Treatment and outcomes in breast cancer patients: a cross section study from the EUSOMA Breast Centre Network

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Abstract

Introduction: The present study was designed to describe tumour features and treatments for patients with breast cancer. It also aimed at assessing the risk of distant metastases in relation to biological profiles, disease stages and treatment.

Methods: Data were analysed from 81,882 patients in the EUSOMA database (disease stages at diagnosis 0-IV; median age 61 years; range 20-100 years). All patients were treated between January 2016 and December 2021 in 53 Breast Centres within the EUSOMA certification process in 13 European countries. Cases were classified as HR+/HER2-, HR+/HER2+, HR-/HER2+ or HR-/HER2- and data were analysed accordingly.

Results: Univariable and multivariable analyses for distant metastases were conducted on a subset of 38,119 cases with information on whether or not they had developed them. Potential determinants included sub-group type, Ki67 value, disease stage, adjuvant systemic therapies and post-operative radiation therapy. In multivariable analysis, the HR-/HER2+ and HR-/HER2- sub-groups were associated with a higher risk of distant metastases than HR+/HER2-. Ki67 > 20% and advanced stage disease also carried a high risk. Radiation therapy emerged as a protective factor against distant metastases.

Conclusions: Present results show a large patient database offers an information stream that can be applied to reduce uncertainties in clinical practice. Database parameters need to be updated dynamically for outcome monitoring. Molecular prognostic factors, gene-expression signatures, tumour-infiltrating lymphocytes and circulating tumoral DNA should be added.

Key words: Breast cancer; Breast cancer treatments, Large database; Metastases; Risk factors; Protective factors

Highlights:

- European multi-centre data analysis of breast cancer, describing tumour features and treatments
- HR-/HER2+ and HR-/HER2- sub-types were linked with a high risk of distant metastases

- Ki67 > 20% and advanced stage disease carried a high risk
- Radiation therapy emerged as a protective factor against distant metastases

1. Introduction

Breast cancer, the most frequent malignancy in women worldwide, had an estimated 2.2 million plus new cases in 2020 and 685,000 related deaths (1). Overtime the mortality rate decreased in countries with better health services and earlier-stage diagnosis (2). In improving cancer care, an accurate estimate of an individual patient's risk of relapse is crucial.

Each of the four breast cancer subtypes is distinguished by expression of hormone receptors (HR) i.e. estrogen and progesterone receptors (respectively, ER and PgR) and human epidermal growth factor receptor-2 (HER2). They are designated as HR+/HER2-, HR+/HER2+, HR-/HER2+ and HR-/HER2. Each subtype has a different prognosis (3) which determines the choice of neo- and/or adjuvant systemic therapy (3-5) and, to a lesser extent, post-operative radiation therapy (6-9).

With the goal of improving and standardizing patient care, EUSOMA, the European Society of Breast Cancer Specialists, set up a central data-warehouse of prospectively collected information (EUSOMA-DB) for breast cancer patients in 2006. It includes pseudonymized individual records of cases that were diagnosed and treated in European Breast Cancer Centres undergoing voluntary certification in accordance with EUSOMA requirements (10,11). The EUSOMA-DB collects 166 variables, which include patient and tumour characteristics, information on treatment and follow-up. No personal identifiers exist on the entire database.

Each participating Breast Centre uploads data according to EUSOMA instructions, consenting to its use for certification, benchmarking and research projects. For certification purposes the EUSOMA data centre produces a yearly data report for each Breast Centre to show its compliance with EUSOMA Quality Indicators (12). In December 2021 the EUSOMA-DB encompassed data on over 200,000 patients.

By extrapolating from the EUSOMA-DB, this study aimed at:

1. describing tumour features and treatments for patients with invasive breast cancer at diagnosis who were enrolled between 2016 and 2021 so as to ensure a minimum follow-up;
2. evaluating the risk of distant metastases in relation to biological profiles, disease stages and treatments in a subgroup of patients with stage I-III disease.

2. Materials and methods

Between January 2016 and December 2021, data from 94,235 patients with newly diagnosed breast cancer were accrued from 53 Breast Centres within the EUSOMA certification process in 13 European countries (Austria=1, Belgium=8, Croatia=1, Cyprus=1, France=1, Germany=2, Italy=27, Poland=1, Portugal=3, Spain=1, Sweden=1, Switzerland=4, The Netherlands=2). After excluding 12,353 cases (13.1%) who could not be staged, 81,882 patients (disease stages at diagnosis 0-IV, median age 61 years; range 20-100 years) remained to constitute the cohort of this analysis.
Available variables were as follow: year of diagnosis; age at diagnosis; disease stage, ER status, PgR status, HR status (which includes ER and/or PgR receptor cases); HER2 status; Ki-67 value; type of surgery (breast conserving surgery or mastectomy); axillary treatment (sentinel lymph node biopsy, axillary dissection); systemic therapies (neoadjuvant therapy; adjuvant chemo- hormonal- targeted therapy); radiation therapy and treatment details; treatment discontinuation and reasons for it (toxicity, technical reason).

2.1 Statistical analysis

The four biological subtypes were compared. Categorical information was presented as distribution frequencies. Quantitative and qualitative variables were described using means/medians/ranges and frequencies/percentages, respectively.
In a subset of 38,119 cases with stage 0-III and data on whether or not they had developed distant metastases, inter-group comparisons were performed with the Cox proportional hazards model. Univariable analyses for distant metastases included sub-group type, Ki67 value, disease stage, adjuvant systemic therapies and post-operative radiation therapy. Variables that correlated significantly with outcome were inserted into the multivariable analysis.
All statistical analyses were performed using R version 4.0.5 (© The R Foundation); statistical significance was set at $p<0.05$.

3. Results

Table 1 reports data on age, tumour features and treatments as divided into the 4 breast cancer sub-types for the entire cohort of 81,882 cases.

Briefly, data accrual increased from 6,577 cases in 2016 to 18,905 in 2019. During the pandemic years of 2020 and 2021, accrual dropped markedly to 16,678 in 2020 and 12,663 in 2021.

Missing data varied for each parameter, ranging from 0.3 % for age to 14.7% for clinical stage. Over time, information completeness improved significantly: missing data dropped from 53.0% in 2016 to 2.0% in 2021 (trend test p-value < 0.001).

HR+/HER2- disease was prevalent (62,813 cases; 76.7%). After exclusion of missing data, stages I and II were prevalent (clinically staged: 61,884 cases (75.6%); pathologically staged: 60,958 cases (74.4%)). Also prevalent was Ki67 up to 20% (41,772 cases; 56.2%) which was mainly associated with HR+/HER2- disease.

Neoadjuvant chemotherapy was administered to 12,200 patients (16.7%) who, as expected, were distributed as follow across breast cancer sub-types: HR+/HER2-: 4,315/55,703 (7.7%); HR+/HER2+: 3,054/7,505 (40.7%); HR-/HER2+: 1,621/3,205 (50.6%); HR-/HER2-: 3,210/6,580 (48.8%).

Adjuvant chemotherapy was administered to 20,385 patients (27.1%) particularly in the HR+/ HER2+, HR-/HER2+ and HR-/HER2- sub-groups. Hormonal therapy was given to 63,680 cases (81.7%) who were almost exclusively HR+. Trastuzumab was prescribed for 10,595 patients (14.5%) who were mainly HER2+.

Mastectomy was undergone by 33.4% of patients with the others receiving breast conserving surgery. Sentinel node biopsy was performed in 80.8% of cases.

Radiation therapy was administered to 54,737 cases (72.4%), with a homogenous distribution across all four sub-groups, ranging from 65.7% in HR-/HER2+ to 73.2% in HR+/HER2-. It was delivered to the breast in 29,017 cases (86.3%); a boost was given to 18,898 cases (60.5%). The chest wall was irradiated in 9,310 cases (24.8%). Axillary lymph nodes were irradiated in 3,964 (12.3%), the supra-clavicular nodes in 6,512 cases (17.6%) and the internal mammary nodes in 4,163 (11.4).

Table 2 reports outcomes. At a median follow-up of 17.45 months (range 0.03-78.52 months) 2,358 patients (4.0%) died in the entire cohort compared with 9.4% in the HR-/HER2- sub-group, with a median time to death of 18.17 months (range: 0.07-72.28 months).

In 79,671 patients with stage 0-III disease, 32.3% had missing data on distant metastases. In 53,919 cases with available information, distant metastases occurred in 2,012 cases (3.7%), with 10.0% of the HR-/HER2- sub-group suffering metastases. Median time to distant metastases was 14.11 months (range: 0.03-72.71 months).

According to univariate analysis (Table 3), the risk of metastases was significantly higher in the other 3 sub-types than in HR+/HER2-. The maximum hazard ratio (HR) of 4.16 (CI 95%: 3.65-4.74) was observed in HR-/HER2-. Compared with Ki67 ≤ 20%, the HR of Ki67 > 20% was 3.22 (CI 95%,

2.86-3.61). Compared with stage I disease, all other stages were associated with a higher risk of distant metastases, with the risk being highest for stage III (HR 11.62; CI 95%: 10.00-13.45). The risk of distant metastases was significantly reduced by radiation therapy (HR 0.51; CI 95%: 0.45-0.57) and adjuvant systemic therapies (i.e. chemotherapy, hormonal therapy and targeted therapy) (HR 0.46; CI 95%: 0.39-0.53).

In multivariable analysis (Table 3), the HR-/HER2+ and HR-/HER2- sub-groups were associated with a higher risk of distant metastases than HR+/HER2-. Ki67 > 20% as well as stage II and III disease were confirmed to be associated with a high risk of distant metastases.

As far as regards treatments, radiation therapy was associated with better outcome while adjuvant systemic therapies emerged as non-significant.

4.Discussion

The EUSOMA voluntary certification process for specialist Breast Centres (11) is a major tool for monitoring and improving quality of patient care and breast centre performance because each Centre has to comply with EUSOMA Quality Indicators when contributing to the database (12), thus clearly providing useful cross-section information on dealing with the challenge of reaching and maintaining a high standard of care. The Eusoma datacentre issues each breast centre with an annual assessment of its performance for each quality indicator, which is used for an internal audit and quality indicators evaluation within the certification process.

Another advantage of such a large database is that it may overcome the limitations of randomized clinical trials, for which patients are selected by age, good clinical condition and with few or no comorbidities and the results of which risk being obsolete by time of publication. In fact, data from a large database provide information that can be applied to smooth out uncertainties in clinical practice. In this perspective, a specific strength of database evidence is that it may better reflect actuarial clinical care. Indeed, careful comparisons between randomized clinical trials and real-world evidence may present a productive line of research (13).

As present data derive only from EUSOMA-certified Centres, they may not provide a full picture of breast cancer care and treatment across Europe. Despite this limitation, database participation increased steadily from 2016 to 2019 as more centres entered the EUSOMA certification program. Accrual dropped markedly during the Covid pandemic years of 2020-21. One may hypothesize that fewer women were screened for breast cancer, leading to fewer operations and less attendance at specialist centres for post-operative treatment. In spite of this, quality of care was well maintained,

confirming that the certification process created robust structures, audit and quality control mechanisms that were capable of facing even unforeseen challenges (14).

The major finding in the present study is, in our opinion, data from over 80,000 real-world cases, which provide strong evidence in support of reports from elsewhere. Tumour features and treatments were as expected for European patients with breast cancer. Most patients were affected by early stage or locally advanced, invasive, breast cancer with stage IV accounting for under 3%. HR+/HER2- tumours were the most frequent, with HR-/HER2- occurring in only about 9% of cases. All HER2+ cases fell between these two extremes. Early-stage disease was detected in almost 75% of cases due, perhaps, to efficacious European screening programs (8). As expected 67% of patients received breast conserving surgery.

Evidence that centres involved in the EUSOMA certification process have been compliant with international guidelines derives from two major results. Sentinel node biopsy was peformed in 81% of cases and axillary lymph node dissection in only 24% in a series in which 82% of patients had pN0-1 disease (7,9,15,16). Secondly, neoadjuvant chemotherapy was delivered to 3,210 patients (49%) of HR-/HER2- patients, 3,536 of whom had a disease stage ranging from IIA to IIIC (17). All these data indicated that EUSOMA-certified Breast Centres had achieved a high standard of patient care.

With the aim of improving day-to-day clinical decisions the present analysis was conducted to identify the links between pathological sub-types, disease stage, adjuvant systemic treatments, radiation therapy and risk of distant metastases in patients with stage I-III disease. Present observations confirmed that patients with advanced disease and/or unfavourable biological sub-types (HR-/HER2+ and HR-/HER2) are at increased risk of distant metastases. Notably, time to metastases did not vary across sub-groups. In multivariable analysis systemic adjuvant therapies, i.e. chemotherapy, hormonal therapy and targeted therapy were not associated with a lower risk of metastases. This unexpected finding (18-25) may be due to only 5% of patients (2,264/38,119) not receiving adjuvant systemic treatment, thus preventing any significant difference from emerging. Post-operative radiation therapy was associated with a reduced risk of distant metastases (26,27), confirming its pivotal role in a multi-disciplinary approach.

One major limitation in the present study is its relatively short follow-up of approximately 18 months which precludes a long-term assessment of risk and incidence of metastases. It is worth nothing that after 18 months, the early relapse rate was very low (<5%) in patients still undergoing hormonal therapy (28). Missing data for the outcome of interest constitutes another limitation as univariate and multivariate analyses could be conducted on only 38,119 cases with follow-up data indicating whether distant metastases had occurred. Although missing variables are usually found in large

national cancer registries, they may introduce unintended bias into statistical analyses, thus lowering statistical power (29). EUSOMA Centres are being urged to make special efforts to routinely insert all items (diagnosis, therapy and follow-up data) for all cases. This is monitored during certification, along with adequate data managing expertise (30) in the core teams (10). To reflect progress, identify adequate quality indicators and provide for in-depth analysis EUSOMA has set up a working group to focus on updating the 2017 EUSOMA Quality Indicators and has newly developed Quality Indicators for metastatic breast cancer (31).

5.Conclusion

Data analysis of EUSOMA-DB cohort of over 80.000 breast cancer cases from 52 Breast Centres in 13 European countries that were treated from 2016 to 2019, provided evidence that the HR-/HER2+ and HR-/HER2- subgroups were associated with a higher risk of distant metastases than HR+/HER2-. Ki67 > 20% and advanced stage disease also carried a high risk. Radiation therapy emerged as a protective factor against distant metastases.

As EUSOMA certification is a continual process which encompasses advances in the field of breast cancer from diagnosis to cure, its database parameters need to be implemented dynamically for outcome monitoring, benchmarking activities and research projects. In addition to well-consolidated prognostic factors, such as nodal and tumor stage, prognostic factors such as gene-expression signatures, tumour-infiltrating lymphocytes and circulating tumoral DNA should be added forthwith. These will help satisfy the trend in modern medicine towards precision medicine which aims at tailoring treatment, surgery, systemic therapies and radiation therapy according to tumour biology and each patient's clinical features and genetics. For example, in clinical practice gaps currently exist between genomic-based adjuvant systemic therapy and non-genomic based radiation therapy. In the future, data from the EUSOMA data-warehouse should help stratify patients by genomic tests so as to identify suitable candidates for post-operative RT and determine its target volumes (32,33).

Table 1: Age, tumour features and treatment as divided into the 4 biological sub-types

81,882 invasive breast ca 2016-2021 (unclassifiable excluded)								
		HR+ / HER2-	HR+ / HER2+	HR- / HER2+	HR- / HER2-	Total		Missing
Cases		62813	8300	3506	7263	81882		
Year of diagnosis	2016	4978	697	301	601	6577		0,0%
	2017	8796	1226	499	1104	11625		
	2018	11739	1634	706	1355	15434		
	2019	14522	1902	819	1662	18905		
	2020	12841	1630	697	1510	16678		
	2021	9937	1211	484	1031	12663		
Age	Median	62	56	57	57	61		0,3%
	Range	20-100	20-97	21-100	20-98	20-100		
Clinical Stage	0	1278	244	202	143	1867		14,7%
	IA/B	32054	2912	862	2354	38182		
	IIA	12192	2022	782	2022	17018		
	IIB	4157	1093	551	883	6684		
	IIIA	1060	308	201	300	1869		
	IIIB	936	214	143	232	1525		
	IIIC	253	98	61	99	511		
	IV	1502	301	154	254	2211		
Pathological Stage	0	666	908	785	938	3297		10,6%
	IA	29772	3105	1074	2541	36492		
	IB	1728	215	79	107	2129		
	IIA	12431	1508	440	1336	15715		
	IIB	5452	572	153	445	6622		
	IIIA	3385	490	153	324	4352		
	IIIB	75	11	2	11	99		
	IIIC	1749	231	103	197	2280		
	IV	1502	301	154	254	2211		
pT	0	456	719	650	910	2735		6,7%
	1	41580	4530	1501	3487	51098		
	2	15291	1755	540	1575	19161		
	3	2179	251	85	331	2846		
	4	121	18	5	15	159		
	X	203	62	50	62	377		
pN	0	38387	5203	2391	4907	50888		6,6%
	1	13216	1610	483	1040	16349		
	2	2922	448	144	295	3809		
	3	1866	249	110	214	2439		
	X	2380	253	98	235	2966		
ER	ER-	282	162	3504	7262	11210		0,01%
	ER+	62528	8137	0	0	70665		
PgR	PgR-	7004	2143	3498	7252	19897		0,1%
	PgR+	55724	6139	0	0	61863		
HR	HR-	0	0	3506	7263	10769		0,0%

	HR+	62813	8300	0	0	71113		
HER2	HER2-	62813	0	0	7263	70076		0,0%
	HER2+	0	8300	3506	0	11806		
Ki67	Up to 20%	38357	2055	466	844	41722		9,4%
	21%+	18961	5418	2590	5510	32479		
Breast surgery	Breast conserving	41383	4687	1663	4109	51842		4,9%
	Mastectomy	18579	3166	1572	2704	26021		
% BCS	%	69,0%	59,7%	51,4%	60,3%	66,6%		
Sentinel Lymph Node Biopsy	No	10586	1923	1023	1809	15341		2,2%
	Yes	51079	6102	2330	5190	64701		
	%	82,8%	76,0%	69,5%	74,2%	80,8%		
Axillary Dissection	No	47873	5495	2189	5023	60580		2,1%
	Yes	13821	2560	1184	2024	19589		
	%	22,4%	31,8%	35,1%	28,7%	24,4%		
Neoadjuvant CT	No	51388	4451	1584	3370	60793		10,9%
	Yes	4315	3054	1621	3210	12200		
	%	7,7%	40,7%	50,6%	48,8%	16,7%		
Adjuvant CT	No	46741	3370	1491	3165	54767		8,2%
	Yes	10908	4289	1690	3498	20385		
	%	18,9%	56,0%	53,1%	52,5%	27,1%		
Months from index date	Mean	4,96	5,10	5,65	5,95	5,20		32,0%
Suspension for toxicity	%	8,2%	11,3%	11,4%	13,8%	10,1%		53,4%
HT	No	4013	1014	2957	6250	14234		4,8%
	Yes	56204	6893	255	328	63680		
	%	93,3%	87,2%	7,9%	5,0%	81,7%		
Months from index date	Mean	1,99	5,33	5,01	3,30	2,32		36,5%
Anti-HER2 drugs	No	54181	1618	674	6088	62561		10,7%
	Yes	1702	6054	2533	306	10595		
	%	3,0%	78,9%	79,0%	4,8%	14,5%		
Months from index date	Mean	4,30	3,83	3,88	4,66	3,97		36,2%
RT	No	15665	2153	1073	1977	20868		7,7%
	Yes	42769	5339	2051	4578	54737		
% RT	%	73,2%	71,3%	65,7%	69,8%	72,4%		
Months from index date	Mean	2,33	5,62	5,97	5,80	3,04		32,3%
RT technical suspension	No	26237	3082	1153	2599	33071		35,1%
	Yes	1880	242	89	218	2429		
	%	6,7%	7,3%	7,2%	7,7%	6,8%		

Abbreviations: HR = Hormone Receptors; HT = Hormonal Therapy; RT = Radiation Therapy;

Legend: Stage 0 = no residual disease after biopsy or neoadjuvant systemic therapy

Table 2: Outcomes: death and distant metastases

81,882 invasive breast cancer 2016-2021 (unclassifiable excluded)						
Outcomes		**HR+ / HER2-**	**HR+ / HER2+**	**HR- / HER2+**	**HR- / HER2-**	**Total**
Cases		62813	8300	3506	7263	81882
Months of follow-up	Median	17,28	18,60	17,54	17,28	17,45
(Overall)	Range	0,03 - 78,52	0,03 - 77,37	0,03 - 77,31	0,03 - 78,46	0,03 - 78,52
Life status (Missing 28%)	Alive	44008	5859	2313	4664	56844
	Dead	1567	191	115	485	2358
	% dead	3,4%	3,2%	4,7%	9,4%	4,0%
Months to death	Median	19,63	21,01	14,85	14,23	18,17
	Range	0,10 - 72,28	0,16 - 65,31	0,07 - 59,33	0,20 - 68,40	0,07 - 72,28

53,919 cases with invasive breast cancer and available information on distant metastases (2016-2021; Stage IV and unclassificble exscluded)						
		HR+ / HER2-	**HR+ / HER2+**	**HR- / HER2+**	**HR- / HER2-**	**Total**
Distant metastases	No	40517	5104	2056	4230	51907
(Missing 32,3%)	Yes	1184	230	129	469	2012
	%	2,8%	4,3%	5,9%	10,0%	3,7%
Months to distant met.	Median	15,34	13,68	13,4	13,13	14,11
	Range	0,03 - 68,83	0,07 - 72,71	0,07 - 71,39	0,16 - 61,17	0,03 - 72,71

Table 3: Distant metastases: results of univariable and multivariable analyses

		Cases	Mts (N)	Mts (%)	Univariable				Multivariable			
		38119	**1318**	**3,5%**	**HR**	**IC 95%**		**p-value**	**HR**	**IC 95%**		**p-value**
Type	HR+/HER2-	29972	781	2,6%	ref.				ref.			
	HR+/HER2+	3751	152	4,1%	1,48	1,24	1,76	**<0,001**	1,1	0,92	1,31	0,314
	HR-/HER2+	1401	65	4,6%	1,72	1,34	2,22	**<0,001**	1,45	1,12	1,88	**0,005**
	HR-/HER2-	2995	320	10,7%	4,16	3,65	4,74	**<0,001**	3,32	2,84	3,87	**<0,001**
Ki67	Up to 20%	22444	427	1,9%	ref.				ref.			
	21%+	15675	891	5,7%	3,22	2,86	3,61	**<0,001**	2,01	1,77	2,28	**<0,001**
Pathological stage	I	21346	278	1,3%	ref.				ref.			
	0	1656	34	2,1%	1,55	1,08	2,21	**0,016**	0,7	0,48	1	0,058
	II	11637	494	4,2%	3,19	2,75	3,69	**<0,001**	2,65	2,29	3,08	**<0,001**
	III	3480	512	14,7%	11,62	10,04	13,45	**<0,001**	11,54	9,94	13,39	**<0,001**
Adjuvant therapy	No	2664	174	6,5%	ref.				ref.			
	Yes	35455	1144	3,2%	0,46	0,39	0,53	**<0,001**	0,88	0,73	1,06	0,222
RT	No	9222	480	5,2%	ref.				ref.			
	Yes	28897	838	2,9%	0,51	0,45	0,57	**<0,001**	0,44	0,4	0,5	**<0,001**

Abbreviations: RT: Radiation Therapy

Stage 0 = no residual disease after biopsy or neoadjuvant systemic therapy

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Conflict of interests

LG: Advisory Board: Astra Zeneca/Daiichi Sankyo, Seagen. Support for attending meetings and/or travel: Ipsen, Novartis, Pfizer. Other non-financial interests: Member of Olympia Steering committee
FPD: Grants or contracts from any entity: Fondation belge contre le cancer (post-doctoral research grant). Consulting fees: Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, Daiichi Sankyo, Pierre Fabre, Gilead Sciences, Seagen, MSD (payment made to my institution). Support for attending meetings and/or travel: Amgen, Roche, Teva, Pfizer, Daiichi Sankyo/AstraZeneca, Gilead Sciences

References

1. Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians 7193): 209-249, 2021. DOI: 10.3322/caac.21660

2. Duggan C, Trapani D, Ilbawi AM *et al.* National health system characteristics, breast cancer stage at diagnosis, and breast cancer mortality: a population-based analysis. Lancet Oncol. 2021 Nov;22(11):1632-1642. DOI: 10.1016/S1470-2045(21)00462-9

3. Harbeck N, Penault-Llorca F, Cortes J, *et al* Breast cancer, Nature Reviews, Disease Primers Article citation ID: (2019) 5:66 doi.org/10.1038/s41572-019-0111-2

4. Loibl S, Poortmans P, Morrow M, *et al*. Breast Cancer Published Online April 1, 2021 doi.org/10.1016/S0140-6736(20)32381-3

5. Garutti M, Griguolo G, Botticelli A, *et al.* Definition of High-Risk Early Hormone-Positive HER2□Negative Breast Cancer: A Consensus Review Cancers 2022, 14, 1898. doi.org/10.3390/cancers14081898

6. Recht A, Comen EA, Fine RE, *et al.* Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. Practical Radiation Oncology (2016) 6, e219-e234 doi.org/10.1016/j.prro.2016.08.009

7. Burstein HJ, Curigliano G, Thürlimann B, *et al*. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021 Annals of Oncology, Vol. 32 issue 10: 1216-1235 doi.org/10.1016/j.annonc.2021.06.023

8. Cardoso F , Kyriakides S, Ohno S, *et al.* Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 30: 1194–1220, 2019 doi:10.1093/annonc/mdz173 Published online 4 June 2019

9. Ciabattoni A , Fabiana Gregucci F, De Rose F, *et al.* AIRO Breast Cancer Group Best Clinical Practice 2022 Update. Tumori Journal 2022, Vol. 108(2S) 1–144 DOI: 10.1177/03008916221088885

10. Biganzoli L, Cardoso F, Beishon M, *et al*. The requirements of a specialist breast centre. Breast. 2020 Jun;51:65-84. doi: 10.1016/j.breast.2020.02.003. Epub 2020 Feb 26. PMID: 32217457; PMCID: PMC7375681

11. www.breastcentrescertification.com

12. Biganzoli L, Marotti L, Hart CD, *et al*. Quality Indicators in Breast Cancer Care: un update from the Eusoma Working Group, European Journal of Cancer 86 (2017): 59-81 DOI: 10.1016/j.ejca.2017.08.017

13. Sheldrick RC. Randomized Trials vs Real-world Evidence: How Can Both Inform Decision-making? JAMA 2023 Apr 25;329(16):1352-1353. doi: 10.1001/jama.2023.4855

14. van Dam P, Tomatis M, Ponti A, *et al*. The impact of the SARS-COV-2 pandemic on the quality of breast cancer care in EUSOMA-certified breast centres. Eur J Cancer 177 (2022) 72-79 doi.org/10.1016/j.ejca.2022.09.027

15. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Breast Cancer. Version 4.2023 — March 23, 2023, www.nccn.org

16. Brackstone M, Baldassarre FG, Perera FE, *et al.* Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol July 20, 2021:DOI https://doi.org/10.1200/JCO.21.00934

17. Korde LA, Somerfield MR, Carey LA, *et al.* Neoadjuvant Chemotherapy, Endocrine Therapy,
and Targeted Therapy for Breast Cancer: ASCO Guideline. J Clin Oncol 39:1485-1505 DOI https://doi.org/10.1200/JCO.20.03399

18. Pondé, NF, Zardavas, D, Piccart, M. Progress in adjuvant systemic therapy for breast cancer. Nat Rev Clin Oncol 16, 27–44 (2019). https://doi.org/10.1038/s41571-018-0089-9

19. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other- factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials Lancet 2011; 378: 771–84. Published Online July 29, 2011 DOI:10.1016/S0140-6736(11)60993-8

20. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015; 386: 1341–52. Published Online July 24, 2015 http://dx.doi.org/10.1016/S0140-6736(15)61074-1

21. Francis PA, Pagani O, Fleming GF, *et al*. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. N Engl J Med 2018;379:122-37. DOI: 10.1056/NEJMoa1803164

22. Lambertini M, Blondeaux E, Perrone F, *et al.* Improving Adjuvant Endocrine Treatment Tailoring in Premenopausal Women With Hormone Receptor–Positive Breast Cancer. JCO Volume 38, Issue 12: 1258-1267 https://doi.org/10.1200/JCO.19.02242

23. Early Breast Cancer Trialists' Collaborative group (EBCTCG) Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. Lancet Oncol 2021; 22: 1139–50 DOI: 10.1016/S1470-2045(21)00288-6

24. von Minckwitz G, Huang CS, Mano MS, *et al.* Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019; 380:617-628 DOI: 10.1056/NEJMoa1814017

25. Masuda N, Lee SJ, Ohtani S, *et al*. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017; 376:2147-2159 DOI: 10.1056/NEJMoa1612645

26. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death:meta-analysis of individual patient data for 10 801 womenin 17 randomised trials. Published Online October 20, 2011 DOI:10.1016/S0140-6736(11)61629-2

27. EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality:meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014; 383: 2127–35 Published Online March 19, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60488-8

28. Mauriac L, Keshaviah A, Debled M, *et al*. Predictors of early relapse in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1-98 trial Annals of Oncology 18: 859–867, 2007 doi:10.1093/annonc/mdm001 Published online 14 February 2007

29. Plichta JK, Rushing CN, Lewis HC, *et al.* Implications of missing data on reported breast cancer mortality Breast Cancer Research and Treatment (2023) 197:177–187 https://doi.org/10.1007/s10549-022-06764-4

30. Schnapper G, Marotti L, Casella D, *et al*. Data managers: A survey of the European Society of Breast Cancer Specialists in certified multi-disciplinary breast centers. Breast J. 2018 Sep;24(5):811-815.doi: 10.1111/tbj.13043. Epub 2018 Apr 23.

31. Cardoso F, McCartney A, Ponti A et al, EUSOMA/ABC Global Alliance quality indicators for metastatic breast cancer care. In publication, Eur Journal Cancer, 2022

32. Mamounas EP, Mitchell MP, Woodward WA. Molecular predictive and prognostic markers in locoregional management. *J Clin Oncol.* (2020) 38:2310-2320. doi: 10.1200/JCO.19.02905

33. Regional Radiotherapy in Biomarker Low Risk Node Positive Breast Cancer (TAILOR RT) at ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03488693