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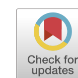
Original Research

Trends and variation in treatment of early breast cancer in European certified breast centres: an EUSOMA-based analysis



Lien van Walle [a,*,1], Didier Verhoeven [b,c,1], Lorenza Marotti [d], Antonio Ponti [e], Mariano Tomatis [d], Isabel T. Rubio [f], EUSOMA Working Group [2]

[a] *Belgian Cancer Registry, Brussels, Belgium*
[b] *Department of Medical Oncology, Breast Centre Voorkempen, AZ Klina, Brasschaat, Belgium*
[c] *University of Antwerp, Antwerpen, Belgium*
[d] *European Society of Breast Cancer Specialists (EUSOMA), Florence, Italy*
[e] *CPO Piemonte, Turin and European Society of Breast Cancer Specialists (EUSOMA), Florence, Italy*
[f] *Breast Surgical Oncology, Clinica Universidad de Navarra, Madrid, Spain*

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KEYWORDS
EUSOMA database;
Early breast cancer;
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Quality management

Abstract ***Background:*** Practice indicators (PI) measure provided care making use of real-world data. This study describes trends and variations in adjuvant treatment of early breast cancer (EBC) using the European Society of Breast Cancer Specialists (EUSOMA) database.
Methods: The analysis was conducted on anonymous cumulative data registered by 56 certified breast centres, which all entered at least 500 new diagnoses in the database in the 10-year period 2010–2019. Practice trends of radiotherapy, endocrine treatment, chemotherapy, and anti-HER2 therapy were evaluated. The association with age group (< 50, 50–69, ≥70) and geographical area of the centre (Northern, Central, Southern Europe; NE, CE, SE) was assessed with the Pearson Chi^2 test for independence in contingency tables.
Results: In total, 150,150 patients with EBC were selected. Overall, radiotherapy was administered more frequently in NE centres, and conversely, endocrine, chemo-, and anti-HER2 therapy were used more frequently in SE centres ($p < 0.001$). 46.9% of the pN1 patients

* *Corresponding author:* Belgian Cancer Registry, Koningsstraat 215 B7, 1210 Brussel, Belgium.
E-mail address: vanwalle.l@gmail.com (L. van Walle).

[1] Equally contributed as first authors.
[2] See Appendix.

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received postmastectomy radiotherapy, with significant differences by age and geographical region ($p < 0.001$). Adjuvant endocrine treatment for endocrine-sensitive carcinoma in situ was administered in 46.1%, with a decreasing trend during the study period (58.5–34.5%; $p < 0.001$). Anti-HER2 therapy was delivered in 75.6% of all patients with HER2BC T1a/bN0, patients older than 70 received anti-HER2 in 67.6% in SE compared to 31.3% in NE centres.
Conclusion: Important variations in EBC management between European certified breast centres have been demonstrated. PI using real-world data can help to monitor, evaluate, and eventually guide and align good clinical practice in the management of breast cancer.
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1. Introduction

Survival of breast cancer (BC) varies substantially worldwide, but standard of care practice also differs between countries and regions [1,2]. To improve global cancer survival, monitoring of different national and regional healthcare programs, reaching down to practices at the individual centre level becomes crucial [1].

Besides surgery, medical oncology and radiation oncology play an essential role in the management of early and locally advanced BC. The European Society for Medical Oncology takes care of updates on practical guidelines for the management of early BC [3]. Unfortunately, few data about the real-world use of different treatments and adherence to the guidelines in Europe are available [4–9].

Recommendations specifically focusing on the management of older patients with BC were recently updated [10]. Real-world data about the treatment of older patients at the population level were published by the EURECCA Breast Cancer Group and suggested a lack of consensus on how to treat geriatric patients [11].

For early BC, different subgroups were identified for adjuvant radiotherapy, the highest survival benefit being observed in patients with ≥4 positive lymph nodes [12,13]. Large variations in the use of radiotherapy for cancer patients altogether are observed across Europe [14]. For BC, considerable practice variation has been reported for indication, radiation dose, fractionation, and treatment planning [15].

Moreover, optimal management of ductal carcinoma in situ (DCIS), namely the role of adjuvant endocrine treatment, remains a challenge [16,17]. Real-world data related to this topic are rare and, to our knowledge, currently unavailable for Europe [18,19].

The first step to decrease practice variation is to reveal existing practice differences between countries and institutes. This study aims to report on the real-world use of adjuvant systemic therapy and radiotherapy for early BC in breast centres undergoing the European Society of Breast Cancer Specialists (EUSOMA) certification.

2. Material & methods

2.1. Data sources

The EUSOMA database is a central data warehouse of prospectively collected information, including records on primary BC cases diagnosed and treated in European breast centres that undergo the voluntary certification process and wish to participate in benchmarking and research activities. The EUSOMA database includes a set of quality indicators incorporated by the breast centres to allow standardised auditing and quality assurance. The database was started in 2006 and includes (dec.2021) over 200,000 patients. For this study, from the anonymous data of 67 European breast centres (Belgium = 8; The Netherlands = 2; Sweden = 1; Austria = 2; Switzerland = 5; Germany = 16; France = 1; Portugal = 3; Italy = 26; Spain = 1; Croatia = 1; Cyprus = 1) in the period 2010–2019, data from the centres with at least 500 new diagnoses were selected. To comply with privacy regulations, for the selected 56 centres, the name of the country was removed, and only the geographical area of each centre (Northern [Belgium, The Netherlands, Sweden], Central [Austria, France, Germany, Switzerland], and Southern [Italy, Portugal] Europe; NEuropean, CEuropean, and SEuropean) is available.

2.2. Practice indicators

The practice indicators (PI) were derived from the quality indicators published by EUSOMA [20]. For PI focused on older patients, specific recommendations were used [6].

2.3. Statistical analyses

The PI are classified into four domains: radiotherapy, endocrine treatment, triple-negative BC (TNBC), and HER2+ BC (HER2BC). Each PI is a proportion based on an eligibility criterion (the denominator) and another criterion selecting the subset of cases to be assessed (the numerator). For each PI, the association with age group (< 50, 50–69, ≥70) and geographical area of the breast

Table 1
Breast cancer in Europe, EUSOMA-data [2010–2019]; practice indicators and association with age and geographical area of centres.

Demographics	Total	Northern EU	Central EU	Southern EU	
N patients registered in EUSOMA	150,150 (100%)	18,894 (13%)	41,826 (28%)	89,430 (59%)	
N breast centres	56	9	21	26	
Average N patients registered by centre	2681	2099	1992	3440	
N of patients registered by year					
2010	8324	620	5888	1816	
2011	10,140	1216	6089	2835	
2012	9324	1300	4616	3408	
2013	11,317	1625	3544	6148	
2014	14,437	1570	3376	9491	
2015	16,243	1676	4258	10,309	
2016	17,848	2456	3505	11,887	
2017	19,554	2694	3113	13,747	
2018	20,084	2599	3036	14,449	
2019	22,879	3138	4401	15,340	
Age of patients at diagnosis					$p < 0.0001$
< 50	42,293 (29%)	4421 (24%)	9556 (23%)	28,316 (32%)	
50–69	69,584 (47%)	9116 (50%)	20,674 (51%)	39,794 (26%)	
≥70	34,701 (24%)	4849 (26%)	10,630 (26%)	19,222 (22%)	
Missing	3572 (-)	508 (-)	966 (-)	2098 (-)	
Practice indicators					
Radiotherapy	Total N	n	n/N (%)	Association with age[a] (*p*-value)	Association with geographical area of the centre (*p*-value)
PI1 - Radiotherapy after breast-conserving surgery for invasive BC	69081	63,981	**92,6%**	$p < 0.0001$	$p < 0.0001$
PI2 - Radiotherapy after mastectomy for BC ≤ pT2N0	12,846	1480	**11,5%**	$p < 0.0001$	$p < 0.0001$
PI3 - Radiotherapy after mastectomy for BC pN1	8162	3829	**46,9%**	$p < 0.0001$	$p < 0.0001$
PI4 - Radiotherapy after mastectomy for BC pN2/3	6083	5168	**85,0%**	$p < 0.0001$	$p < 0.0001$
Endocrine treatment in endocrine-sensitive BC					
PI5 - Endocrine treatment in operated endocrine-sensitive invasive BC	72,749	68,590	**94,3%**	$p < 0.0001$	$p < 0.0001$
PI6 - Endocrine treatment in operated endocrine-sensitive in situ BC	5086	2343	**46,1%**	$p < 0.0001$	$p < 0.0001$
PI7 - Patients with endocrine-sensitive invasive BC with endocrine treatment but no surgery	89,517	2427	**2,7%**	$p < 0.0001$	$p < 0.0001$
PI8 - Patients with endocrine-sensitive in situ BC with endocrine treatment but no surgery	3387	51	**1,5%**	$p < 0.0001$	$p < 0.0001$
TNBC					
PI9 - Patients with TNBC $T > 1$ and N0 receiving chemotherapy	778	628	**80,7%**	$p < 0.0001$	$p < 0.0001$
PI10 - Patients with TNBC N+ receiving chemotherapy	1139	987	**86,7%**	$p < 0.0001$	$p = 0.0013$
HER2+ BC					
PI11 - Patients with HER2+ BC > 1 cm or N+ receiving (neo-)adjuvant chemotherapy and no anti-HER2 therapy	6379	505	**7,9%**	$p = 0.0085$	$p < 0.0001$
PI12 - Patients with HER2+ BC > 1 cm or N+ receiving (neo-)adjuvant chemotherapy and trastuzumab	6379	5726	**89,8%**	$p = 0.0219$	$p < 0.0001$
PI13 - Patients with HER2+ BC ≤1 cm and N0 receiving adjuvant trastuzumab	1317	996	**75,6%**	$p < 0.0001$	$p < 0.0001$

[a] For the association with age, only patients with known age were included in the analysis; PI, practice indicator; BC, breast cancer; TNBC, triple-negative BC; EUSOMA, European Society of Breast Cancer Specialists.

centre (NEuropean, CEuropean, SEuropean) was assessed with the Pearson Chi^2 test for independence in contingency tables. Time trends have been assessed by the Chi^2 test for trends in proportions.

3. Results

3.1. Patient population

In total, 150,150 patients were included. Table 1 shows the distribution of the study population by geographical area of the centre, by year, and by age group. Contributions to the data set were delivered by 9 NEuropean centres, 21 CEuropean centres, and 26 SEuropean centres covering the registration of 18,894 patients (13%), 41,826 patients (28%), and 89,430 patients (59%), respectively. Fig. 1 depicts the proportional contribution of the three geographical groups of centres throughout the study period. NEuropean centres contributed stable in time, in contrast with the decreasing contribution of CEuropean centres and increasing contribution of SEuropean centres in time. The overall distribution of the registered patients by age category is very similar in centres located in NEurope and CEurope, 23–24% < 50, 50–51% 50–69, and 26% ≥70, but differs in centres located in SEurope where 32% of the population was < 50, 26% 50–69, and 22% ≥70 ($p < 0.0001$).

3.2. Practice indicators

The results of the 13 PI can be found in Table 1.

3.2.1. Radiotherapy: PI 1–4

3.2.1.1. PI1 Radiotherapy after breast-conserving surgery (BCS) for invasive BC

Out of 69081 patients with BCS, 63,981 received adjuvant radiotherapy (92.6%). Patients older than 70 received significantly less adjuvant radiotherapy (82%) in comparison to younger patients (96%), $p < 0.001$. Patients treated in NEuropean centres received significantly more radiotherapy in comparison to the rest, $p < 0.001$.

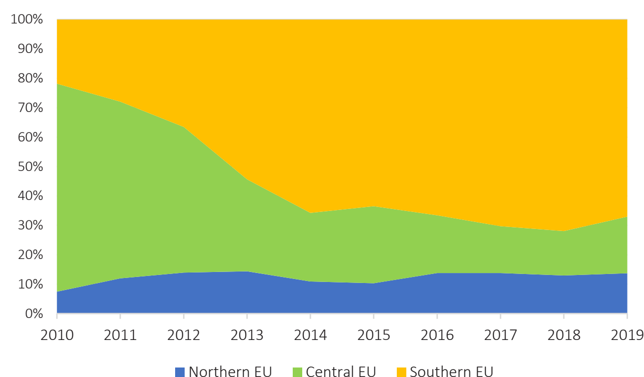

Fig. 1. Breast cancer in Europe, EUSOMA-data [2010–2019]; proportional registration contribution during the study period, by geographical area of the centre.

3.2.1.2. PI2-4 Radiotherapy after mastectomy (PMRT)

a) *For BC ≤pT2N0*; 11.5% (N = 1480) of the patients received PMRT; a significant declining trend is noted throughout the study period, $p = 0.005$ (Fig. 2). Patients older than 70 received significantly less PMRT (8%) in comparison to younger patients (12–13%), $p < 0.001$. Patients treated in NEuropean centres received significantly more PMRT in comparison to the rest (NEurope 24%, CEurope 13%, SEurope 8%), $p < 0.001$.
b) *For BC pN1*; 46.9% of the patients received PMRT, with fluctuating results in time. There was a significant association with age groups and with geographical area, $p < 0.001$ (Fig. 3).
c) *For BC pN2/3*; 85% of the patients received PMRT, with stable results in time, $p = 0.387$. There was a significant association with age groups and with geographical area, $p < 0.001$. In general, patients older than 70 received less PMRT, and patients in NEuropean centres received more PMRT.

3.2.2. Endocrine treatment in endocrine-sensitive BC: PI 5–8

3.2.2.1. PI5-6 Endocrine treatment in operated endocrine-sensitive BC

a) *Invasive BC;* 68,590 out of 72,749 patients (94.3%) received adjuvant endocrine treatment. There was a significant association with age groups ($p < 0.001$), 95% in patients younger versus 92% in patients older than 70, and with the geographical area ($p < 0.001$), patients receiving generally more endocrine treatment in SEuropean centres (NEurope 91%, CEurope 92%, SEurope 97%). Throughout the study period, the overall result remained > 90% (Fig. 5).
b) *In situ BC*; 46.1% of the patients received adjuvant endocrine treatment, and the associations with age groups and geographical area were significant, $p < 0.001$ (Fig. 4). Patients in SEuropean centres received generally more endocrine treatment (52% in SEurope versus 39–41% in N/CEurope). There is a decreasing trend throughout the study period, from 58.5% in 2010 to 34.5% in 2019, $p < 0.001$ (Fig. 5).

3.2.2.2. PI7-8 Patients with endocrine-sensitive BC with endocrine treatment but no surgery

a) *Invasive BC*; 2.7% of the patients (N = 2427) received endocrine treatment and no surgery of the primary tumour; the associations with age groups and geographical area were significant ($p < 0.001$), in NEuropean 7%, CEuropean 4%, and SEuropean centres 1%.
b) *In situ BC*; 1.5% of the patients (N = 51) received endocrine treatment and no surgery of the primary tumour; the associations with age groups and geographical area were significant ($p < 0.001$), in NEuropean 4%, CEuropean 4%, and SEuropean centres 0%.

3.2.3. Chemotherapy practice in TNBC: PI 9-10

3.2.3.1. PI9-10 Patients with TNBC receiving chemotherapy

a) *T > 1 and N0*; 628 out of 778 patients (80.7%) received (neo-)adjuvant chemotherapy; the associations with age

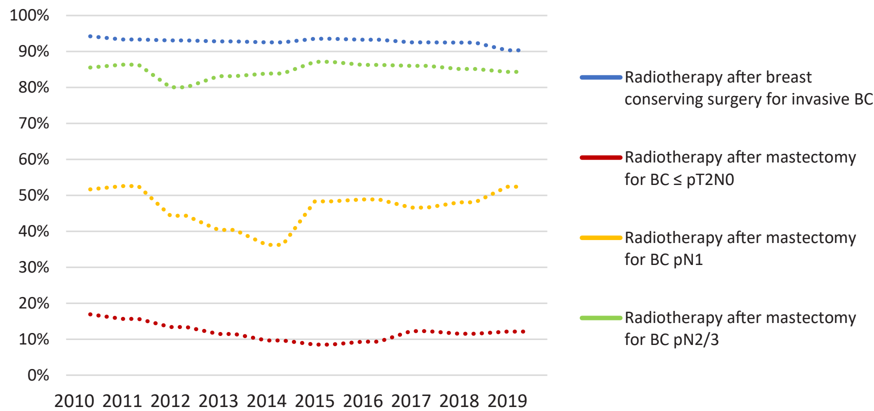

Fig. 2. Breast cancer in Europe, EUSOMA-data [2010–2019]; time trends radiotherapy practice for early breast cancer. BC, breast cancer; EUSOMA, European Society of Breast Cancer Specialists.

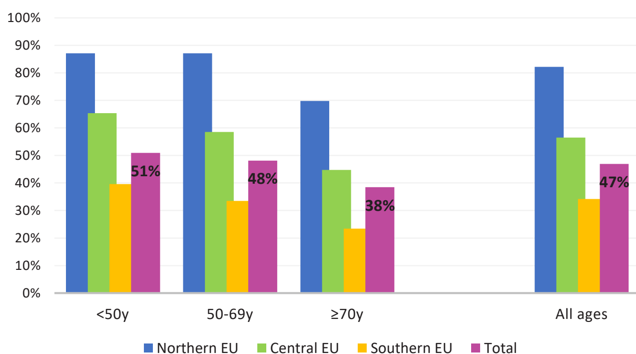

Fig. 3. Breast cancer in Europe, EUSOMA-data [2010–2019]; radiotherapy practice after mastectomy for breast cancer pN1, by age and by geographical area of the centre.

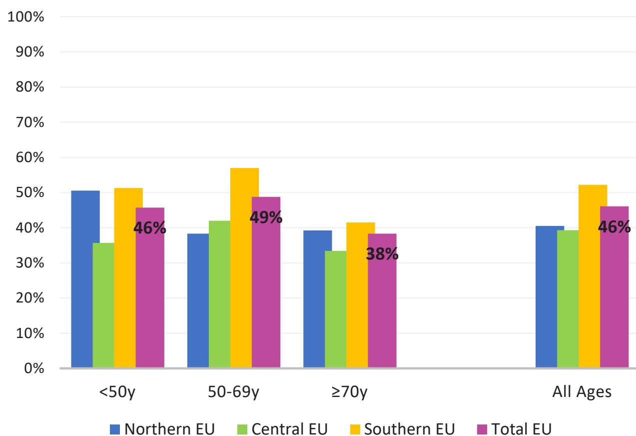

Fig. 4. Breast cancer in Europe, EUSOMA-data [2010–2019]; endocrine treatment practice for operated endocrine-sensitive in situ breast cancer, by age and by geographical area of the centre.

groups and geographical area were significant ($p < 0.001$). Patients older than 70 received significantly less chemotherapy (47%) compared to younger patients (> 90%), as did patients treated in NEuropean centres in comparison to the rest (NEurope 66%, CEurope 73%, SEurope 86%) (Fig. 6).

b) *N+*; 86.7% of the patients received (neo-)adjuvant chemotherapy; the associations with age groups and geographical area were significant. Patients older than 70 received significantly less chemotherapy (70%) compared to younger patients (> 95%), $p < 0.001$, as did patients treated in CEuropean centres in comparison to the rest (NEurope 88%, CEurope 81%, SEurope 89%), $p = 0.0013$.

3.2.4. HER2BC treatment: PI 11–13

3.2.4.1. PI11 Patients with HER2BC ≤1 cm and N0 receiving adjuvant trastuzumab

In total, 75.6% (N = 996) of the patients received trastuzumab. Both the associations with age groups and geographical area were significant. Patients older than 70 received significantly less trastuzumab (59%) in comparison to 50–69-year-old patients (76%) and patients younger than 50 (83%), $p < 0.001$. Patients treated in SEuropean centres received more trastuzumab in comparison to the rest (NEurope 68%, CEurope 67%, SEurope 79%), $p < 0.001$.

3.2.4.2. PI12-13 Patients with HER2BC > 1 cm or N+

a) *Receiving (neo-)adjuvant chemotherapy and no biological drug;* 7.9% (N = 505) of the patients received chemotherapy without a biological drug. There was a significant association with age groups ($p = 0.0085$), although the variation was small. Differences between geographical areas were significant with 8% in NEuropean, 14% in CEuropean, and 6% in SEuropean centres ($p < 0.001$).
b) *Receiving (neo-)adjuvant chemotherapy and trastuzumab;* 89.8% (N = 5726) of the patients received chemotherapy and trastuzumab combined. There was a significant association with age groups ($p = 0.0219$), although the variation was small. Differences between geographical areas were significant, with 87% in NEuropean, 83% in CEuropean and 92% in SEuropean centres ($p < 0.001$).

4. Discussion

This study reveals a considerable variation in adjuvant treatment practice of early BC within a selection of

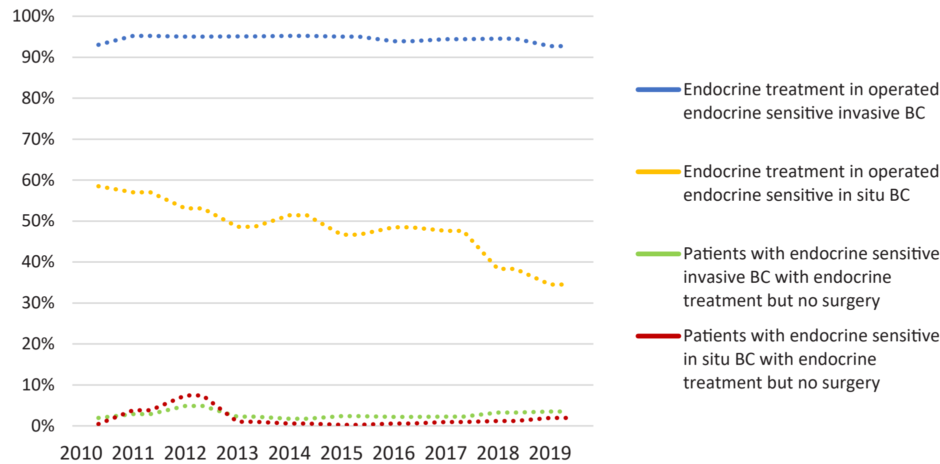

Fig. 5. Breast cancer in Europe, EUSOMA-data [2010–2019]; time trends endocrine treatment practice for endocrine-sensitive early breast cancer. BC, breast cancer; EUSOMA, European Society of Breast Cancer Specialists.

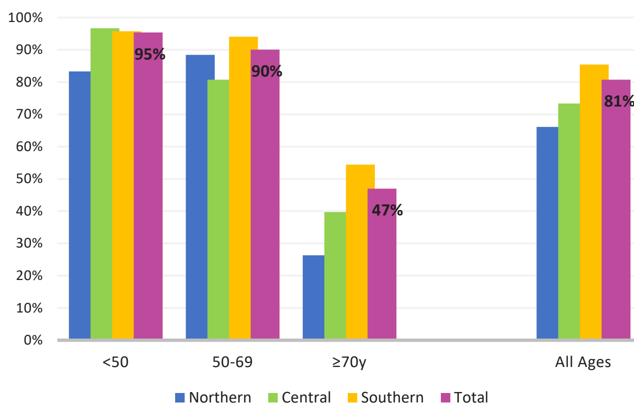

Fig. 6. Breast cancer in Europe, EUSOMA-data [2010–2019]; chemotherapy practice for triple-negative breast cancer $T > 1$ and N0, by age and by geographical area of the centre.

European breast centres that undergo the voluntary EUSOMA certification and wish to participate in benchmarking and research activities. Overall, radiotherapy is administered more frequently in NEuropean centres, and conversely, endocrine treatment, chemotherapy, and anti-HER2 treatment are used more frequently in SEuropean centres. Substantial practice variation was observed as for radiotherapy for BC with minimal lymph node invasion and endocrine treatment for in situ BC.

4.1. Radiotherapy practice

Our results show a geographical trend, with generally more radiotherapy administration in NEuropean centres. Moreover, the association between age and the use of radiotherapy was consistently smaller in NEuropean centres.

In our study, adjuvant radiotherapy after BCS was offered to the majority (82%) of patients aged 70 or older. Randomised controlled trial data showed that, in older women, radiotherapy after BCS with adjuvant endocrine treatment resulted in only a modest reduction in local recurrence without a difference in survival [21].

For PMRT, the clinical benefit in patients with high-risk disease has been demonstrated several years ago [22]. An important meta-analysis demonstrated that, both for patients with four or more (pN2/3) and patients with one to three positive nodes (pN1), radiotherapy reduces loco-regional recurrence and BC mortality [12]. In 2016, updated guidelines were proposed for PMRT, recommending to strongly consider radiotherapy in patients with pN1 [23]. Nevertheless, the advantage in the latter population is often debated [24,25]. The observed time trends of the PI in our study nicely illustrate the uniform practice for high-risk disease (pN2/3) throughout the study period, in clear contrast with the heterogeneous practice for pN1 disease. For pN1 disease, after a decreasing trend was noted between 2010 and 2014, a catch-up process is observed, illustrating the ongoing debate on this indication throughout the study period. In our study, 47% of the patients with pN1 disease were treated with PMRT, ranging from 34% in SEuropean to 82% in NEuropean centres.

A similar controversy exists for PMRT among node-negative (pN0) patients with large primary tumour size (≥5 cm) [26]. In our study, even for pN0 patients with tumour size smaller than 5 cm PMRT was given in 12%, ranging from 8% in SEurope to 24% in NEuropean centres.

4.2. Endocrine treatment practice

Our results reveal a geographical trend, with generally more endocrine treatment administration in SEuropean centres for invasive and in situ disease.

Tamoxifen reduces rates of ipsi- and contralateral BC recurrence and increases event-free survival; however, no difference in overall survival and more side-effects were observed [27]. Dose de-escalation of adjuvant

tamoxifen for intraepithelial neoplasia was shown to be effective at DCIS/invasive recurrence or contralateral BC without significant toxicity [28]. Recent findings suggest that cost-effective and clinical optimal treatment strategy of DCIS is surgery with radiotherapy for standard risk and surgery alone for good-risk DCIS [29]. The real-world data presented in our study reflect the ongoing search for optimal care, showing that adjuvant endocrine treatment for endocrine-sensitive in situ carcinoma is administered in one out of two patients in the EUSOMA-certified breast centres. Different national guidelines on this topic within Europe are known to play a role. In general, a decreasing trend is observed during the study period, from 59% of the patients who received adjuvant endocrine treatment in 2010 to 35% in 2019.

A place for primary endocrine treatment for elderly patients with early BC was demonstrated, with inferior local disease control but non-inferior survival compared to surgery [30,31]. Recently updated recommendations acknowledge this role in a specific setting [10]. The real-world data in our study reflect on the period prior to these latest recommendations, showing that 7% of elderly patients with endocrine-sensitive BC received primary endocrine treatment. Differences between NEuropean and SEuropean centres were substantial, ranging from 16% to 3%, respectively.

4.3. Chemotherapy practice for TNBC

TNBC is a heterogeneous disease with generally the worst prognosis of all BC [32]. The management of TNBC is continuously evolving, with particularly chemotherapy playing a central role [33].

Real-world data on chemotherapy administration in elderly BC patients showed a marked variation within Europe [11]. Unfortunately, data on chemotherapy use by molecular subtype are scarce. Our results revealed that, in TNBC, age plays a dominant role in the decision to start chemotherapy, with more than 90% of the patients younger than 70 receiving chemotherapy compared to 50–60% of the older patients. This result is in line with the latest recommendations [10].

4.4. Anti-HER2 treatment practice

Current guidelines restrict anti-HER2 treatment to HER2BC ≥0.5 cm (T1a), also in geriatric patients [3,10]. However, a recent population-based cohort study evaluated women with T1a/bN0 HER2BC, showing a BC recurrence of 3% with trastuzumab versus 12% without, and, respectively, a 5-year overall survival of 100% versus 90% [34].

In our study, anti-HER2 therapy was delivered in 76% of all patients with HER2BC T1a/bN0 and in 59% of the patients older than 70. Moreover, of the patients older than 70, in SEuropean centres 68% received anti-HER2 compared to 31% in NEuropean centres.

4.5. Strengths and limitations

Even though our study selects on EUSOMA-certified treatment centres, thereby introducing bias, we believe that real-world data on the management of early BC in recognised breast centres throughout Europe are a valuable source of information and provide supplementary information compared with data from randomised controlled trials. Recent CONCORD-3 data show differences in the 5-year survival of BC in the countries participating to this study, age-standardised 5-year survival ranging from 84.8% in Austria to 88.8% in Sweden, which emphasises the need to reflect on differences in daily practice between European countries and areas [1]. Unfortunately, the country of each centre needed to be anonymised and only the geographical area of each centre could be used, which limits the profundity of the geographical analyses. In addition, the choice to consider Belgium and The Netherlands as Northern Europe, together with Sweden, was pragmatic to enlarge the proportion of Northern European centres and not completely in line with European references [35].

4.6. Concluding remarks

Important variations in BC management in certified breast centres throughout Europe were revealed, presumably often grounded in a lack of clear evidence-based guidelines. Real-world data show opportunities supplementary to randomised controlled trial data, and PI making use of real-world data can help to monitor, evaluate, and eventually guide and align good clinical practice in the management of BC. International databases such as EUSOMA, which provide information on delivered care, are interesting both for benchmarking and improvement projects.

CRediT author statement

Conception/design: LvW, DV, LM, AP, MT. Provision of study material or patients: EUSOMA Working Group, LM, AP, MT. Collection and/or assembly of data: LM, AP, MT. Data analysis and interpretation: MT, LvW, DV. Manuscript writing: LvW, DV. Final approval of the manuscript: all authors.

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Declaration of Competing Interest

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.

Appendix

EUSOMA Working Group:

Valentina Baldini[7], Bettina Ballardini[8], Elisabetta Benozzi[9], Johannes Berger[10], Martine Berlière[11], Renzo Boldorini[12], Andrea Bonetti[13], Marina Bortul[14], Barbara Bussels[15], Katia Cagossi[16], Maria João Cardoso[17], Birgit Carly[18], Francesco Caruso[19], Carla Cedolini[20], Fabio Corsi[21 a,b], Elisabetta Cretella[22], Evelyn Despierre[23], Luca Despini[24], Rudy Leon De Wilde[25], Antonio Esgueva[26], Gianluca Fogazzi[27], Lucio Fortunato[28], José Luis Fougo[29], Daniele Generali[30], Matteo Ghilli[31], Simona Grossi[32], Alessandra Huscher[33], Christelle Levy[34], Guy Orye[35], Lorenzo Rossi[36], Stefania Montemezzi[37], Antonino Musolino[38 a,b], Ida Negreiros[39], Roger Olofsson Bagge[40], Gianmatteo Pagani[41], Ana Car Peterko[42], Annemie Prové[43], Gianni Saguatti[44], Dimitri Sarlos[45], Adele Sgarella[46], Gracienne Staelens[47], Mario Taffurelli[48], Giovanni Tazzioli[49], Corrado Tinterri[50], Hans Torrenga[51], Didier Verhoeven[b].

[7]Breast Center Rimini/Santarcangelo, Rimini, Italy.

[8]Centro di Senologia Gruppo MultiMedica, Ospedale San Giuseppe, Ospedale MultiMedica Castellanza, IRCCS MultiMedica, Italy.

[9]Centro di Riferimento Oncologico CRO Aviano IRCCS, National Cancer Institute, Aviano (PN) Italy.

[10]Johannes Berger, Brustgesundheitszentrum Tumorzentrum OÖ, Austria.

[11]Clinique du Sein Institut Roi Albert II, Cliniques Universitaires Saint-Luc, Bruxelles, Belgium.

[12]Breast Center AOU Maggiore della Carità di Novara.

[13]Breast Centre Azienda Ulss9 Scaligera, Legnago, Italy.

[14]Breast Unit Trieste - Azienda Ospedaliero Universitaria Giuliano Isontina (ASUGI).

[15]Radiotherapie, Gastro-Intestinale Oncologie en Senologie, AZ Delta Roeselare, Belgium.

[16]Breast Centre AUSL Modena Carpi, Italy.

[17]Breast Unit, Champalimaud Clinical Center/ Champalimaud Foundation, Lisbon, Portugal.

[18]Breast Unit and Prevention Center Isala, Department Gynecology-Obstetrics, CHU St. Pierre, Brussels, Belgium.

[19]Breast Centre Humanitas Catania, Humanitas Istituto Clinico Catanese S.p.A., Misterbianco, Catania, Italy.

[20]Unità Senologica Azienda Ospedaliero Universitaria Friuli Centrale - Udine Italy.

[21] [a]Breast Unit, Department of Surgery, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy.

[b]Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy.

[22]Oncologia Medica, Ospedale di Bolzano, Azienda Sanitaria Alto Adige, Italy.

[23]Breast Clinic – Department of Gynaecology and Obstetrics, OLV-ziekenhuis, Aalst, Belgium.

[24]Breast Surgery Unit, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy.

[25]University Hospital für Gynecology, Pius Hospital, Carl von Ossietzky University, Oldenburg, Germany.

[26]Clinica Universidad de Navarra, Regional multi-centre, Madrid, Spain.

[27]Medical Oncology, Istituto Clinico S.Anna – Brescia, Italy.

[28]Breast Center, UOC Senologia, Azienda Ospedaliera San Giovanni Addolorata, Roma, Italy.

[29]Breast Centre, Centro Hospitalar Universitário São João, Porto, Portugal.

[30] [a] Department of Medical, Surgery and Health Sciences, University of Trieste, Trieste, Italy.

[b] Breast Cancer Unit, ASST Cremona, Italy.

[31] Breast Centre AOUP, University Hospital of Pisa.

[32] Breast Centre ASL2 Abruzzo, Ortona, Italy.

[33]Centro Senologico Multidisciplinare Fondazione Poliambulanza, Brescia, Italy.

[34]Institut Norman du Sein, Centre François Baclesse, Caen, France.

[35] Jessa Ziekenhuis - Hasselt – Belgium.

[36]Breast Unit of Italian Switzerland and Oncological Institute of Italian Switzerland, Bellinzona, Switzerland.

[37]Centro Hub di Senologia Azienda Ospedaliera Universitaria Integrata Verona, Italy.

[38a]Department of Medicine and Surgery, University of Parma, Italy.

[b] Medical Oncology and Breast Unit, University Hospital of Parma, Italy.

[39]Lisbon Breast Unit, CUF Oncology, CUF, S.A. Lisbon, Portugal.

[40]Sahlgrenska Breast Center, Sahlgrenska University Hospital, Gothenburg, Sweden.

[41]Breast Centre, Istituto Europeo di Oncologia, Milano Italy.

[42]Department of General Surgery and Surgical Oncology, Clinical Hospital Centre Rijeka, Rijeka, Croatia.

[43]Medische Oncologie, GZA Ziekenhuizen, Oncologisch Centrum. Wilrijk, Belgium.

[44]Breast Centre AUSL di Bologna -Azienda USL di Bologna - IRCCS Scienze Neurologiche, Bologna, Italy.

[45]Departement of Gynaecologie, Breast and Gynaecological Tumorcenter, Kantonspital Aarau, Switzerland.

[46]Breast Centre, Unità Operativa Complessa di Chirurgia Generale 3 Senologica e dei tessuti molli, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
[47]Breast Clinic AZ Groeninge Kortrijk.
[48] UOC Chirurgia Senologica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy.
[49]Breast Unit Azienda Ospedaliero-Universitaria Policlinico Modena Italy.
[50] [a] Breast Unit, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy.
[b] Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve.
Emanuele, Milan, Italy.
[51]Deventer Ziekenhuis Hospital, Deventer, The Netherlands.

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