



A European, Observational Study of Endocrine Therapy Administration in Patients With an Initial Diagnosis of Hormone Receptor-Positive Advanced Breast Cancer

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Abstract

In this observational study we estimated the proportion of postmenopausal breast cancer patients initially diagnosed with hormone receptor (HR)-positive locally advanced or metastatic breast cancer (LA/MBC), using data from 6 European cancer registries (n = 244,268 with known HR status and disease stage). Approximately 19,002 patients (7.8%) received an initial diagnosis of HR-positive LA/MBC; 74.5% (n = 14,157) of these received subsequent endocrine therapy as per guideline recommendations.

Background: Despite guideline recommendations, reports suggest that a proportion of patients with hormone receptor (HR)-positive locally advanced or metastatic breast cancer (LA/MBC) might not receive endocrine therapy. The aims of this study were to estimate the proportion of postmenopausal patients with an initial (primary) diagnosis of HR-positive LA/MBC in Europe, and to assess the administration of endocrine treatment in these patients.

Materials and Methods: Fourteen national and regional cancer registries across Europe were invited to participate in this observational study. Six registries each provided anonymized clinical information on > 5000 postmenopausal women with breast cancer diagnosed between January 2000 and December 2014, including age at diagnosis, estrogen and/or progesterone receptor status, disease stage, and receipt of endocrine therapy. The proportion of patients with an initial diagnosis of HR-positive LA/MBC and, of these, the proportion who received endocrine therapy, was calculated. **Results:** Registries from Belgium, England, Ireland, Norway, The Netherlands, and Munich, Germany provided data. In total, 316,680 postmenopausal women were diagnosed with breast cancer, including 244,268 with known HR status and disease stage. Of these patients, 19,002 (7.8%) had a primary diagnosis of HR-positive LA/MBC. This proportion ranged from 5.4% (N = 4484) in England to 12.7% (N = 4085) in Germany. Most of these patients (n = 14,157; 74.5%) received endocrine treatment, ranging from 55.5% (n = 445) in

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Submitted: Nov 16, 2017; Accepted: Nov 24, 2017; Epub: Nov 29, 2017

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Norway to 88.1% (n = 443) in Belgium. **Conclusion:** These results indicate that a sizeable proportion of postmenopausal patients in Europe received a primary diagnosis of HR-positive LA/MBC, and that almost three-quarters received subsequent endocrine therapy as per guideline recommendations.

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Keywords: Endocrine treatment, European comparison, Locally advanced/metastatic breast cancer, Population-based cancer registries

Introduction

Breast cancer is one of the most prevalent cancers among women,¹ and most breast cancers are classified as hormone receptor (HR)-positive at diagnosis.² Endocrine therapy is the current standard treatment for patients with HR-positive breast cancer, in the adjuvant setting as well as for advanced disease, in the absence of rapidly progressive disease or proven endocrine resistance.³⁻⁵ Therefore, only a small proportion of patients with locally advanced (LA) or metastatic breast cancer (MBC) might be expected to be endocrine therapy-naïve. This patient subgroup might comprise patients who received an initial (primary) diagnosis of HR-positive LA/MBC, and patients with recurrence or metastasis from an early stage breast cancer who did not receive endocrine therapy for their previous disease. There are limited data reporting the prevalence of these patient subgroups.

Studies of small retrospective databases have reported that of all patients with known HR status, approximately 13% to 17% had a primary diagnosis of HR-positive advanced disease (LA/MBC).⁶⁻⁸ However, these studies did not assess subsequent therapy in this patient group, and, to our knowledge, a comprehensive evaluation of the size of this patient population has not been performed.

The aims of this study were to ascertain the proportion of postmenopausal women with HR-positive LA/MBC at primary diagnosis, and to calculate the proportion of these patients who received endocrine therapy.

Materials and Methods

Study Population

This was an observational, retrospective study conducted by the European Registration of Cancer Care collaboration, which recruited patients from national and regional cancer registries across Europe. Participating registries provided anonymized data on postmenopausal women diagnosed with breast cancer, and only registries that provided data on > 5000 patients were included in the analysis.

Patients who met the following inclusion criteria were eligible for inclusion in the study: female sex, postmenopausal (55 years of age or older), and diagnosed with invasive breast cancer according to the *International Classification of Diseases for Oncology* (third edition)⁹ breast cancer criteria between January 2000 and December 2014. The population-based cohort included all patients fulfilling the inclusion criteria. For this type of study, ethical approval and informed consent were not required.

Data Collection

Anonymized data were collated from the cancer registries, which employ trained registrars to collect data from patient hospital files

after notification by pathology laboratories, or from other sources such as radiation facilities and hospital inpatient databases. Most registries recorded the first line of treatment prescribed within a year of diagnosis.

Patient clinical information requested included: date of diagnosis, age of patient, and tumor, node, metastasis [TNM] stage of tumor at diagnosis (clinical stage) and pathological stage. LA breast cancer was defined as TNM stage IIIb or IIIc (according to the *TNM Classification of Malignant Tumours*, sixth and seventh editions^{10,11}); MBC was defined as TNM stage IV. Estrogen receptor (ER) and progesterone receptor (PR) status (positive, negative, or unknown) was obtained, along with information on subsequent endocrine therapy (yes or no). HR-positive status was defined as having pathologically confirmed ER-positive and/or PR-positive breast cancer. Patients with known HR status were selected for inclusion in further analyses. Missing data (stage and HR status) for patients were classified as unknown; these patients were initially included in the cohort.

Data Analysis

Using the pooled as well as country-specific data, the proportion of patients with HR-positive LA/MBC at primary diagnosis was calculated, as well as the proportion of patients who received subsequent endocrine treatment. Descriptive results are presented; no formal statistical analyses were performed, because raw data were not provided by all registries.

Results

Patient Population

Fourteen cancer registries in Europe were invited to participate in the study. Five national registries (Belgium, England, Ireland, Norway, and The Netherlands) and 1 regional registry (Munich, Germany), who each contributed data from > 5000 patients, participated in this study. Registries that did not participate either did not respond to the invitation, or did not record the relevant data in the format required.

Data received (January 2000 to December 2014) were analyzed in November 2016. Data from Belgium were included for 2008 only, because this was the only year for which HR status was available. At the time of this analysis, not all diagnosed patients in England for 2014—or in Ireland for 2013 and 2014—were registered in the cohort.

In total, data for 316,680 postmenopausal women with breast cancer were collected (Table 1). Median patient age at diagnosis ranged across countries from 67.0 years in Ireland to 69.0 years in England and Belgium.

Table 1 Identification of HR-Positive Patients With Known Disease Stage, Overall and According to Country

	England ^a	Norway	Ireland ^b	Germany ^c	Belgium ^d	The Netherlands	Total
All Postmenopausal Breast Cancer Cases 2000-2014, n	125,408	27,159	19,179	40,181	6658	98,095	316,680
Median Age of Included Patients, Years (Range)	69.0 (55.0-112.0)	67.6 (55.0-105.6)	67.0 (55.0-101.0)	68.1 (55.0-107.5)	69.0 (55.0-99.0)	68.7 (55.0-103.0) ^e	
Assessed for HR (ER and/or PR) Status and Known Disease Stage, n (% All Breast Cancer Cases)	83,370 (66.5)	12,962 (47.7)	15,393 (80.3)	32,218 (80.2)	4848 (72.8)	95,477 (97.3)	244,268 (77.1)
Assessed for ER status, n (% of All Breast Cancer Cases)	81,646 (65.1)	14,414 (53.1)	16,059 (83.7)	37,378 (93.0)	5706 (85.7)	95,782 (97.6)	250,985 (79.3)
ER-Positive, n (% Assessed for Known ER Status)	70,690 (86.6)	12,267 (85.1)	13,254 (82.5)	32,385 (86.6)	4863 (85.2)	81,591 (85.2)	215,050 (85.7)
ER-Negative, n (% Assessed for Known ER Status)	10,956 (13.4)	2147 (14.9)	2805 (17.5)	4993 (13.4)	843 (14.8)	14,191 (14.8)	35,935 (14.3)
Assessed for PR Status, n (% of All Breast Cancer Cases)	37,188 (29.7)	14,305 (52.7)	13,137 (68.5)	37,301 (92.8)	5685 (85.4)	93,529 (95.3)	201,145 (63.5)
PR-Positive, n (% Assessed for Known PR Status)	25,047 (67.4)	9356 (65.4)	8292 (63.1)	29,134 (78.1)	4287 (75.4)	61,714 (66.0)	137,830 (68.5)
PR-Negative, n (% Assessed for Known PR Status)	12,141 (32.6)	4949 (34.6)	4845 (36.9)	8167 (21.9)	1398 (24.6)	31,815 (34.0)	63,315 (31.5)
HR-Positive With Known Disease Stage, n (% All Breast Cancer Cases)	53,197 (42.4)	11,012 (40.5)	12,693 (66.2)	28,264 (70.3)	4197 (63.0)	81,837 (83.4)	191,200 (60.4)

Abbreviations: ER = estrogen receptor; HR = hormone receptor; PR = progesterone receptor.

^aData from 2014 were not included (data not complete at the time of this analysis).

^bData from 2013 and 2014 were not included (data not complete at the time of this analysis).

^cRegional data set.

^dData for 2008 only.

^eAge reported by The Netherlands registry as mean values, rather than median.

Endocrine Therapy in Patients With HR-Positive LA/MBC

Hormone Receptor Status

Of the female postmenopausal breast cancer patients included in the analysis, 77.1% had known disease stage and were assessed for HR status (n = 244,268 of 316,680). There was variation in the availability of HR status across the different countries, ranging from 47.7% (n = 12,962) in Norway to 97.3% (n = 95,477) in The Netherlands. ER status was available for 250,985 patients, 85.7% (n = 215,050) of whom were ER-positive. PR status was available for 201,145 patients, of whom 68.5% (n = 137,830) were PR-positive. The proportion of patients who had ER-positive breast cancer ranged from 82.5% (n = 13,254) in Ireland to 86.6% in England (n = 70,690) as well as Germany (n = 32,385), and those with PR-positive breast cancer ranged from 63.1% (n = 8292) in Ireland to 78.1% (n = 29,134) in Germany.

Hormone Receptor-Positive LA/MBC at Primary Diagnosis

Disease stage and HR status was known for 244,268 patients. Of these, 7.8% (n = 19,002 of 244,268) had a primary diagnosis of HR-positive LA/MBC, of which 3.5% (n = 8540 of 244,268) were LA and 4.3% (n = 10,462 of 244,268) were MBC (Figure 1; Table 2).

The proportion of patients with a primary diagnosis of HR-positive LA/MBC ranged across countries from 5.4% (n = 4484) in England to 12.7% (n = 4085) in Germany. Of patients with a primary diagnosis of HR-positive LA/MBC, 44.9% (n = 8540 of 19,002) were diagnosed with LA breast cancer, and 55.1% (n = 10,462 of 19,002) were diagnosed with MBC (Figure 2; Table 2). The percentage varied between countries (LA: 29.8% (n = 374) in Ireland to 52.4% (n = 4126) in The Netherlands; MBC: 47.6% (n = 3745) in The Netherlands to 70.2% (n = 883) in Ireland).

Most patients with a primary diagnosis of LA/MBC went on to receive subsequent endocrine therapy (74.5%; n = 14,157 of 19,002; Figure 3; Table 2). This proportion ranged across countries from 55.5% (n = 445) in Norway to 88.1% (n = 443) in Belgium. In total, 25.5% (n = 4845 of 19,002) of patients with a primary diagnosis of HR-positive LA/MBC did not receive endocrine therapy.

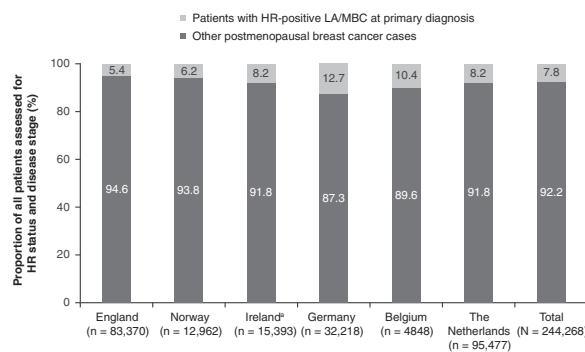
Discussion

This large retrospective review of data from > 300,000 patient cases from 1 regional registry and 5 national European registries provides an estimate of the prevalence of postmenopausal women with a primary diagnosis of HR-positive advanced disease. In summary, approximately 8% of women (> 19,000 patients) with known HR status and disease stage were diagnosed with LA/MBC at primary diagnosis. These results indicate that there might be a substantial population of women with a primary diagnosis of HR-positive LA/MBC, and that the size of this population could vary between European countries. Furthermore, this study shows that almost three-quarters (74.5%) of these patients received subsequent endocrine treatment. However, it should be noted that treatment compliance was not recorded for this study.

Although most patients were prescribed endocrine therapy, approximately one-quarter of patients (25.5%) did not receive endocrine therapy after a primary diagnosis of HR-positive LA/MBC. Some patients might not have received endocrine therapy because of chemotherapy being the preferred treatment option (ie, in patients with rapidly progressing disease, or visceral spread^{3,4}). In addition, we investigated patients with stage IIIB, stage IIIC, and stage IV breast cancer, and did not ascertain whether any of these patients underwent surgery with curative intent. Guidelines recommend surgery for LA breast cancer only after initial systemic therapy,^{3,4} whereas policies on surgery for metastatic disease differ according to country, and can depend on the disease localization and number of metastases. The results of larger prospective studies on the role of surgery for patients who present with MBC at primary diagnosis are eagerly awaited.^{3,4}

Despite similar proportions of patients with a primary diagnosis of HR-positive LA/MBC (5%-13%), the percentage of these who received subsequent endocrine therapy differed between countries, ranging from 55.5% in Norway to 88.1% in Belgium. This could reflect potential differences in practice between cancer registries in the different countries, which might have led to variances in the degree of underdocumentation of endocrine therapy, or could represent actual differences in the administration of endocrine therapy in these countries. For example, a recent physician case-

Figure 1 Proportion of Patients With Known HR Status and Disease Stage Who Had LA/MBC at Primary Diagnosis



Abbreviations: HR = hormone receptor; LA/MBC = locally advanced/metastatic breast cancer. ^a Locally advanced cases might be under-represented in the Irish data set (see Discussion).

Table 2 Patients With a Primary Diagnosis of HR-Positive LA/MBC and Endocrine Therapy Use, Overall and According to Country

	England ^a	Norway	Ireland ^b	Germany ^c	Belgium ^d	The Netherlands	Total
Patients Assessed for HR Status and Disease Stage, n	83,370	12,962	15,393	32,218	4848	95,477	244,268
HR-Positive LA/MBC at Primary Diagnosis, n (% of Patients Assessed for HR Status and Disease Stage)	4484 (5.4)	802 (6.2)	1257 (8.2)	4085 (12.7)	503 (10.4)	7871 (8.2)	19,002 (7.8)
LA, n (% HR-Positive LA/MBC at Primary Diagnosis)	1772 (39.5)	384 (47.9)	374 (29.8)	1648 (40.3)	236 (46.9)	4126 (52.4)	8540 (44.9)
MBC, n (% HR-Positive LA/MBC at Primary Diagnosis)	2712 (60.5)	418 (52.1)	883 (70.2)	2437 (59.7)	267 (53.1)	3745 (47.6)	10,462 (55.1)
With Subsequent Endocrine Therapy, n (% HR-Positive LA/MBC at Primary Diagnosis)	2796 (62.4)	445 (55.5) ^e	1019 (81.1)	2526 (61.8)	443 (88.1)	6928 (88.0)	14,157 (74.5)

Abbreviations: HR = hormone receptor; LA = locally advanced; MBC = metastatic breast cancer.

^aData from 2014 not included (data not complete at the time of this analysis).

^bData from 2013 and 2014 not included (data not complete at the time of this analysis).

^cRegional data set.

^dData for 2008 only.

^eEndocrine therapy unknown in some patients.

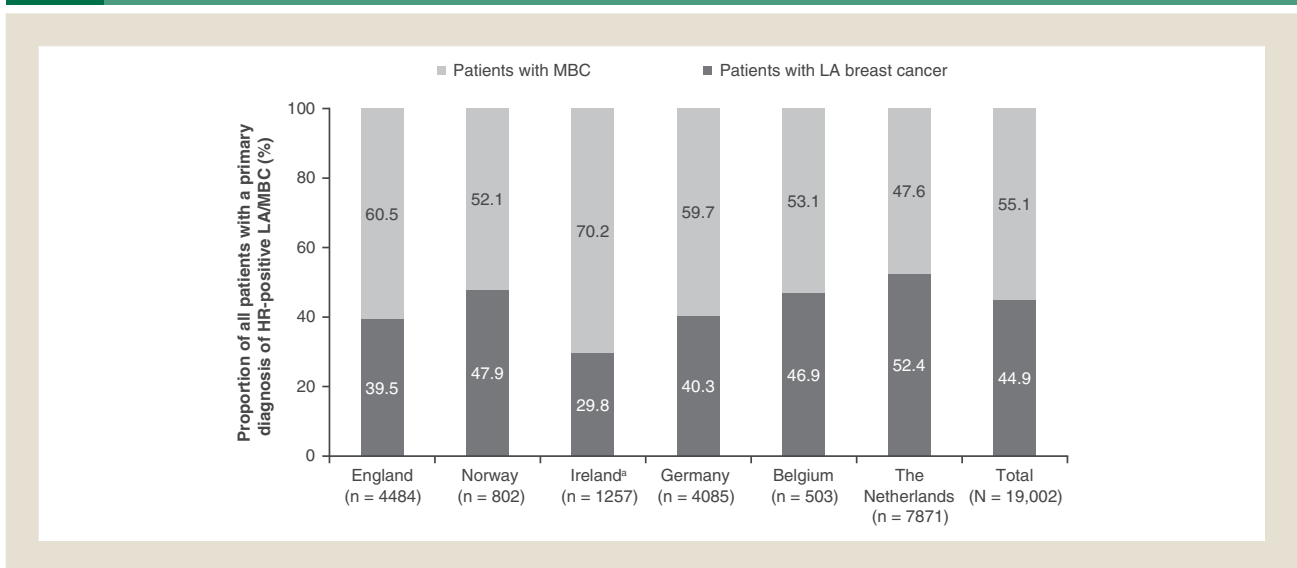
reporting database study of > 27,000 postmenopausal women with HR-positive MBC showed that, in routine clinical practice, chemotherapy-based regimens were used more commonly than endocrine therapy as first-line treatment (in the range of 51.3%-69.1% vs. 30.1%-47.2%, respectively) in France, Germany, Italy, and Spain, between 2004 and 2013.¹²

Several recent phase III clinical trials have evaluated different treatment options for patients with HR-positive LA/MBC who have not received previous endocrine therapy. The recently completed Fulvestrant and Anastrozole Compared in hormonal therapy-Naïve advanced breast cancer (FALCON) trial (NCT01602380) assessed the efficacy of fulvestrant 500 mg versus anastrozole as first-line endocrine therapy in postmenopausal women with HR-positive advanced breast cancer who had not received previous endocrine therapy (n = 462).

The study reported that the primary outcome of progression-free survival was significantly improved with fulvestrant compared with anastrozole.¹³ In addition, the PALbociclib: Ongoing trials in the Management of breast cAncer-2 (PALOMA-2) (NCT01740427)¹⁴ and Mammary ONcology Assessment of LEE011's Efficacy and SAFETY (MONALEESA-2) (NCT01958021)¹⁵ studies compared letrozole in combination with palbociclib and ribociclib, respectively, with letrozole alone, and included a considerable proportion of patients (43.7% and 48.2%, respectively) who had not received previous endocrine therapy. In both studies, the combination of letrozole with a cyclin-dependent kinase 4/6 inhibitor was reported to be significantly more effective than letrozole alone.

In addition to the registries included in the main analysis, a data set was also obtained from Barcelona, Spain, comprising 338

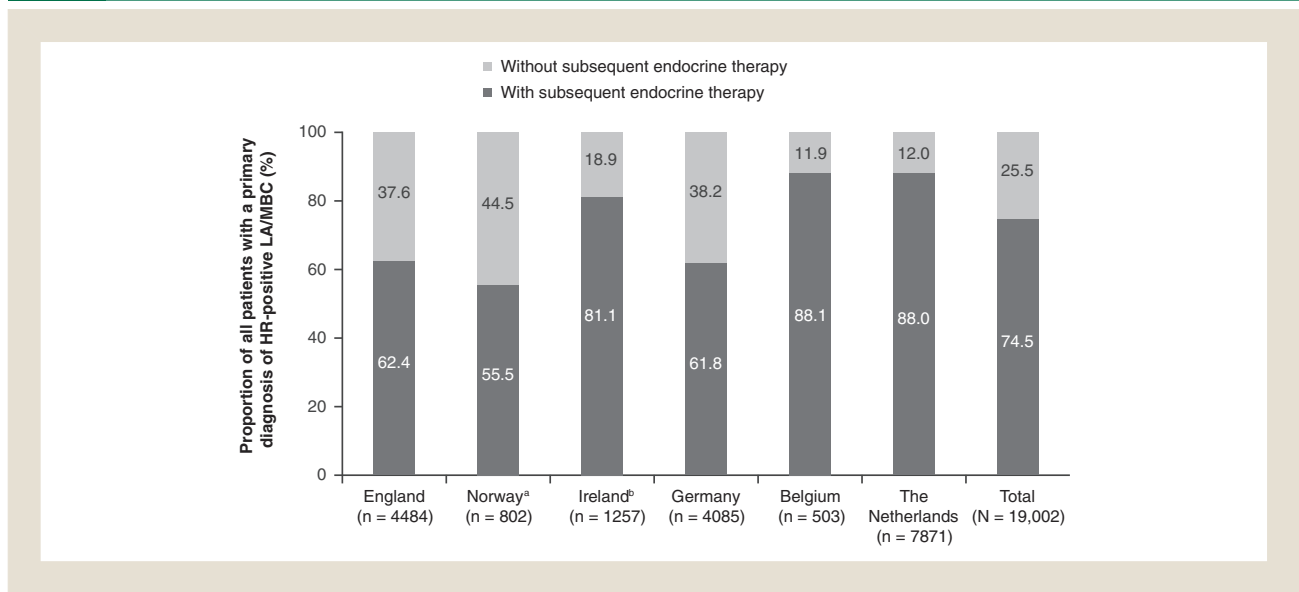
Figure 2 Proportion of Patients With Either LA or Metastatic Breast Cancer at Primary Diagnosis



Abbreviations: HR = hormone receptor; LA = locally advanced; MBC = metastatic breast cancer. ^a LA cases might be under-represented in the Irish data set (see Discussion).

Endocrine Therapy in Patients With HR-Positive LA/MBC

Figure 3 Proportion of Patients With HR-Positive LA/MBC at Primary Diagnosis Who Went On to Receive Subsequent Endocrine Therapy



Abbreviations: HR = hormone receptor; LA/MBC = locally advanced/metastatic breast cancer. ^a Endocrine therapy unknown in some patients in the Norwegian data set. ^b Locally advanced cases might be under-represented in the Irish data set (see Discussion).

patients with postmenopausal breast cancer. This was not included in the main analysis, because the sample size was too small for meaningful assessment. In this data set, ER status was available for 337 patients (99.7%), of whom 267 (79.2%) were ER-positive. PR status was available for 334 patients (98.8%), and 194 (58.1%) were PR-positive. Of the 334 patients with known disease stage and HR status, 83 (24.9%) had a primary diagnosis of LA/MBC (67 patients with LA, and 16 patients with MBC). The proportion of patients in Barcelona with a primary diagnosis of HR-positive LA/MBC was larger than that observed in the main data set in this study (24.9% vs. 7.8%), possibly because of the small sample size of the Barcelona data set. Of the 83 patients with a primary diagnosis of HR-positive LA/MBC in Barcelona, 61 (73.5%) received subsequent endocrine therapy, a proportion similar to the main data set (74.5%).

The proportion of patients in Norway assessed for HR status and with known disease stage was low (47.7%), likely because of issues in reporting HR status and disease stage to the registry. In comparison, The Netherlands had a high proportion of patients who were assessed for HR status (97.3%). Compared with the other countries, Ireland had a markedly lower proportion of HR-positive advanced breast cancer cases that were LA (29.8% vs. 39.5%-52.4%). A possible explanation for this is a potential underestimation of cases of LA breast cancer in Ireland, compared with other participating countries. Until recently, the Irish National Cancer Registry coded breast cancer stage using the fifth edition¹⁶ of the *TNM Classification of Malignant Tumours*. However, most countries adopted the sixth edition¹⁰—which markedly revised the classification of lymph node metastases—soon after it was published in 2002, and, from 2010, the seventh edition.¹¹ As a result, some cases that might have been assigned as stage IIIc in countries that adhered to criteria in the sixth¹⁰ and seventh¹¹ editions of the *TNM*

Classification of Malignant Tumours were not included or, in the case of ipsilateral supraclavicular node involvement, were categorized as stage IV in the Irish data set. This might have applied to a lesser extent (for cases in 2000 and 2001) in other countries' data sets.

Overall, the proportion of patients in this study with known HR status who had a primary diagnosis of HR-positive LA/MBC was lower (7.8%) than in previously published estimates (approximately 13%-17%).⁶⁻⁸ However, the generalizability of the previous findings is limited, because they were derived from a small number of patient records. In addition, the range of years and geographic regions included in these studies differed from the present study, and comparisons should therefore be interpreted with caution.

Limitations of this study include those inherent to any database study, such as potential misclassification and missing data. Not all registries were able to contribute data for all of the specified diagnostic parameters (eg, HR status was not available for all patients). In addition, by restricting this analysis to postmenopausal patients older than 55 years of age, this study excluded younger postmenopausal patients. Therefore, these results might not fully represent the population of patients with HR-positive breast cancer.

The subpopulation of patients with HR-positive LA/MBC without previous endocrine therapy might also include patients with a recurrence of early breast cancer who did not receive endocrine therapy for their early disease. These patients were not considered in this study, because of limitations in the way recurrences were recorded by most participating registries. Therefore, the proportion of postmenopausal patients reported in this study as having a primary diagnosis of HR-positive LA/MBC could be an underestimate of the total population of patients with HR-positive LA/MBC who have not received previous endocrine therapy. In this study, data on

recurrence was obtained from German and Norwegian registries (data not shown). On the basis of this small data set ($n = 3260$), patients with HR-positive LA/MBC who did not receive endocrine therapy after a previous diagnosis of early breast cancer could account for approximately 4% of all postmenopausal breast cancer patients with known HR status and disease stage.

It should be noted that these results might only be applicable to Europe. However, the prevalence of patients with a primary diagnosis of HR-positive LA/MBC might be higher in developing countries, where patients are more likely to present with advanced disease.¹⁷ Elderly patients with breast cancer, who might not be included in routine breast cancer screening programs,¹⁸ are also more likely to present with advanced disease.¹⁹ Therefore, it would also be interesting to investigate endocrine therapy in this specific patient population, which might have fewer perceived treatment options.²⁰

Conclusion

Overall, the results of the present study indicate that a sizeable population of patients presented with a primary diagnosis of HR-positive LA/MBC, nearly three-quarters of whom went on to receive endocrine therapy.

Clinical Practice Points

- Endocrine therapy is recommended for patients with HR-positive breast cancer in the absence of rapidly progressing disease or visceral crisis.
- Several recent studies have assessed different treatment options in patients with HR-positive LA or MBC who have not previously received endocrine therapy (ie, are endocrine therapy-naïve). This patient population might comprise those who received an initial diagnosis of HR-positive LA/MBC, or who did not receive endocrine therapy for their early disease. Previous estimates as to the size of this population are on the basis of small retrospective studies. However, to our knowledge, a comprehensive estimate has not yet been performed.
- This retrospective, observational study used data from 6 European cancer registries (Belgium, England, Ireland, Norway, the Netherlands, and Munich, Germany) to estimate the proportion of postmenopausal patients with breast cancer who received an initial diagnosis of HR-positive LA/MBC between January 2000 and December 2014.
- Of 244,268 patients with breast cancer and known HR status and disease stage, 19,002 (7.8%) received an initial diagnosis of HR-positive LA/MBC. Almost three-quarters of these patients ($n = 14,157$; 74.5%) went on to receive endocrine therapy in line with guideline recommendations. This proportion differed between countries, from 55.5% in Norway to 88.1% in Belgium, and could reflect potential differences in recording practices between cancer registries in Europe, or actual differences in the administration of endocrine therapy in these countries.

Acknowledgments

Medical writing support, funded by AstraZeneca, was provided by Laura Fullerton-Batten, PhD, of Complete Medical Communications.

The authors thank all cancer registration clerks and their staff for gathering the data.

Assistance and guidance in supporting the provision of United Kingdom data and its interpretation was given by John Broggio, Principal Analyst (Cancer) and Matthew Lynch, Data Liaison Manager, both of the National Cancer Registration and Analysis Service, Public Health England, Birmingham, United Kingdom.

Disclosure

Nick Jones is an employee and stockholder of AstraZeneca. Jan Lewis is a former employee of AstraZeneca. Both were involved in the data collection, analysis and interpretation, and writing of the report, and the decision to submit the report for publication. The remaining authors have stated that they have no conflicts of interest.

References

1. World Cancer Research Fund International. Breast cancer statistics. Available at: <http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics>. Accessed: September 1, 2017.
2. Lobbzoo DJ, van Kampen RJ, Voogd AC, et al. Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome. *Breast Cancer Res Treat* 2013; 141: 507-14.
3. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Ann Oncol* 2017; 28:16-33.
4. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Breast* 2017; 31:244-59.
5. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline focused update. *J Clin Oncol* 2014; 32:2255-69.
6. Dawood S, Broglio K, Ensor J, et al. Survival differences among women with de novo stage IV and relapsed breast cancer. *Ann Oncol* 2010; 21:2169-74.
7. Kitagawa D, Horiguchi S, Yamashita T, et al. Comparison of outcomes between women with de novo stage IV and relapsed breast cancer. *J Nippon Med Sch* 2014; 81:139-47.
8. Lobbzoo DJ, van Kampen RJ, Voogd AC, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? *Br J Cancer* 2015; 112:1445-51.
9. Fritz A, Percy C, Jack A, eds. *International Classification of Diseases for Oncology (ICD-O)*. Geneva: World Health Organization; 2000.
10. International Union Against Cancer (UICC). Sobin LH, Wittekind Ch, eds. *TNM Classification of Malignant Tumours. Sixth edition*. New York: Wiley-Blackwell; 2002.
11. International Union Against Cancer (UICC). Sobin LH, Gospodarowicz MK, Wittekind Ch, eds. *TNM Classification of Malignant Tumours. Seventh edition*. Oxford: Wiley-Blackwell; 2009.
12. Marchetti P, Maass N, Gligorov J, et al. Patient database analysis of fulvestrant 500 mg in the treatment of metastatic breast cancer: a European perspective. *Breast* 2017; 32:247-55.
13. Robertson JF, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet* 2016; 388:2997-3005.
14. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016; 375:1925-36.
15. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016; 375:1738-48.
16. International Union Against Cancer (UICC). Sobin LH, Wittekind CH, eds. *TNM Classification of Malignant Tumours. Fifth edition*. New York: John Wiley & Sons, Inc.; 1997.
17. Unger-Saldaña K. Challenges to the early diagnosis and treatment of breast cancer in developing countries. *World J Clin Oncol* 2014; 5:465-77.
18. Botteri E, Bagnardi V, Goldhirsch A, et al. Axillary lymph node involvement in women with breast cancer: does it depend on age? *Clin Breast Cancer* 2010; 10: 318-21.
19. Bastiaannet E, Liefers GJ, de Craen AJ, et al. Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. *Breast Cancer Res Treat* 2010; 124:801-7.
20. Riseberg D. Treating elderly patients with hormone receptor-positive advanced breast cancer. *Clin Med Insights Oncol* 2015; 9:65-73.