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Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries

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Abstract

Background The Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial is an international randomized trial evaluating the efficacy and safety of exemestane, alone or following tamoxifen. The large number of patients already recruited offered the opportunity to explore locoregional treatment practices between countries.

Methods Patients were enrolled in Belgium, France, Germany, Greece, Ireland, Japan, the Netherlands, the UK and the USA. The core protocol had minor differences in eligibility criteria between countries, reflecting variations in national guidelines and practice regarding adjuvant endocrine therapy.

Results Between 2001 and 2006, 9779 patients of mean (s.d.) age 64 (9) years were randomized. Some 58.4% had T1 tumours (range between countries 36.8–75.9%; $p < 0.001$) and 47.3% were axillary node positive (range 25.9–84.6%; $p < 0.001$). Independent factors for type of breast surgery were country, age, tumour status and calendar year of surgery. After breast-conserving surgery, radiotherapy was given to 93.2% of patients, 86.0% in the USA and 100% in France. Axillary lymph node dissection was performed in 82.0% (range 74.6–99.1%).

Conclusion Despite international consensus guidelines, wide global variations were observed in treatment practices of early breast cancer. There should be further efforts to optimize locoregional treatment for breast cancer worldwide.

Introduction

Surgery is the oldest method of treating breast cancer; the radical mastectomy was the treatment of choice for more than 80 years.[1] In the late 20th century, breast-conserving surgery (BCS) was introduced as an alternative to mastectomy.[2,3] Although no differences in overall survival were found between these two surgical procedures, BCS was associated with a significantly increased risk of local recurrence if radiotherapy was omitted.[4] The choice between mastectomy or BCS is influenced by various factors, including age at diagnosis patient's or physician's preference, tumour size and access to healthcare facilities.[5-8] In most countries, BCS followed by radiotherapy of the breast has become the standard of care for the majority of patients with early breast cancer; BCS rates are often considered indicative of quality of care.[9,10] Axillary lymph node dissection (ALND) has long been the standard procedure for staging and treatment of the axilla. Over the past decade, sentinel lymph node biopsy (SNB) has been introduced to identify tumour spread to the axillary lymph nodes, with the aim of decreasing morbidity by omitting ALND. Consequently, the rate of ALND has decreased over time.

In women with hormone-sensitive early breast cancer, adjuvant endocrine therapy is administered to block, counteract or minimize the oestrogenic stimulus to any residual tumour cells. This results in a significant improvement in disease-free and overall survival.[11] For many years, tamoxifen has been the standard. As third-generation aromatase inhibitors have shown superior efficacy to tamoxifen in postmenopausal women with metastatic breast cancer, several clinical trials have investigated the value of these drugs as adjuvant therapy.[12-15] The Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial is a randomized international phase III trial in postmenopausal women with hormone-sensitive breast cancer comparing the efficacy and safety of 2.5–3 years of tamoxifen followed by 2–2.5 years of exemestane (Aromasin®; Pfizer, New York, USA) *versus* 5 years of exemestane alone, as adjuvant endocrine treatment.

In the present analysis, variations in locoregional treatment policies between the different countries were explored, and univariate and multivariable analyses were used to determine which factors influenced the choice of strategy.

Table 1 Eligibility criteria and protocols in the different countries/protocols.

Criteria	The Netherlands / Belgium	France	Germany	Greece	Japan	UK/Ireland	USA
Criteria (besides HR+) for endocrine therapy	>3cm *or* N+ *or* 1-3 cm and grade III / MAI>10	Tumour status T1-T3	>3cm *or* N+ *or* 0.5-3cm and grade II/III	>3cm *or* N+ *or* 1-3 cm and grade III / MAI>10	>3cm *or* N+ *or* nuclear grade III	> 2cm and grade II *or* grade III *or* N+	Tumour status T1-T3
Postmenopausal status	Age ≥50 years and amenorrhoea > 1 year *or* bilateral surgical oophorectomy *or* Age < 50 years and amenorrhoea > 1 year	Age ≥50 and amenorrhoea > 1 year *or* bilateral surgical oophorectomy *or* radiation induced amenorrhoea >3 months *or* age <50 years and year amenorrhoea ≥ 1 year	Age ≥50 years and amenorrhoea > 1 year *or* bilateral surgical oophorectomy *or* Age < 50 years and amenorrhoea > 1 year	Age ≥56 and amenorrhoea ≥ 1 year *or* CT-induced amenorrhoea ≥2 years *or* radiation-induced amenorrhoea >3 months *or* age <56 and amenorrhoea < 5 years with FSH determination	*Age ≥60 *or* *Age ≥45 and >1 year amenorrhoea *or* *Bilateral surgical oophorectomy	Age ≥50 and amenorrhoea > 1 year *or* CT-induced amenorrhoea ≥2 years *or* radiation-induced amenorrhoea >3 months *or* age <50 and amenorrhoea < 5 years	Age ≥50 independent of amenorrhoea *or* age <50 and amenorrhoea ≥1 year *or* bilateral surgical oophorectomy
ECOG status	0,1	0-2	0,1	0,1	0,1	0-2	0-2
Bilateral tumour	Not allowed	Allowed	Allowed	Allowed	Not allowed	Allowed	Allowed
Previous malignancies	DFI > 5 years allowed	Not allowed	DFI > 5 years allowed	DFI > 5 years allowed	DFI > 5 years allowed	DFI > 5 years allowed	DFI > 3 years allowed
Previous breast cancer	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed	Allowed
Neoadjuvant CT	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed
HRT stop	4 weeks before randomization	4 weeks before randomization	4 weeks before randomization	4 weeks before randomization	4 weeks before randomization	4 weeks before randomization	No time interval
Randomization	After end of CT	After end of CT or RT	After surgery, irrespective of CT	Before start of CT	After end of CT	After end of CT	After end of CT or after end of CT and RT
Stratification	Centre CT (yes/no) Interval between endocrine therapy and surgery	CT (yes/no)	Centre	Centre CT (yes/no) Type of CT	Centre Nodal status (N-/ N+) CT (yes/no) *RT (yes/no)	Nodal status (0, 1-3, ≥ 4) CT (no, AC, taxane based, other)	Nodal status (0, 1-3, ≥ 4) CT (no, CMF, AC, taxane based)
Timing of start of therapy	Within 10 weeks after completion of surgery and/or CT	Within 10 weeks after completion of surgery and/or CT	Within 10 weeks after completion of surgery and/or CT	Within 8 weeks after completion of surgery and within 6 weeks after completion of CT	Within 10 weeks after completion of surgery and/or CT	Within 10 weeks after completion of surgery and/or CT	Within 10 weeks after completion of surgery and/or CT and/or RT

There were minor differences in definition of postmenopausal status, indication for receiving adjuvant endocrine treatment and exclusion criteria relating to previous malignancies.
AC Adriamycin and cyclophosphamide; *CMF* cyclophosphamide, methotrexate and fluorouracil; *CT* chemotherapy; *DFI* disease-free interval; *ECOG* Eastern Cooperative Oncology Group; *FSH* follicle-stimulating hormone; *HR* hormone receptor; *HRT* hormone replacement therapy; *MAI* mitotic activity index; *RT* radiotherapy.

Patients and methods

The TEAM trial started in 2001 and was designed to compare 5 years of exemestane (25mg/day) *versus* 5 years of tamoxifen (20mg/day). The interim data of the Intergroup Exemestane Study (IES) showed significantly improved disease-free survival with exemestane after 2–3 years of tamoxifen compared with the standard 5 years of tamoxifen treatment.[16] Therefore, the design of the TEAM study was amended to compare 5 years of exemestane alone *versus* sequential therapy with 2.5–3 years of tamoxifen followed by 2–2.5 years of exemestane. Primary endpoints of the core protocol were disease-free survival at 2.75 years and at 5 years.[17] Secondary endpoints included overall survival, incidence of a new primary breast cancer and relative safety profiles.

The trial was activated in nine countries: Belgium, France, Germany, Greece, Ireland, Japan, the Netherlands, the UK and the USA. The main protocol was adapted into seven separate protocols, with minor differences with regard to eligibility criteria between participating countries reflecting differences in the regulatory environment and clinical approach to endocrine therapy (Table 1). The same protocol was activated in Belgium and the Netherlands, and in Ireland and the UK. All patients gave written informed consent before randomization, which was performed at national data centres.

Data collection

The following data were recorded: patient characteristics (date of birth, menopausal status, medical history, height, weight, centre and country), tumour characteristics including primary disease site, histological grade (in Japan nuclear grade only), tumour node metastasis (TNM) stage, oestrogen receptor and progesterone receptor status, locoregional therapy (date(s) of surgery, type of breast surgery, ALND (yes or no; hence no information concerning different types of axillary node assessment procedure such as SNB, axillary sampling or axillary node clearance), number of nodes examined, radiotherapy (yes or no)) and chemotherapy data. The data were collected using a local case report form at central data centres in each country, and transferred to the TEAM data centre in Leiden, the Netherlands.

Statistical analysis

All data were analysed using the statistical package SPSS® for Windows® version 15.0 (SPSS, Chicago, Illinois, USA). Descriptive data were presented as mean (s.d.) or median (range). Pearson's $\chi 2$ test was used to compare frequencies between groups. Differences in quantitative data between different countries were tested by one-way ANOVA or Kruskal–Wallis test. Univariate and multivariable analyses were carried out using logistic regression to determine factors with an impact on differences. Factors with $p < 0.100$ in univariate analysis were included in the multivariable forward selection model. All testing was two tailed with 0.050 as the level of significance.

Results

A total of 9779 patients from 566 study sites in nine countries were randomized into the TEAM trial between July 2001 and January 2006. Thirteen patients withdrew their consent. Baseline patient and tumour characteristics, and features of locoregional treatment strategies are shown in Tables 2 and *3*. Mean (s.d.) age for the overall group was 64(9) years. Some 58.4% of patients had a T1 tumour (range between countries 36.8–75.9%; $p < 0.001$) and 47.3% had axillary node-positive disease (range 25.9–84.6%; $p < 0.001$). The highest percentage of node-negative disease was observed in the countries with a high percentage of T1 tumours (USA, France and Germany). Most patients included in Japan had a normal body mass index (BMI) (below 25kg/m^2 in 66.8%), whereas 40 and 29.8% of patients from Greece and the UK/Ireland respectively had a BMI over 30kg/m^2. Data on BMI were not available from France and the USA. All patients had oestrogen receptor- and/or progesterone receptor-positive tumours as hormone receptor positivity was an inclusion criterion. The progesterone receptor status was not determined in 40.6% of tumours from the UK/Ireland, 5.6% from the Netherlands and 5.4% from France, whereas this was assessed in all tumours in the other countries.

The mastectomy rate was 44.3% overall, ranging from 19.4% in France to 55.6% in Greece ($p < 0.001$) (Table 3). T2 tumours were more often treated by mastectomy than by BCS. However, this varied widely between countries, ranging from

Table 2 Comparison of patients and tumour characteristics between the participating countries.

	Belgium	France	Germany	Greece	Japan	The Netherlands	UK/Ireland	USA	Total	*p*‡
Total no. of patients	414 *4*	1230 *13*	1471 *15*	207 *2*	184 *2*	2753 *28*	1275 *13*	2232 *23*	9766 *100*	
No. per hospital†										<0.001
<40	103 *25*	630 *51*	596 *41*	100 *48*	184 *100*	709 *26*	1031 *81*	1695 *76*	5048 *52*	
≥40	311 *75*	600 *49*	875 *60*	107 *52*	0 *0*	2044 *74*	244 *19*	537 *24*	4718 *48*	
Age at randomization (years)*	*63 8*	*63 8*	63 *8*	64 *9*	65 *8*	65 *9*	64 *9*	65 *10*	64 *9*	0.237§
Age group (years)										<0.001
<50	13 *3*	31 *3*	83 *6*	8 *4*	0 *0*	59 *2*	48 *4*	89 *4*	331 *3*	
50 - 59	149 *36*	425 *35*	421 *29*	66 *32*	54 *29*	854 *31*	385 *30*	664 *30*	3018 *31*	
60 - 69	168 *41*	510 *42*	672 *46*	74 *36*	82 *45*	966 *35*	492 *39*	766 *34*	3730 *38*	
≥70	84 *20*	264 *22*	295 *20*	59 *29*	48 *26*	874 *32*	350 *28*	713 *32*	2687 *28*	
Body mass index (kg/m²)										<0.001
<25	167 *45*		427 *43*	8 *32*	123 *67*	917 *38*	256 *35*		1898 *40*	
25-30	138 *37*		365 *37*	7 *28*	55 *30*	930 *38*	265 *36*		1760 *37*	
>30	69 *18*		197 *20*	10 *40*	6 *3*	600 *25*	221 *30*		1103 *23*	
Tumour status										<0.001
T1	152 *37*	931 *76*	870 *59*	82 *40*	87 *48*	1235 *45*	689 *54*	1645 *74*	5691 *58*	
T2	216 *52*	271 *22*	505 *34*	107 *52*	89 *49*	1329 *48*	526 *42*	548 *25*	3591 *37*	
T3 or T4	45 *11*	25 *2*	94 *6*	16 *8*	7 *4*	183 *7*	51 *4*	35 *2*	456 *5*	
Nodal status										<0.001
Negative	127 *31*	839 *68*	931 *64*	78 *38*	23 *15*	834 *30*	634 *50*	1647 *74*	5113 *53*	
Positive	287 *69*	388 *32*	527 *36*	127 *62*	126 *85*	1915 *70*	638 *50*	577 *26*	4585 *47*	
Histological grade										<0.001
I	38 *10*	399 *34*	50 *3*	9 *5*	63 *37*	420 *16*	99 *10*	599 *31*	1677 *19*	
II	147 *37*	614 *53*	1112 *76*	106 *56*	26 *15*	1217 *47*	584 *59*	989 *51*	4795 *54*	
III	216 *54*	155 *13*	296 *20*	73 *39*	80 *47*	937 *36*	313 *31*	368 *19*	2438 *27*	
Receptor status										<0.001
OR+ / PgR+	337 *82*	908 *74*	1209 *82*	148 *73*	128 *70*	1950 *71*	609 *48*	1847 *83*	7136 *73*	
OR+ / PgR-	62 *15*	231 *19*	216 *15*	53 *26*	52 *28*	595 *22*	132 *10*	367 *17*	1708 *18*	
OR+ / PgR n.p.	0 *0*	66 *5*	0 *0*	0 *0*	0 *0*	153 *6*	517 *41*	1 *0*	737 *8*	
OR- / PgR+	13 *3*	23 *2*	43 *3*	3 *2*	4 *2*	47 *2*	16 *1*	12 *1*	161 *2*	

Values in parentheses are percentages unless indicated otherwise; *values are mean (s.d.). Missing data are not shown. Data on body mass index were not available from France or the USA. †Number of included study patients per hospital.
‡Pearson's $\chi 2$ test, except §one-way ANOVA
n.p. not performed; *OR* oestrogen receptor; *PgR* progesterone receptor.

Table 3 Locoregional treatment characteristics in the participating countries.

	Belgium	France	Germany	Greece	Japan	The Netherlands	UK/Ireland	USA	Total*	*p* †
Local treatment										< 0.001
MST - RT	22 (5)	30 (2)	275 (19)	70 (35)	58 (32)	1070 (39)	298 (24)	790 (37)	2613 (27)	
MST + RT	189 (46)	209 (17)	176 (12)	40 (20)	8 (4)	453 (17)	265 (21)	314 (15)	1654 (17)	
BCS - RT	1 (0)	0 (0)	86 (6)	6 (3)	16 (9)	17 (1)	92 (7)	147 (7)	365 (4)	
BCS + RT	202 (49)	990 (81)	932 (63)	82 (41)	102 (55)	1206 (44)	611 (48)	905 (42)	5030 (52)	
Year of surgery										< 0.001
2001-2002	42 (10)	943 (77)	643 (44)	107 (52)	0 (0)	932 (34)	476 (37)	1386 (62)	455 (46)	
2003	111 (27)	287 (23)	227 (16)	64 (31)	31 (17)	793 (29)	363 (29)	243 (11)	2119 (22)	
2004	147 (36)	0 (0)	235 (16)	23 (11)	106 (58)	637 (23)	69 (5)	108 (5)	1325 (14)	
2005-2006	114 (28)	0 (0)	364 (25)	13 (6)	47 (26)	391 (14)	366 (29)	494 (22)	1789 (18)	
ALND										< 0.001
No	18 (4)			4 (2)	35 (19)	634 (23)	12 (1)	566 (25)	1269 (18)	
Yes	396 (96)			203 (98)	149 (81)	2118 (77)	1261 (99)	1665 (75)	5792 (82)	
Nodes in ALND*	15 (2-40)			15 (1-43)	13 (2-42)	13 (1-46)	10 (1-37)		13 (1-46)	< 0.001 ‡

Values in numbers (and percentages); *values are median (range). Missing data are not shown.
ALND was not registered in France or Germany, nor was number of nodes excised in the USA. ALND data for the UK/Ireland include axillary sampling.
†Pearson's $\chi 2$ test, except ‡Kruskal–Wallis test. *ALND* Axillary lymph node dissection; *BCS* breast-conserving surgery; *MST* mastectomy; *RT* radiotherapy.

41.7% in France to 69.1% in the USA ($p < 0.001$, data not shown). In general, T1 tumours were more often treated with BCS. Although the percentage of patients with a T1 tumour was similar in the USA and France (73.8 and 75.9% respectively; Table 2), 54.8% of T1 tumours were treated by BCS in the USA compared with up to 88.6% in France ($p < 0.001$, data not shown).

In univariate logistic regression analysis regarding the type of breast surgery, the following variables were available: country, age at diagnosis, tumour status, number of patients included per centre, BMI and year of surgery (Table 4). All factors except the numbers of patients per hospital and BMI were significantly associated with mastectomy and were included inmultivariable logistic regression analysis. Country, age at diagnosis, year of surgery and higher tumour category remained independent factors associated with mastectomy. With respect to age, the highest rate of BCS was observed in patients aged between 50 and 70 years. A higher rate of mastectomy was noted in those younger than 50 years. In addition, the oldest patients (over 70 years) had a significantly lower chance of BCS than those in other age groups, after adjustment for tumour status and country.

International guidelines recommend that radiotherapy should be part of breast-conserving therapy. In the TEAM cohort, this was only the case for all patients treated in France and Belgium; 13.6, 13.1 and 14.0% respectively of patients included in Japan, the UK/Ireland and the USA did not receive radiotherapy in this setting. Furthermore, radiotherapy was given after mastectomy in 38.8% of patients, ranging from 12.1% in Japan to 89.6% in Belgium ($p < 0.001$). To compare factors involved in administration of radiotherapy, analyses were performed separately for mastectomy and BCS. In univariate logistic regression analysis for radiotherapy after mastectomy, the following variables were used: country, age at diagnosis, tumour stage, node status, number of patients included per centre, BMI and year of surgery. All factors except the number of patients per hospital, year of surgery and BMI were significantly associated with radiotherapy after mastectomy and were included in multivariable logistic regression analysis. All included factors remained independent factors associated with mastectomy (all $p < 0.001$). For ra-

diotherapy after BCS, the same variables were included in univariate logistic regression analysis as for radiotherapy after mastectomy. Tumour stage and BMI were not associated with radiotherapy after BCS. In multivariable logistic regression analysis, country ($p < 0.001$), age ($p < 0.001$), number of patients included per centre ($p = 0.023$) and year of surgery ($p < 0.001$) were associated with radiotherapy after BCS. As detailed radiotherapy data were not available, it was not possible to further compare and explore the location(s) (breast/boost, chest wall, axilla) and dose differences in radiotherapy administered between countries.

Some 82.0% of patients underwent ALND, ranging from 74.6% in the USA to 99.1% in the UK/Ireland (Table 3); no data were available from France and Germany. Nearly all patients in Belgium and Greece (95.7 and 98.1% respectively) also had an ALND. The median number of examined lymph nodes was 13 (range 1–46), in overall accordance with international guidelines. In multivariable logistic regression analysis, country, type and year of breast surgery remained independent factors associated with ALND (Table 5).

Discussion

This analysis of postmenopausal patients with breast cancer participating in the TEAM trial showed that country, age at diagnosis, tumour status and year of surgery were predictive of the type of breast surgery performed. After correction for age and tumour status, patients from France had the highest chance of being treated with BCS and patients from the USA the lowest. BCS was per-

Table 4 Univariate and multivariable logistic regression analysis of factors associated with type of local surgery.

	n	Univariate analysis		Multivariable analysis	
		Odds ratio	*p*	Odds ratio	*p*
Country			< 0.001		< 0.001
Belgium	414	1.04 (0.84-1.28)		1.55 (1.23-1.97)	
France	1230	4.46 (3.79-5.26)		5.13 (4.31-6.11)	
Germany	1469	2.43 (2.12-2.79)		3.18 (2.73-3.70)	
Greece	207	0.84 (0.63-1.13)		1.32 (0.96-1.79)	
Japan	184	1.93 (1.41-2.63)		2.41 (1.71-3.39)	
the Netherlands	2752	0.87 (0.77-0.97)		1.22 (1.07-1.38)	
UK/Ireland	1271	1.34 (1.16-1.54)		1.68 (1.44-1.95)	
USA	2228	1.00		1.00	
Age at diagnosis (years)			< 0.001		< 0.001
<50	331	1.38 (1.01-1.73)		1.27 (0.98-1.63)	
50-59	3015	2.06 (1.86-2.29)		1.83 (1.63-2.05)	
60-69	3725	2.03 (1.84-2.25)		1.70 (1.52-1.90)	
≥70	2684	1.00		1.00	
Tumour status			< 0.001		< 0.001
T1	5688	1.00		1.00	
T2	3589	0.33 (0.30-0.36)		0.34 (0.31-0.37)	
T3 or T4	454	0.06 (0.04-0.08)		0.05 (0.04-0.07)	
Included patients per hospital			0.638		
<40	5042	1.00			
≥40	4713	0.98 (0.91-1.06)			
Year of surgery			0.063		< 0.001
≤2002	4525	1.00		1.00	
2003	2117	0.98 (0.89-1.09)		1.09 (0.97-1.23)	
2004	1325	0.92 (0.81-1.04)		1.22 (1.05-1.41)	
2005/2006	1788	1.11 (0.99-1.24)		1.38 (1.22-1.57)	
Body mass index (kg/m^2)			0.966		
≤25	1897	1.00			
25-30	1760	1.02 (0.89-1.16)			
≥30	1103	1.00 (0.87-1.17)			

Values in parentheses are 95% confidence intervals. An odds ratio below 1 indicates an increased likelihood of mastectomy whereas a larger value indicates an increased likelihood of breast-conserving surgery.

formed less frequently in the oldest patient category (over 70 years). Radiotherapy was not always administered as part of breast-conserving therapy, most notably in Japan, the UK/Ireland and the USA. Differences in the rate of ALND and number of nodes examined were found, possibly reflecting variations in types of axillary node assessment.

Treatment practices concerning the type of breast surgery (mastectomy *versus* BCS) differed according to age at diagnosis. The highest rate of BCS was recorded in patients aged between 50 and 70 years. As in other studies, the oldest patients (aged over 70 years) had a significantly lower rate of BCS, even after adjustment for stage of disease and country. Choosing mastectomy in order to avoid radiotherapy in elderly patients might be one explanation. It has been reported that the lack of a local radiotherapy facility and travel distance to a radiotherapy unit after BCS can play a role in the selection of surgical approach, especially for older women.[5,18] However, current guidelines concerning local therapy do not discriminate between young and old patients. In view of the rising proportion of elderly in the population, this becomes increasingly relevant and warrants further investigation. Although France and the USA had the highest proportion of patients with a T1 tumour, patients in the USA had the lowest probability of being treated with BCS, even after correction for tumour size. This pattern has also been observed in the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial.[7] In that study, women from the USA were more likely to undergo a mastectomy than women from the UK, with country remaining an independent determinant of type of breast surgery in multivariable analysis. So, despite the fact that the TEAM trial was conducted later (2001–2006) than the ATAC trial (1996–2000), findings were similar regarding the type of breast surgery. Information on the proportion of patients undergoing breast reconstruction after mastectomy (which may have influenced the surgical approach) was not available. If BCS is indeed considered indicative of quality of care, further prospective studies are warranted, aiming to improve breast cancer care.

Another finding of this analysis was that not all women treated with BCS received radiotherapy. This occurred in 6.8% of the TEAM patients, and was most common in Japan, the UK/Ireland and the USA. Omission of radiotherapy correlates with a higher locoregional recurrence rate and consequently may affect overall survival.[4] The identification of a subgroup of elderly patients in whom radiotherapy can safely be omitted remains an issue of debate.[19] In accordance with these findings, a total of 5.3% of patients who had BCS did not receive radiotherapy in the Breast International Group (BIG) 1–98 trial, which compared tamoxifen with letrozole.[20]

Almost all patients who had a mastectomy in Belgium received postoperative radiotherapy. In contrast, this was given in only 12.1% in Japan and 29.7% in the Netherlands. As the same protocol was used in the Netherlands and Belgium, this variation probably reflected different national guidelines and/or different local preferences. For instance, in Belgium, radiotherapy after mastectomy is given for multicentric tumours, tumours larger than 5 cm and/or if axillary lymph nodes are positive. In Germany, patients need at least three positive axillary lymph nodes, and in Greece, Ireland and the USA at least four positive lymph nodes, before radiotherapy is indicated after mastectomy. In the USA, the distance to a radiotherapy facility influences local treatment. In multivariable logistic regression analysis for radiotherapy after mastectomy, node status and number of patients included per hospital were independently associated; however, country was also a significant factor. The TEAM trial results are consistent with findings from the IES study that compared 5 years of tamoxifen with a sequential therapy with tamoxifen and exemestane. In this study, different policies in postmastectomy radiotherapy between different countries have also been observed.[21]

Almost all patients included in the UK/Ireland and Greece had an ALND, in contrast to three-quarters of patients in the Netherlands and the USA. This difference may have been due to a different speed of implementation of SNB; earlier implementation will have reduced the number of ALND. At the time of recruitment to the TEAM study, SNB was already used widely in the Netherlands, whereas centres in the UK were still involved in a training and validation programme. Furthermore, the study closed earlier in Greece than in other countries, consequently with a higher percentage of ALND. Unfortunately, full information on SNB

Table 5 Univariate and multivariable logistic regression analysis of factors associated with probability of axillary lymph node dissection.

	n	Univariate analysis		Multivariable analysis	
		Odds ratio	*p*	Odds ratio	*p*
Country			< 0.001		< 0.001
Belgium	414	7.48 (4.62-12.11)		9.84 (5.93-16.35)	
Greece	207	17.25 (6.38-46.62)		24.07 (7.60-76.21)	
Japan	184	1.45 (0.99-2.12)		2.15 (1.42-3.26)	
the NL	2752	1.14 (1.00-1.29)		1.10 (0.92-1.32)	
UK/Ireland	1273	35.72 (20.07-63.57)		50.15 (28.01-89.29)	
USA	2231	1.00		1.00	
Age at diagnosis (years)			0.206		
<50	217	1.00			
50-59	2173	0.64 (0.42-0.97)			
60-69	2546	0.68 (0.45-1.02)			
≥70	2125	0.69 (0.46-1.04)			
Tumour status			< 0.001		0.102
T1	3889	1.00		1.00	
T2	2813	1.56 (1.37-1.78)		0.98 (0.84-1.14)	
T3 or T4	337	5.46 (3.29-9.08)		1.75 (1.03-2.88)	
No. of patients per hospital*			0.007		0.746
<40	3824	1.00		1.00	
≥40	3237	0.85 (0.75-0.96)		0.97 (0.83-1.14)	
Year of surgery			0.001		< 0.001
2001/2002	2917	1.00		1.00	
2003	1600	1.09 (0.92-1.28)		0.84 (0.69-1.02)	
2004	1084	0.90 (0.75-1.08)		0.84 (0.68-1.04)	
2005/2006	1414	0.77 (0.66-0.91)		0.61 (0.51-0.73)	
Breast surgery			< 0.001		< 0.001
Mastectomy	3630	1.00		1.00	
Breast conserving surgery	3342	0.20 (0.17-0.23)		0.16 (0.14-0.19)	

Values in parentheses are 95% confidence intervals. *Number of included study patients per hospital. Although the number of nodes examined is known in France, there were no data regarding surgery of the axilla and so France was excluded from this analysis. An odds ratio below 1 indicates a decreased likelihood of axillary lymph node dissection whereas a larger value indicates an increased likelihood.

and ALND was not available for France, Germany and the USA, so it was not possible to explore this further.

This analysis had several limitations. First, not all variables were known for each patient and/or country; for example, BMI data were not available from France and the USA, nor exact ALND data from France and Germany. Second, detailed data relating to the choice of locoregional therapy were not collected. Therefore, further prospective studies are required to explore factors associated with selection of the surgical approach for early breast cancer. Third, there were small differences in eligibility criteria for the TEAM study between countries, relating to variations in national practice patterns regarding the administration of endocrine therapy. These differences still exist in spite of international treatment guidelines (such as those of the American Society of Clinical Oncology and the St Gallen early breast cancer conference consensus). International guidelines have been developed to enable optimal implementation of contemporary evidence and expert opinion-based therapy for patients with breast cancer. Interpretation from international to national and/or local guidelines may lead to variations in treatment policies and implementation rates of new techniques among different countries. All patients included in the TEAM study were treated in hospitals involved in breast cancer research where there is presumably compliance with guidelines and data have been checked centrally. Consequently, it is possible that the present observations under-

estimate the problem occurring outside the study. Despite the limitations of this analysis, the TEAM trial observations are of interest and deserve further research, aiming ultimately at improving breast cancer care for patients worldwide.

Collaborators

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