very detailed and prospective comparative data between these two European countries, and further follow-up studies will help to provide long term comparisons. It was not possible to present disease-specific survival rates in addition to overall survival because the Netherlands does not routinely collect data on the cause of death. A further minor limitation was the fact that the data collected by both cohorts were not identical, so some comparisons needed to be modified, such as the Barthel and the SGA score. The data we included in the comparative analyses were, however, identical.

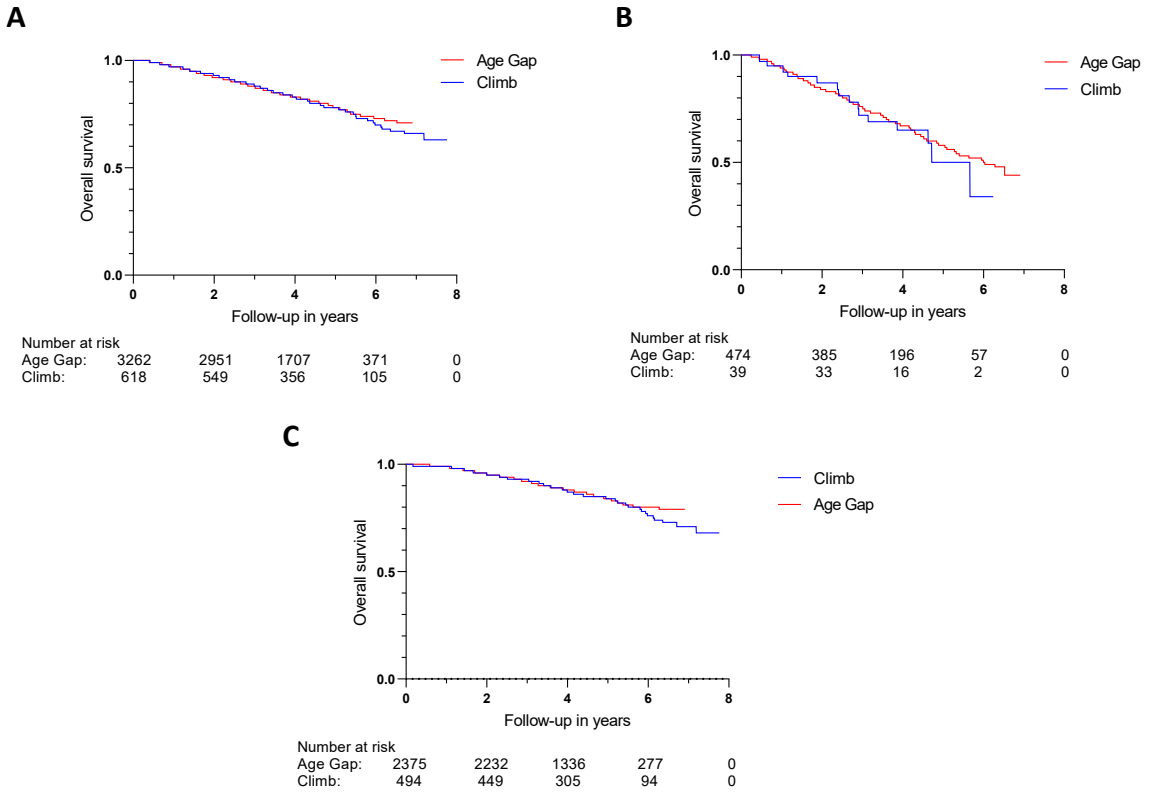


Fig. 2. A. Overall Survival per cohort – all primary treatments combined. B. Overall Survival of patients receiving PET per cohort. C. Overall survival of patients receiving surgery per cohort.

Table 3
Uni- and multivariate Cox proportional hazards models – Overall Survival for both cohorts.

	Overall survival	Univariate			Multivariable[a]		
	No. events (deaths)	HR	95% CI	p-value	HR	95% CI	p-value
Age Gap (UK)	639/3262 (19.6%)	1.00	–	–	1.00	–	–
Climb (NL)	133/618 (21.5%)	1.05	0.87–1.26	0.626	0.94	0.75–1.17	0.568
Age Gap (UK) – PET	181/474 (38.2%)	1.00	–	–			
Climb (NL) - PET	15/39 (38.5%)	1.11	0.65–1.88	0.707			
Age Gap (UK) - Surgery	335/2375 (14.1%)	1.00	–	–			
Climb (NL) - Surgery	83/494 (16.8%)	1.11	0.87–1.41	0.403			

[a] Adjusted for: tumour size, grade, nodal status, estrogen/progesterone status, age, CCI, polypharmacy, BMI, MMSE and Barthel ADL score.

This report includes two large national prospective longitudinal multi-centre cohort studies and demonstrates comparable survival outcomes between older patients with breast cancer treated in the UK and The Netherlands, despite differences in treatment allocation. Future work should focus on the quality of life and functioning after treatment, which is especially relevant in older patients with breast cancer. Longer follow-up is needed to evaluate the long-term effects on survival, quality of life and functioning.

Trial sponsors

Age Gap: Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust, Clinical Research Office, First Floor 'C' Block, Doncaster Royal Infirmary, Armthorpe Road, Doncaster, DN2 5LT, UK.

Climb: KWF Kankerbestrijding, 1070 AM Amsterdam, Netherlands.

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Substantial contributions to the conception of the study: WGvdPK, NAdG, JM, EB, GJL, JEAP, LW, MWR, CM, AZdB.

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Analysis of data: WGvdPK, NAdG, JM.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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