Coming of age : treatment and outcomes in older patients with breast cancer

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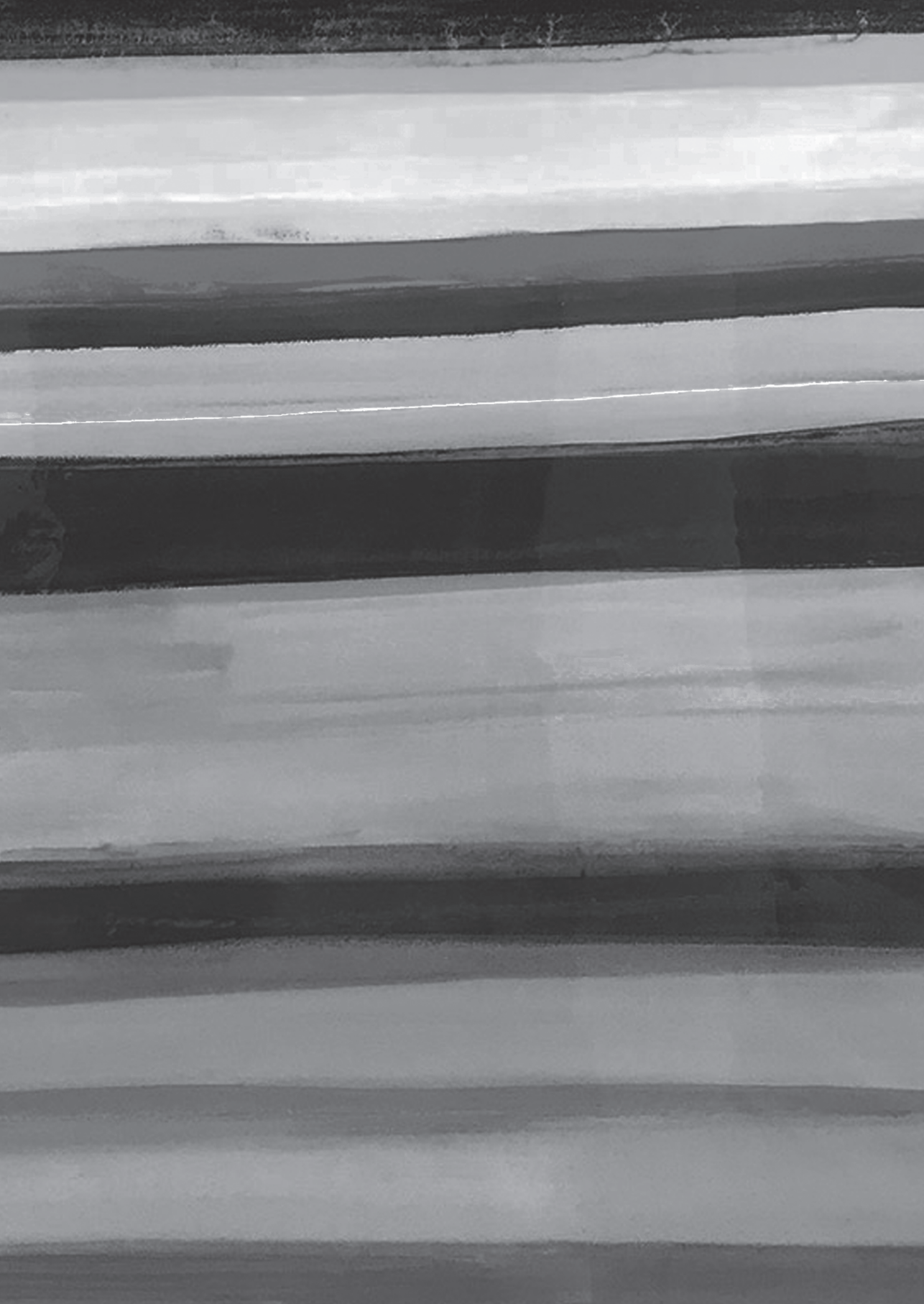
PART I

Evaluating treatment of older patients with breast cancer



CHAPTER 2

Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: A population-based cohort study from the EURECCA Breast Cancer Group

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ABSTRACT

Background: Elderly are poorly represented in breast cancer research. We assessed whether variance in treatment patterns may be associated with variation in survival.

Methods: Population-based study including patients aged ≥ 70 with non-metastatic BC from cancer registries from the Netherlands, Belgium, Ireland, England and Greater Poland. Proportions of local and systemic treatments, five-year relative survival and relative excess risks (RER) between countries were calculated.

Results: 236,015 patients were included. The proportion of stage I breast cancer receiving endocrine therapy ranged from 19.6% (Netherlands) to 84.6% (Belgium). The proportion of stage III breast cancer receiving no breast surgery varied between 22.0% (Belgium) and 50.8% (Ireland). For stage I breast cancer, relative survival was lower in England compared to Belgium (RER 2.96, 95%CI 1.30-6.72, $P<.001$). For stage III BC, England, Ireland and Greater Poland showed significantly worse relative survival compared to Belgium.

Conclusion: There is substantial variation in treatment strategies and survival outcomes in elderly with breast cancer in Europe. For early stage breast cancer, we observed large variation in endocrine therapy but no variation in relative survival, suggesting potential overtreatment. For advanced breast cancer, we observed higher survival in countries with lower proportions of omission of surgery, suggesting potential undertreatment.

INTRODUCTION

Cancer is a disease of the elderly; 30% of patients diagnosed with breast cancer are aged 70 years or older.[1] Although this group of older patients is rapidly growing, evidence to guide treatment of these patients remains scarce.[2] Clinical trials often have inclusion criteria that preclude older patients from participating.[3] Furthermore, older patients participating in trials may not be representative for the wider older population due to selection of fitter older patients, those with higher socio-economic status and those with good cognitive function. These differences impair the external validity of trials and limit the extrapolation of their findings.[4]

The American Society of Clinical Oncology (ASCO) and the International Society of Geriatric Oncology (SIOG) have called for age specific clinical trials to improve treatment in this patient group.[3,5] However, de Glas and colleagues showed that only 4% of the currently running trials for breast cancer treatment are specifically including older patients.[6] Therefore, major improvement in the evidence base for treatment in older patients is not likely to occur within a short period of time. An alternative way to study treatment in older patients is by using observational data. Observational data from cancer registries are highly representative of the older population because there is no selection for inclusion.[4] Furthermore, observational data are currently available and can directly be used for research purposes.[7] They provide better insight into treatment strategies and, when using appropriate methods, may be used to evaluate the efficacy of different treatment strategies.[8] For these reasons, the European Registration of Cancer Care project (EURECCA) Breast Cancer Group, collected data from cancer registries on treatment and survival outcomes in older patients with breast cancer.

The aim of this study was to compare differences in locoregional and systemic treatment patterns and survival outcomes in older patients with non-metastatic breast cancer across five European countries. In addition, this study aimed to assess whether variance in treatment between countries was associated with outcome variation.

MATERIALS AND METHODS

This is an observational cohort study with data obtained from four national (The Netherlands, Belgium, Ireland and England) and one regional (Greater Poland) population-based cancer registry (CR). All patients aged 70 years and older at time of diagnosis with non-metastatic invasive breast cancer were selected. The International Classification of Diseases and Related Health Problems (ICD-10) coding was used for selection of breast cancer.[9] In case of synchronous or bilateral tumours, the tumour with the highest known TNM stage

was selected for analysis. In addition, second primary tumours and patients diagnosed with breast cancer only at the time of death were excluded.

Procedures

The protocol specified that data on all consecutive breast cancer cases available between 2000 and 2013 should be provided with information on stage of disease, treatment and vital status. For all national and regional based CRs coverage rate was approximately 100%. Quality of the CRs and methods and periods of collection of the data are described in Supplementary Table 1.

Stage of disease was defined using the TNM Classification of Malignant Tumours for breast cancer, 6th edition.[10] Information on tumour stage was based on pathology reports. If the pathological T or N category was unknown, clinical stage was used instead. For patients with unknown T or N category (both clinical and pathological) stage of disease was considered unknown, unless patients with only known T or N category could be reliably assigned to a specific stage (for example T4NXMX = stage III). Patients with an unknown M-category were assumed to have non-metastatic disease (unless T and N category were both unknown). When stage directly derived from patient reports was available but was assigned unknown according to the above mentioned stage definition, stage available from reports was used instead. If available, data on tumour grade, morphology and hormone receptor expression were collected. Tumour grade was classified as grade I (well differentiated), grade II (moderately differentiated), or grade III (poorly differentiated). Morphology was classified into ductal, lobular, or mixed/other according to ICD-O-3 classification.[11]

Outcomes

Main outcomes were the proportion of given treatment for locoregional treatment (breast surgery, axillary surgery and radiotherapy) and systemic treatment (endocrine therapy, chemotherapy and primary endocrine therapy) and five-year relative survival for each country. Breast surgery was defined as the most extensive breast surgery (no surgery, breast conserving surgery (BCS), mastectomy, breast surgery not otherwise specified), axillary surgery if any breast surgery (yes or no) and radiotherapy if BCS (yes or no). Adjuvant endocrine therapy was defined as endocrine therapy if any breast surgery was performed (yes or no). Adjuvant chemotherapy was defined as chemotherapy if any breast surgery was performed (yes or no). Most registries did not distinguish between adjuvant or neo-adjuvant systemic therapy. Therefore, these were combined. Primary endocrine therapy was defined as endocrine therapy without receiving surgery (yes or no). Vital status was provided by the CRs and defined as alive, dead, or unknown. Follow up time for vital status was defined as time in days from diagnosis until death or end of follow up. Vital status and date of last follow-up were established either directly from the patient's medical record or through linkage of

cancer registry data with mortality or population registries (Supplementary Table 1). All outcomes were stratified for stage (I-III).

Statistical analysis

All analyses were performed in Stata/MP. Data from national or regional data registries were compared between countries. Proportions of patients undergoing each treatment were calculated. Due to the large number of cases, no statistical tests were conducted to assess statistical significant proportional differences. Median follow up and interquartile range (IQR) were calculated according to the reverse Kaplan-Meier method.[12] Relative survival reflects the ratio of overall survival of cancer patients compared with survival that would have been expected based on the corresponding general population (matched by country, age by single year and year of diagnosis). Relative survival for the complete cohort was estimated using the Pohar-Perme method.[13] National life tables from The Human Mortality Database were used to estimate expected survival.[14] To model the effect of covariates on relative survival an additive hazard model was employed. The effect of covariates on the excess hazard was estimated using the expectation-maximisation method.[15] Estimates of the covariates are expressed as relative excess risk of death (RER) and they quantify the relative cancer related excess mortality between the categories of the included covariates in the model.[16] When the excess mortality is low (for instance in a population with a high population mortality and generally curable cancer), standard errors become large and hamper the interpretation of the RER.[15] To compare RER between countries, country was included as a covariate in the univariate model. Differences in relative survival between countries were adjusted for the following potential confounders in a multivariable model: age (continuous), year of diagnosis, stage (not when stratified for stage), grade and morphology. A two-sided p-value of <0.05 was considered statistically significant. In Table 3 and Figure 2, countries were ranked according to the sum of proportions of given treatment and the country with the highest sum was assigned as reference country.

Multiple imputation was used to account for missing values for each country separately after exclusion of tumors diagnosed at time of death, second primary breast cancer and smaller synchronous tumours and age younger than 70 years (Figure 1). Multiple imputation by chained equation was performed, assuming that data are missing at random. For each incomplete variable (stage, grade, morphology, hormone receptor expression), imputation models were applied that included the other incomplete variables, as well was complete variables (age, year of diagnosis), treatment variables and outcome variables (vital status, follow up time in days). When data for a variable was 100% missing it was not imputed. Analyses were based on pooled results of five imputed data sets.[17]

Additional analyses

A sensitivity analysis was performed to assess the impact of variation in time periods on treatment and survival outcomes between the participating countries only including the years with data available from all countries (2008 and 2009). Based on expert panel discussion, a proportional difference of 10% or higher between treatment outcomes was defined as clinically relevant.

Ethical approval

Data from cancer registries provided anonymised patient data. Therefore, informed consent from patients or ethical approval were not required for this study.

RESULTS

Patients

The original dataset included 829,131 patients diagnosed with breast cancer between 2000 and 2013. Patients with synchronous or bilateral tumours, second primary tumours, tumours diagnosed at time of death and patients aged younger than 70 years were excluded (Figure 1). 40,448 patients from the Netherlands, 11,305 patients from Belgium, 4,319 patients from Ireland, 179,239 patients from England and 704 patients from Greater Poland were included (Table 1, step 1). Multiple imputation analysis was performed to account for missing values (Table 1, step 2) and selected patients stage I-III breast cancer for further analyses (Table 1, step 3). Median follow up was 8.8 years (IQR 5.9-12.5 years).

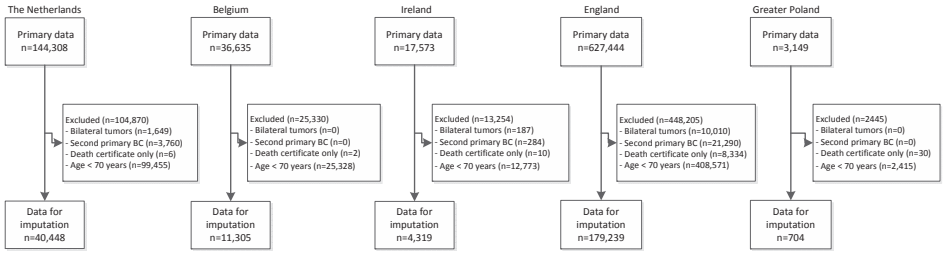

Figure 1. Flow chart
Bilateral tumours: in case of synchronous tumours, the smallest stage tumour was excluded.

Patient characteristics

Stage distribution varied slightly across countries; patients from the Netherlands were more frequently diagnosed with stage I breast cancer compared to other countries (Table 1, step 3). Overall, tumour characteristics were broadly comparable across countries (Table 1, step 3). Patients from the Netherlands and Greater Poland were more likely to have grade I breast cancer.

Locoregional treatment

As shown in Table 2, the majority of patients with stage I breast cancer received BCS (between 48.9% (England) and 65.1% (Belgium), except for Greater Poland (21.1%)). Omission of surgery was commonly used in England (24.2%) and Ireland (17.8%) compared to other countries. For stage II breast cancer, the majority of patients received a mastectomy (between 44.0% (Ireland) and 66.1% (Greater Poland)). The proportions of patients not receiving any surgery showed a similar pattern as seen in patients with stage I breast cancer (Table 2). For stage III breast cancer, the proportion of patients not receiving any surgery increased compared to lower stages of breast cancer: this is most pronounced in The Netherlands (30.1%), England (44.1%) and Ireland (50.8%). The majority of patients who had breast surgery received axillary treatment with no clinically relevant differences between countries and across stages (Figure 2, Supplementary Table 2). In England (across all stages) and Greater Poland (for stage III), the proportion of patients receiving radiotherapy after breast conserving surgery was lower (Figure 2, Supplementary Table 2).

Systemic treatment

Use of adjuvant endocrine therapy differed considerably between countries: for stage I breast cancer the proportion was substantially lower in the Netherlands (20%), compared to the other countries (Belgium 84.6%; Ireland 79.5%; England 47.5%; Greater Poland 68.9%, Figure 2A, Supplementary Table 2). In England, systemic therapy was not registered for a large proportion of patients but this could not be considered as not given, hence this is considered as unknown (Figure 2). For higher stages of breast cancer, variation was less pronounced between countries (Figure 2B and 2C, Supplementary Table 2). In addition, substantial variation in the administration of chemotherapy across countries was observed. The proportion of patients with stage I breast cancer receiving chemotherapy was very low across all countries but showed marked variation (range from 0.5% (the Netherlands) to 6.0% (Ireland) and 11.4% (Greater Poland), Figure 2A, Supplementary Table 2). For stage II breast cancer, chemotherapy use was higher but again varied markedly between countries (range from 2.2% (the Netherlands) to 19.4% (Ireland) and 23.1% (Greater Poland), Figure 2B, Supplementary Table 2). For stage III breast cancer, chemotherapy use increased further but still varied markedly, from 10.3% of patients in the Netherlands to 35.2% in Belgium and 42.7% in Greater Poland (Figure 2C, Supplementary Table 2). As shown in Figure 2, use of primary endocrine therapy (PET) was a commonly used strategy among older patients with breast cancer (Figure 3, Supplementary Table 3). In stage III disease differences between countries were most pronounced; in Ireland 39% of the patients received primary endocrine therapy, compared to 23.6% in the Netherlands, 24.9% in England, 15.1% in Belgium and 1.8% in Greater Poland (Figure 3, Supplementary Table 3).

Table 1. Distribution of patient and tumour characteristics by country, before and after imputation (Step 1 and 2) and after selection of patients with stage I-III breast cancer (Step 3)

	Netherlands				Belgium			
	Step 1		Step 2	Step 3	Step 1		Step 2	Step 3
	N	%	%	%	*N*	%	%	%
Total N	40,448				11,305			
Year of diagnosis								
2000	3745	9.3	9.3	9.2	0	0.0	0.0	0.0
2001	3688	9.1	9.1	9.1	0	0.0	0.0	0.0
2002	3555	8.8	8.8	8.7	0	0.0	0.0	0.0
2003	3553	8.8	8.8	8.7	0	0.0	0.0	0.0
2004	3656	9.0	9.0	9.0	0	0.0	0.0	0.0
2005	3609	8.9	8.9	8.9	0	0.0	0.0	0.0
2006	3590	8.9	8.9	8.9	0	0.0	0.0	0.0
2007	3771	9.3	9.3	9.5	2763	24.4	24.4	24.7
2008	3797	9.4	9.4	9.4	2805	24.8	24.8	24.7
2009	3666	9.1	9.1	9.1	2842	25.1	25.1	24.9
2010	3818	9.4	9.4	9.5	2895	25.6	25.6	25.7
2011	0	0.0	0.0	0.0	0	0.0	0.0	0.0
2012	0	0.0	0.0	0.0	0	0.0	0.0	0.0
2013	0	0.0	0.0	0.0	0	0.0	0.0	0.0
Stage								
0	5	0.0	0.4		11	0.1	0.1	
I	14416	35.6	36.1	39.0	2986	26.4	28.7	32.4
II	17234	42.6	43.2	46.6	4333	38.3	42.3	47.8
III	5159	12.8	13.3	14.4	1779	15.7	17.5	19.8
IV	2662	6.6	7.0		918	8.1	11.4	
Unknown	972	2.4			1278	11.3		
Grade								
G1	6839	16.9	22.1	22.9	1399	12.4	15.0	15.6
G2	14376	35.5	48.2	48.9	4414	39.0	48.0	48.1
G3	8245	20.4	28.5	28.2	3549	31.4	37.0	36.3
Unknown	10988	27.2			1943	17.2		
Morphology								
Ductal	25812	63.8	63.8	65.2	8058	71.3	71.3	71.6
Lobular	5276	13.0	13.0	12.9	1643	14.5	14.5	14.3
Mixed/other	9360	23.1	23.1	21.9	1604	14.2	14.2	14.1
Unknown	0	0.0			0	0.0		
Hormone receptor expression								
ER- and PR-	2798	6.9	14.4	14.1	0	0.0	0.0	0.0
ER+ and/or PR+	18576	45.9	85.6	85.9	0	0.0	0.0	0.0
Unknown	19074	47.2			11305	100.0	100.0	100.0

Step 1: Distribution of patients aged 70 years and older by category before imputation; Step 2: Distribution of patients aged 70 years and older by category after imputation; Step 3: Distribution of patients aged 70 years and older with stage I-III breast cancer by category after imputation.

Ireland				England				Greater Poland			
Step 1		Step 2	Step 3	Step 1		Step 2	Step 3	Step 1		Step 2	Step 3
N	%	%	%	*N*	%	%	%	*N*	%	%	%
4,319				179,239				704			
0	0.0	0.0	0.0	11837	6.6	6.6	6.4	0	0.0	0.0	0.0
0	0.0	0.0	0.0	12073	6.7	6.7	6.6	0	0.0	0.0	0.0
0	0.0	0.0	0.0	11995	6.7	6.7	6.7	0	0.0	0.0	0.0
533	12.3	12.3	12.4	12409	6.9	6.9	6.9	0	0.0	0.0	0.0
566	13.1	13.1	13.1	12302	6.9	6.9	6.8	0	0.0	0.0	0.0
567	13.1	13.1	12.7	12935	7.2	7.2	7.1	0	0.0	0.0	0.0
638	14.8	14.8	14.6	12666	7.1	7.1	7.0	0	0.0	0.0	0.0
641	14.8	14.8	15.0	12645	7.1	7.1	7.0	0	0.0	0.0	0.0
662	15.3	15.3	15.2	12994	7.2	7.2	7.2	325	46.2	46.2	47.9
712	16.5	16.5	17.0	12902	7.2	7.2	7.2	379	53.8	53.8	52.1
0	0.0	0.0	0.0	13231	7.4	7.4	7.4	0	0.0	0.0	0.0
0	0.0	0.0	0.0	13294	7.4	7.4	7.5	0	0.0	0.0	0.0
0	0.0	0.0	0.0	13685	7.6	7.6	7.9	0	0.0	0.0	0.0
0	0.0	0.0	0.0	14271	8.0	8.0	8.2	0	0.0	0.0	0.0
0	0.0	0.0		7727	4.3	8.8		19	2.7	9.9	
740	17.1	21.3	25.6	29581	16.5	26.6	33.7	113	16.1	19.6	28.7
1553	36.0	42.3	50.8	44115	24.6	39.2	49.7	190	27.0	31.4	45.9
664	15.4	19.7	23.6	13091	7.3	13.1	16.6	110	15.6	17.3	25.3
444	10.3	16.8		8200	4.6	12.3		110	15.6	21.8	
918	21.3			76525	42.7			162	23.0		
370	8.6	10.3	11.1	21261	11.9	16.5	16.8	82	11.6	20.1	23.5
2102	48.7	57.9	57.6	73916	41.2	53.5	54.5	176	25.0	48.3	46.7
1169	27.1	31.7	31.3	42223	23.6	30.0	28.7	135	19.2	31.6	29.8
678	15.7			41839	23.3			311	44.2		
2771	64.2	64.2	65.3	115345	64.4	64.4	66.7	401	57.0	59.6	69.3
591	13.7	13.7	13.9	21634	12.1	12.1	12.8	53	7.5	7.7	8.8
957	22.2	22.2	20.8	42260	23.6	23.6	20.5	189	26.8	32.7	21.9
0	0.0			0	0.0			61	8.7		
570	13.2	16.6	16.4	6823	3.8	16.1	15.1	115	16.3	28.5	23.8
3142	72.7	83.4	83.6	44586	24.9	83.9	84.9	380	54.0	71.5	76.2
607	14.1			127830	71.3			209	29.7		

Table 2. Proportional distribution of most extensive breast surgery by stage of disease

	No surgery	BCS	Mastectomy	Not specified
	%	%	%	%
Stage I				
The Netherlands	11.7	50.3	38.0	0.0
Belgium	11.1	65.1	23.8	0.0
Ireland	17.8	54.4	27.8	0.0
England	24.2	48.9	26.9	0.0
Greater Poland	2.5	21.1	52.4	24.0
Stage II				
The Netherlands	18.2	22.3	59.5	0.0
Belgium	16.9	35.8	47.3	0.0
Ireland	21.2	34.8	44.0	0.0
England	28.1	27.5	44.4	.0
Greater Poland	8.9	8.3	66.1	16.7
Stage III				
The Netherlands	30.1	8.3	61.5	0.0
Belgium	22.0	14.4	63.6	0.0
Ireland	50.8	10.4	38.8	0.0
England	44.1	9.5	46.3	0.0
Greater Poland	4.6	3.4	81.8	10.2

Survival outcomes

As shown in Table 3, five-year relative survival for patients with stage I breast cancer was high for all countries, indicating that there is little to no excess mortality in this stage of disease. For England, relative survival was significantly lower compared to Belgium (93.4% 95% CI 93.1-93.7, adjusted RER 2.96, P <0.001). Due to low excess mortality in this specific group, RERs for some countries could not be estimated (Table 3, Figure 2A). For patients with stage II breast cancer, five-year relative survival was lowest in England (79.1%, 95% CI 78.8-79.4) and highest in Ireland (86.3%, 95% CI 84.9-87.7). Relative survival was significantly lower in England when compared to Belgium (adjusted RER 1.45, 95% CI 1.27-1.66, Table 3, Figure 2B). For patients with stage III breast cancer, relative survival was lowest in England (48.2%) and highest in Belgium (60.1%). England, Ireland and Greater Poland showed a significantly worse relative survival compared to Belgium (Table 3, Figure 2C).

Table 3. Five-year relative survival and RER stratified by stage

	RS	95% CI	Crude RER	95% CI	*P*	Adjusted RER	95% CI	*P*
Stage I								
Belgium	97.3	96.2-98.1	reference			reference		
Greater Poland	103.2	103.2-103.3	NA#		0.543	0.18#	0.001-3000#	0.996
Ireland	99.4	89.0-100.0	NA#		0.702	0.43#	0.001-377#	0.805
The Netherlands	96.0	95.5-96.5	0.81	0.24-2.72	0.402	1.32	0.46-3.84	0.547
England	93.4	93.1-93.7	1.13	1.04-6.10	0.004	2.96	1.30-6.72	<0.001
Stage II								
Belgium	85.2	84.3-86.1	reference			reference		
Ireland	86.3	84.9-87.7	0.92	0.69-1.23	0.574	0.94	0.72-1.22	0.625
The Netherlands	82.5	82.0-83.1	1.10	0.94-1.30	0.224	1.02	0.87-1.18	0.828
Greater Poland	85.3	80.7-88.9	1.26	0.72-2.20	0.418	1.46	0.79-2.69	0.227
England	79.1	78.8-79.4	1.43	1.24-1.66	<0.001	1.45	1.27-1.66	<0.001
Stage III								
Belgium	60.1	58.7-61.7	reference			reference		
Greater Poland	58.5	52.7-63.8	1.33	0.91-1.95	0.139	1.51	1.05-2.18	0.026
The Netherlands	55.1	54.1-56.0	1.24	1.00-1.52	0.046	1.07	0.90-1.27	0.418
Ireland	53.5	51.3-55.7	1.40	1.18-1.67	<0.001	1.27	1.07-1.50	0.007
England	48.2	47.8-48.7	1.56	1.40-1.74	<0.001	1.46	1.31-1.62	<0.001

Countries were ranked according to the sum of proportions of each given treatment and the country with the highest sum of given treatment was assigned as reference country. n/N: numbers of events/numbers at risk, RS: five-year relative survival, 95% CI: 95% Confidence Interval, crude RER: univariate relative excess risk, adjusted RER: multivariable relative excess risk, adjusted for the following confounders: age (continuous), year of diagnosis, grade, morphology. NA: not addressed. # Due to low excess mortality, RER could not be interpreted.

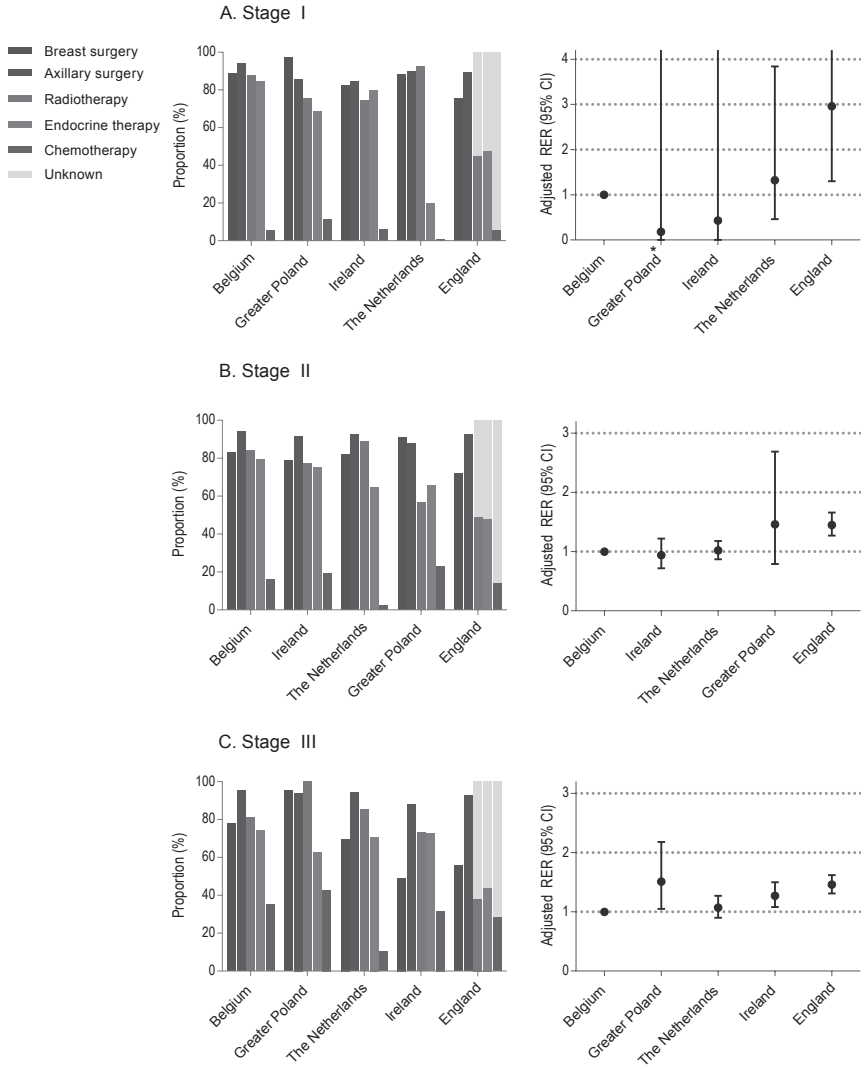

Figure 2. Proportion of patients receiving treatment and adjusted relative excess risks (RERs) of death by stage of disease

Proportions of patients receiving therapy and adjusted relative excess risks (RER) of death by country for patients with stage I (A), stage II (B) or stage III (C) breast cancer. Countries were ranked according to the sum of proportions of each given treatment and the country with the highest sum of given treatment was assigned as reference country. Breast surgery: % of patients receiving any type of breast surgery; axillary surgery: % of patients receiving axillary surgery if they received any type of breast surgery; radiotherapy: % of patients receiving radiotherapy if they have received breast conserving surgery; endocrine therapy: % of patients receiving endocrine therapy if they have received any type of breast surgery; chemotherapy: % of patients receiving chemotherapy if they have received any type of breast surgery. Error bars represent 95% confidence intervals. RER was adjusted for the following variables: age, year of diagnosis, grade and morphology.

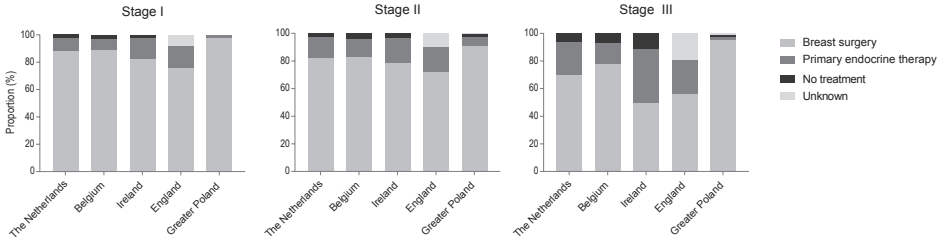

Figure 3. Proportion of patients receiving breast surgery, primary endocrine therapy or no therapy by stage of disease

Treatment patterns and survival differences

As shown in Figure 2A, representing stage I breast cancer, the proportion of patients receiving adjuvant endocrine therapy was considerably lower in the Netherlands while all other treatment modalities were comparable. No corresponding differences in adjusted RERs were observed. For stage II breast cancer, no evident pattern between treatment and survival outcomes between countries was observed. For stage III breast cancer, the proportion of patients receiving chemotherapy was substantially lower in the Netherlands compared to Belgium, while other treatment modalities did not differ greatly. Relative survival was not significantly different between Belgium and the Netherlands (Figure 2C). However, the proportion of patients receiving any type of surgery was lower in Ireland and England compared to Belgium while other treatment modalities were similar. Concordantly, relative survival was significantly lower in England and Ireland, compared to Belgium.

Sensitivity analyses

The additional sensitivity analysis showed little variation in treatment outcomes between patients diagnosed in 2008 or 2009 and the complete cohort within a country (Supplementary tables 4 to 6). Supplementary Table 7 shows five-year relative survival outcomes for all patients diagnosed in 2008 and 2009. The estimated relative survival and the crude and adjusted RERs in this cohort were comparable to estimates found in the complete cohort.

DISCUSSION

To our knowledge, this is the largest and most recent European population-based study presenting information on stage, tumour characteristics, treatment and survival outcomes in older patients with breast cancer. First, this study showed substantial variation in Europe for treatment of older patients with non-metastatic breast cancer diagnosed between 2000 and 2013. Second, this study reports substantial variation, most pronounced in advanced stage breast cancer, in survival among older patients between European countries. Third, substantially lower proportions of endocrine therapy in patients with stage I breast cancer

reported in the Netherlands was not accompanied by poorer survival outcomes; but for stage III breast cancer, poorer survival outcomes were observed in those countries were breast surgery was more frequently omitted. In general, this study suggests that how national and European guidelines lack evidence for treatment of breast cancer in older patients, resulting in poor consensus in the international community on how to optimally treat older patients.

The major strength of our study is that we have the largest available and most detailed population-based dataset in Europe. Although a randomized controlled trial (RCT) remains the golden standard for assessment of effectiveness of therapy, real world data has some advantages over RCTs, especially for older patients. It provides a broader and more faithful presentation of patterns of care and comparative effectiveness than RCTs. It furthermore shows a more balanced outcome of benefits and harms of treatment as relative survival represents all excess mortality due to breast cancer: both death directly related to breast cancer itself and death indirectly related to breast cancer.

Limitations in this study should be addressed. Most importantly, data provided by the CRs was not complete for all cases. We performed multiple imputation for missing patient and tumour characteristics. Simulation studies have shown that handling missing data by multiple imputation produces more accurate estimates of relative survival rates, especially for late-stage and high-grade tumours when compared to complete-case analysis.[17,18] Due to the high proportion of unknown hormone receptor status in England (71.3%), the imputed proportions of hormone receptor status as described in Table 1 might be more uncertain. For Belgium, hormone receptor expression was not available for the cohort at time of analysis but an additional analysis for the year of 2008 showed that hormone receptor distribution was comparable to other countries (data available on request). In England, data on systemic treatment was not complete but completeness improved over time. Due to incompleteness, non-registered treatment could not be interpreted as not given and therefore this was marked as unknown in tables and figures. For surgical outcomes in England, audits of selected data have shown good completeness but an element of uncertainty should be borne in mind. Moreover, in patients with very high age there might have been poorer diagnostic work-up leading to higher data incompleteness. Although age itself was available for all patients and included as a predictive factor in the multiple imputation, the imputed data for the oldest patients may be more uncertain compared to younger patients. Another potential weakness is the broad timeline for inclusion of patients and changes in diagnostic procedures and treatment in this period that could have affected variation in survival outcomes. For this reason we performed a sensitivity analyses, but survival rates in the cohort of the years 2008 and 2009 were comparable to complete cohort outcomes. This is in line with previous studies, showing no or limited improvement in survival rates for older patients with breast cancer over the last decade.[19-21] Data on individual factors that could af-

fect treatment outcomes and survival such as comorbidities, patient preferences and breast cancer subtypes as well as anti-Her2Neu therapy were not available or not complete in the CRs. In addition, there was great variation in the numbers of patients included between the participating countries. This has resulted in less precise estimates for the smallest groups of patients included hampering the interpretation of the data.

The design of this study allowed us to explore possible associations between treatment patterns and survival outcomes. Across Europe, large treatment variation exists and these variations can be used as a natural experiment as variation in assignment to a specific type of treatment was based on country of residence and was therefore not related to the outcome. This enabled us to draw a comparison between treatment patterns and outcomes in an observational setting.[8]

A notable finding was the low proportion of patients receiving adjuvant endocrine therapy with stage I breast cancer in the Netherlands compared to the other countries (19.6% vs. up to 84.6% in Belgium), while other treatments did not differ substantially between countries (Figure 2A). In the Netherlands, endocrine therapy is only recommended in hormone receptor positive patients with lymph node positive disease or otherwise unfavourable tumour characteristics (high grade or size ≥ 2 cm)[22], while in all the other countries adjuvant endocrine therapy is prescribed in all patients with hormone receptor positive breast cancer (for an overview of guidelines we refer to Supplementary Table 8). This variation in endocrine therapy was not linked with variation in survival between countries (Belgium 98.6%, Ireland 100.0%, The Netherlands 98.7%), potentially suggesting that adjuvant endocrine therapy does not influence breast cancer related mortality in a low risk group (Table 3). A previous study comparing Ireland and The Netherlands found similar results.[23] In addition, a population-based study from Denmark identified a subgroup of older patients with low risk breast cancer not treated with adjuvant endocrine therapy that was not at increased risk of mortality.[24] The pattern described in this study potentially suggests that adjuvant endocrine therapy might not contribute to additional survival benefit but further studies are necessary to validate these findings.

In patients with stage III breast cancer, variation in local treatment as well as systemic treatment was apparent. In Belgium, proportions of given local and systemic treatment were high compared to other countries. The proportion of patients in whom breast surgery was omitted was considerably lower in Belgium (22.0%) compared to Ireland (50.8%) while other treatment modalities were similar. Only limited evidence is available for the effectiveness of primary endocrine therapy. A meta-analysis showed inferior disease control for two to three years after diagnosis but no differences in overall survival compared to surgical treatment followed by adjuvant endocrine therapy.[25] The SIOG guideline recommends that

it should only be considered in patients with a life expectancy of less than five years.[2] In our study, Ireland had a significantly lower survival rate from stage III compared to Belgium (53.5% versus 60.1%, adjusted RER 1.27, 95% CI 1.07-1.50, P 0.007). Part of these differences might be explained by variation in breast surgery. It suggests that in this group of high risk patients breast surgery could result in additional breast cancer survival benefit.

This study demonstrates substantial international variation in type of locoregional treatment, while the various guidelines apply largely similar recommendations (Supplementary Table 8). Particularly in Poland, patients with early stage breast cancer were less likely to receive BCS (Table 2). In those patients with stage II breast cancer who received BCS, we found that radiotherapy was considerably lower in Poland than in other countries. For early stage breast cancer, omission of radiotherapy after BCS may be justified following publication of the PRIME II trial showing no overall survival difference and a small increase in local recurrences in patients aged 70 years or older with low risk hormone receptor positive breast cancer.[26] However, no such evidence is available for patients with higher stage disease.

The Netherlands was most conservative in the administration of chemotherapy. For stage III breast cancer, only 10.3% of the Dutch patients received chemotherapy, compared to 35.2% in Belgium. Other international observational studies have found similar patterns.[23,27] The conservative prescription of chemotherapy in the Netherlands can partly be explained by their national guidelines. It states explicitly that patients aged over 70 years should not receive chemotherapy, unless they are considered very fit.[22] No other national or European guidelines use this explicit age criterion (Supplementary Table 8).[28] The SIOG opposes guidelines using age as a criterion for any treatment as they state that 'age alone should not dictate any aspect of management of older individuals with breast cancer'.[2] Unfortunately, evidence for the effectiveness of chemotherapy in older patients is scarce. In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) polychemotherapy overview patients aged 70 years or older were significantly underrepresented. Despite this, the EBCTCG did not find evidence for differences in the effectiveness of chemotherapy for (fit) older patients.[29] Two clinical trials assessing the effect of chemotherapy versus no chemotherapy in older patients with breast cancer were closed prematurely due to poor accrual.[30,31] This also demonstrates the difficulty of performing trials in older patients. Although this study showed that relative survival was lower in The Netherlands (55.1%) compared to Belgium (60.1%), this difference was not significant after adjusting for confounders. Whether chemotherapy could be beneficial in a broader selection of older patients and if it should be offered more frequently in countries with low proportions of chemotherapy remains debatable.

In addition to given treatment, other factors could explain variation in both treatment and relative survival between countries. These include access to and quality of healthcare, varia-

tion in general health and comorbidities and variation in breast cancer subtypes between countries. For instance, national wealth and total national expenditure on health are related to breast cancer guideline adherence and breast cancer survival.[27] In Poland, the St. Gallen Consensus Conference guidelines were used during 2008 and 2009 but adherence to guidelines was affected by suboptimal reimbursement of treatment costs.[32] This could explain poorer survival outcomes for Greater Poland. The EUROCARE-5 study attributed lower survival outcomes in the UK partly to poor access to health care and hence a higher proportion of advanced stage of disease.[19] However, when looking further within specific stages, variation in survival was still apparent in our study. Furthermore, it has been suggested that cancer survival correlates with general health and burden of comorbidities.[33] For instance, if patients are unfit for surgery, radiotherapy, or chemotherapy due to comorbidities unrelated to cancer itself, it can also affect cancer related outcomes. Unfortunately, CRs could not provide us with comprehensive or comparable information on comorbidities for individual patients. Further information on other factors such as comorbidities and quality of life, may be key to gaining a better understanding of treatment processes and patient related outcomes. Additional studies should address the relationship between geriatric characteristics, comorbidities, cancer treatment and quality of life and survival outcomes to bridge the knowledge gap for a rapidly growing older population where more evidence-based treatment is urgently needed. Moreover, cultural factors across countries both in patient preferences and health care professionals could impact decision making in cancer treatment. For instance, we hypothesize that primary endocrine therapy is more common in the United Kingdom and Ireland because trials investigating this treatment have mostly been performed in these countries and this might have enhanced the enthusiasm to propose this type of treatment by health care providers.[25] Moreover, patient preferences for treatment might vary between younger and older patients and there might be differences in these preferences across countries. For the majority of older patients maintaining or increasing quality of life becomes more important than increasing length of life.[34] The burden of frequent hospital visits associated with radiotherapy and the risk of a second surgery are treatment-related aspects that withhold some older patients to undergo breast-conserving surgery.[35] Although a majority of patients would accept adjuvant chemotherapy, older patients are less willing to trade of cognitive or physical capacity for survival benefit.[36,37]

With this study from the EURECCA breast cancer group, we showed large variation in the treatment of older patients with breast cancer between European countries. This implies a lack of consensus in the international community on how to optimally treat older patients with breast cancer, reflecting the lack of evidence based knowledge and the struggle in clinical practice to treat the very heterogeneous older population. Overall, this study shows that for older patients with low risk breast cancer, differences in adjuvant endocrine therapy do not appear to impact survival outcomes, potentially suggesting overtreatment of these low

risk patients with adjuvant endocrine therapy. On the other hand, variation in the omission of breast surgery in older patients with high risk breast cancer appeared to impact survival substantially, indicating potential undertreatment in this high risk group. Balancing risk of death due to breast cancer and risk of death due to other causes seems essential for personalised treatment of older patients with breast cancer.

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Supplementary Table 1. Coverage, time period and methods of data collection and follow up for CRs

Country or region	Name of data registry	Incidence years	Approximate coverage of country or region (%)	Consecutive data	Identification of breast cancer diagnosis	Collection of data on treatment	Collection of data on vital status	Date of last follow up
The Netherlands	The Netherlands Cancer Registry	2000-2010	100%	Yes	Linkage with Dutch histopathology and cytopathology registry and national hospital discharge databank	Abstraction from individual patient records by the cancer registry	Linkage with municipal registry	1-1-2015
Belgium	Belgian Cancer Registry	2007-2010	100% (estimated case completeness: 98%)	Yes	Linkage with data of oncological care programs and laboratories for pathological anatomy	Linkage on patient level with health insurance databases (medical claims data)	Linkage with Crossroads Bank for Social Security	1-7-2015
Ireland	National Cancer Registry Ireland	2003-2009	100% nominal (98% case completeness)	Yes	Pathology reports & patient records from all hospitals & other treatment centres (active & passive registration); some additional cases from death certificates	Abstraction from patient notes & pathology reports by the cancer registry, additional linkage to prescription data to improve completeness of hormonal therapy data	Linkage with national death certificate database	31-12-2015
England	Public Health England	2000-2013	98%	Yes	All treating and diagnosing institutions send details of registered tumours to PHEs National Cancer Registration Service, which are cross-referenced to each other and national databases.	The treatment records for each tumour are added to by the National Cancer Registry Service.	Linkage with the Office for National Statistics.	31-12-2015

Supplementary Table 1. Coverage, time period and methods of data collection and follow up for CRs (*continued*)

Country or region	Name of data registry	Incidence years	Approximate coverage of country or region (%)	Consecutive data	Identification of breast cancer diagnosis	Collection of data on treatment	Collection of data on vital status	Date of last follow up
Greater Poland	Greater Poland Cancer Registry	2008-2009	100%	Yes	Information from cancer case report card, supplementary information from Greater Poland Cancer Centre patient records and Poznań University of Medical Sciences Pathology Department	Information from cancer case report card, supplementary information from Greater Poland Cancer Centre patient records.	Linkage with municipal registry - Central Statistical Office of Poland.	31-12-2013

Supplementary Table 2. Proportional distribution of locoregional and systemic treatment modalities by stage of disease

	Axillary surgery	Radiotherapy		Endocrine therapy		Chemotherapy	
	Yes %	Yes %	Unknown %	Yes %	Unknown %	Yes %	Unknown %
Stage I							
The Netherlands	89.7	92.4	0.0	19.6	0.0	0.5	0.0
Belgium	94.3	87.7	0.0	84.6	0.0	5.4	0.0
Ireland	84.4	74.7	0.0	79.5	0.0	6.0	0.0
England	89.2	44.6	55.4	47.5	52.5	5.9	94.1
Greater Poland	85.9	75.3	0.0	68.9	0.0	11.4	0.0
Stage II							
The Netherlands	92.8	88.8	0.0	64.5	0.0	2.2	0.0
Belgium	94.3	84.8	0.0	79.5	0.0	16.1	0.0
Ireland	91.6	77.4	0.0	75.3	0.0	19.4	0.0
England	92.8	48.9	51.1	47.9	52.1	14.0	86.0
Greater Poland	87.8	56.5	0.0	65.4	0.0	23.1	0.0
Stage III							
The Netherlands	94.2	85.4	0.0	70.7	0.0	10.3	0.0
Belgium	95.3	81.2	0.0	74.0	0.0	35.2	0.0
Ireland	87.9	73.2	0.0	72.6	0.0	31.6	0.0
England	92.5	38.0	62.0	43.8	56.2	28.1	71.9
Greater Poland	94.0	100.0	0.0	62.6	0.0	42.7	0.0

Axillary surgery: % of patients receiving axillary surgery if they received any type of breast surgery; radiotherapy: % of patients receiving radiotherapy if they have received breast conserving surgery; endocrine therapy: % of patients receiving endocrine therapy if they have received any type of breast surgery; chemotherapy: % of patients receiving chemotherapy if they have received any type of breast surgery.

Supplementary Table 3. Proportional distribution of patients receiving breast surgery, primary endocrine therapy or no therapy by stage of disease

	Any type of breast surgery	Primary endocrine therapy	No treatment	Unknown
	%	%	%	%
Stage I				
The Netherlands	88.3	9.4	2.3	0.0
Belgium	88.9	8.0	3.1	0.0
Ireland	82.2	15.1	2.7	0.0
England	75.8	15.6	0.0	8.6
Greater Poland	97.5	2.0	0.0	0.4
Stage II				
The Netherlands	81.8	15.6	2.6	0.0
Belgium	83.1	12.6	4.3	0.0
Ireland	78.8	17.9	3.3	0.0
England	71.9	18.3	0.0	9.9
Greater Poland	91.1	6.5	2.0	0.4
Stage III				
The Netherlands	69.9	23.6	6.5	0.0
Belgium	78.0	15.1	6.9	0.0
Ireland	49.2	39.2	11.6	0.0
England	55.9	24.9	0.0	19.3
Greater Poland	95.4	1.8	1.8	1.0

Supplementary Table 4. Proportional distribution of most extensive breast surgery for patients diagnosed in 2008 or 2009 by stage of disease

	No surgery	BCS	Mastectomy	Not specified
	%	%	%	%
Stage I				
The Netherlands	13.3	51.9	34.9	0.0
Belgium	11.5	65.1	23.3	0.0
Ireland	24.3	56.8	18.9	0.0
England	24.2	50.3	25.5	0.0
Greater Poland	2.5	21.1	52.4	24.0
Stage II				
The Netherlands	22.4	22.5	55.2	0.0
Belgium	16.5	36.6	46.9	0.0
Ireland	26.3	34.0	39.7	0.0
England	28.9	27.0	44.1	0.0
Greater Poland	8.9	8.3	66.1	16.7
Stage III				
The Netherlands	28.1	10.0	62.0	0.0
Belgium	23.1	14.6	62.3	0.0
Ireland	53.4	8.0	38.7	0.0
England	42.0	10.5	47.5	0.0
Greater Poland	4.6	3.4	81.8	10.2

BCS= breast conserving surgery

Supplementary Table 5. Proportional distribution of locoregional and systemic treatment modalities for patients diagnosed in 2008 or 2009

	Axillary surgery	Radiotherapy		Endocrine therapy		Chemotherapy	
	Yes %	Yes %	Unknown %	Yes %	Unknown %	Yes %	Unknown %
Stage I							
The Netherlands	96.2	93.2	0.0	29.8	0.0	1.1	
Belgium	94.4	88.6	0.0	84.5	0.0	5.4	0.0
Ireland	90.5	81.9	0.0	77.5	0.0	6.9	0.0
England	91.6	38.4	61.6	46.1	53.9	6.7	0.0
Greater Poland	85.9	75.3	0.0	68.9	0.0	11.4	93.3
Stage II							0.0
The Netherlands	95.6	89.9	0.0	72.4	0.0	2.8	
Belgium	93.7	84.9	0.0	79.6	0.0	17.0	0.0
Ireland	94.2	85.2	0.0	75.4	0.0	23.4	0.0
England	94.4	44.0	56.0	45.6	54.4	15.6	0.0
Greater Poland	87.8	56.5	0.0	65.4	0.0	23.1	84.4
Stage III							0.0
The Netherlands	96.6	89.9	0.0	70.5	0.0	16.0	
Belgium	95.4	79.7	0.0	73.1	0.0	37.0	0.0
Ireland	94.6	85.5	0.0	71.0	0.0	37.1	0.0
England	94.3	33.1	66.9	40.1	59.9	29.7	0.0
Greater Poland	94.0	100.0	0.0	62.6	0.0	42.7	70.3

Axillary surgery: % of patients receiving axillary surgery if they received any type of breast surgery; radiotherapy: % of patients receiving radiotherapy if they have received breast conserving surgery; endocrine therapy: % of patients receiving endocrine therapy if they have received any type of breast surgery; chemotherapy: % of patients receiving chemotherapy if they have received any type of breast surgery.

Supplementary Table 6. Proportion of patients diagnosed in 2008 and 2009 receiving breast surgery, primary endocrine therapy or no therapy by stage of disease

	Any type of breast surgery	Primary endocrine therapy	No treatment	Unknown
	%	%	%	%
Stage I				
The Netherlands	86.7	11.5	1.8	0.0
Belgium	88.5	8.6	2.9	0.0
Ireland	75.7	20.6	3.7	0.0
England	75.8	15.8	0.0	8.4
Greater Poland	97.5	2.0	0.0	0.4
Stage II				
The Netherlands	77.6	19.5	2.8	0.0
Belgium	83.5	12.4	4.1	0.0
Ireland	73.7	23.7	2.5	0.0
England	71.1	18.5	0.0	10.4
Greater Poland	91.1	6.5	2.0	0.4
Stage III				
The Netherlands	71.9	22.4	5.7	0.0
Belgium	76.9	16.4	6.6	0.0
Ireland	46.6	43.3	10.1	0.0
England	58.0	22.4	0.0	19.6
Greater Poland	95.4	1.8	1.8	1.0

Supplementary Table 7. Five year relative survival for patients diagnosed in 2008 and 2009

	RS	95% CI	Crude RER	95% CI	*P*	Adjusted RER	95% CI	*P*
Stage I								
Belgium	97.9	96.1-98.9	reference			reference		
Greater Poland	103.2	103.2-103.3	NA#		0.998	1.71#	0.02-117	0.801
Ireland	100.6	100.6-100.6	0.92#	0.11-7.48	0.938	0.28#	0.001-1600#	0.926
The Netherlands	95.9	94.6-96.8	0.61	0.21-1.81	0.374	1.41	0.35-5.61	0.617
England	94.0	93.2-94.7	0.99	0.41-2.40	0.981	2.42	0.54-10.93	0.229
Stage II								
Belgium	85.1	83.8-86.4	reference			reference		
Ireland	86.8	84.2-89.0	0.70	0.41-1.20	0.193	0.84	0.53-1.33	0.456
The Netherlands	81.4	80.1-82.7	1.08	0.84-1.38	0.559	1.11	0.88-1.40	0.401
Greater Poland	85.3	80.7-88.9	1.19	0.67-2.11	0.548	1.40	0.73-2.66	0.308
England	80.5	79.8-81.1	1.20	0.98-1.47	0.080	1.33	1.10-1.61	0.004
Stage III								
Belgium	60.9	58.7-62.9	reference			reference		
Greater Poland	58.5	52.7-63.8	1.37	0.93-2.02	0.113	1.59	1.38-1.79	0.015
The Netherlands	57.1	54.9-59.2	1.11	0.85-1.45	0.442	1.12	0.87-1.44	0.355
Ireland	54.7	50.7-58.6	1.35	1.00-1.83	0.053	1.36	1.02-1.82	0.038
England	50.6	49.3-51.8	1.50	1.26-1.78	<0.001	1.50	1.27-1.76	<0.001

Countries were ranked according to the sum of proportions of each given treatment and the country with the highest sum of given treatment was assigned as reference country. n/N: numbers of events/numbers at risk, RS: five-year relative survival, 95% CI: 95% Confidence Interval, crude RER: univariate relative excess risk, adjusted RER: multivariable relative excess risk, adjusted for the following confounders: age (continuous), year of diagnosis, grade, morphology. NA: not addressed. # Due to low excess mortality, RER could not be interpreted.

Supplementary Table 8. National treatment guidelines during 2000-2013 for each participating country

	The Netherlands[1,2]	Ireland[3]	Belgium[4]	England[5,6]	Poland[7,8]
Local surgery	**BCS: in all** patients with T1-2; N0-1 breast cancer	BCS: unifocal, anticipated acceptable cosmetic result, not occurring in 1st/2nd trimester of pregnancy, possibility to obtain histologically clear margins (5mm), patient preference, no contraindications to RT	BCS stage I or II	BCS: tumours <2.5 cm	2007: No BCS for multifocal disease Exclusion of multifocal disease by MRI may improve selection for conservative surgery.
	Mastectomy: patient preference contraindications to BCS and/ or RT	Mastectomy if contraindications to BCS and/or RT			
Axillary surgery	**Sentinel node i**n all patients, except when axillary metastasis is proven, or with a ≥ T2 and multicentric primary tumor, or the patient had previous axillary surgery	2000: Sentinel node still investigational, ALND (level I and II or I-III) in all patients 2007: - sonographic normal LN's and cytology not performed/negative: SN - proved LN involvement (by cytology or SN): axillary clearance (levels I and II or I-III)	Sentinel node: T < 3 cm, clinical and sonographic normal lymfenodes ALND when: Positive sentinel node Large T2 (3cm), or T3-4 Inflammatory BC Clinical palpable lymph nodes Multipel tumors	1996: Sentinel node biopsy is an accurate diagnostic tool in patients with clinically node negative breast cancer ALND in: Positive SLN and clinical proven positive lymph nodes	2007: Sentinel node biopsy was accepted as reliable and safe even in elderly patients ALND in: Positive sentinel node (including micrometastasis) and clinical proven or palpable positive lymph nodes
	Axillary lymph node dissection after positive sentinel node or in case of contraindications to sentinel node	2000: sentinel node still investigational, ALND (level I and II or I-III) in all patients 2007: - sonographic normal lymph nodes and cytology not performed/negative: sentinel node - proved sentinel node involvement (by cytology or sentinel lymph node biopsy): axillary clearance (levels I and II or I-III) After BCS		2009: ALND if: the sentinel node is positive (macrometastasis or micrometastasis), further axillary treatment (axillary dissection or radiotherapy) as well as adjuvant systemic therapy is recommended	

Supplementary Table 8. National treatment guidelines during 2000-2013 for each participating country (*continued*)

	The Netherlands[1,2]	Ireland[3]	Belgium[4]	England[5,6]	Poland[7,8]
Radiation therapy	Always after BCS After mastectomy: irradical resection, cT4, pT3 and ≥ pN2, involvement of pectoral muscle, or a positive axillary apex	After BCS After mastectomy in cases of high risk of local chest wall recurrence (tumor ≤3 mm of pectoral fascia or >4 positive axillary nodes)	After BCS After Mastectomy: when high risk for local recurrence: 4 or more positive lymph nodes Irradical resection	1996: After BCS, unless radiotherapy is contra-indicated or the patient is entered into a clinical trial. After mastectomy: consider radiotherapy	2007: Radiation therapy is clearly indicated after breast conserving surgery including a boost in younger patients. post-mastectomy radiation therapy for all patients with 4 or more involved lymph nodes
				2009: After BCS, unless radiotherapy is contra-indicated or the patient is entered into a clinical trial.	
Endocrine therapy	Postmenopausal N+ ER+/PR+	N+, ER/PR+	Postmenopausal ER+/PR+	1996: All patients with ER+ disease	2007: all patients with ER+ disease
	N0, tumour size ≤ 1 cm: none	N0, tumour size ≤ 1 cm, ER/PR+, grade 1: none or tamoxifen		2009: All patients with ER+ invasive breast carcinoma can potentially benefit from endocrine therapy	
	Since 2008: N0 tumour size 1-2 cm, grade 3 N0 tumour size 2-3 cm, grade 2-3 N0 tumour size ≥ 3 cm.	N0, tumour size ≥ 1 cm, ER/PR+, grade > 1			

Supplementary Table 8. National treatment guidelines during 2000-2013 for each participating country (*continued*)

	The Netherlands[1,2]	Ireland[3]	Belgium[4]	England[5,6]	Poland[7,8]
Chemo-therapy	Premenopausal N+	All N0 ER+/PR+ patients except "elderly": tumour size >1cm, all grades (before endocrine therapy)		1998:No specific recommendation: especially in premenopausal women with ER negative tumours	2007: Features that raise doubt about the adequacy of endocrine therapy alone include relatively lower expression of steroid hormone receptor, involvement (and particularly extensive involvement) of axillary lymph nodes, higher grade or proliferative markers, larger tumor size and extensive peri-tumoral vascular invasion.

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