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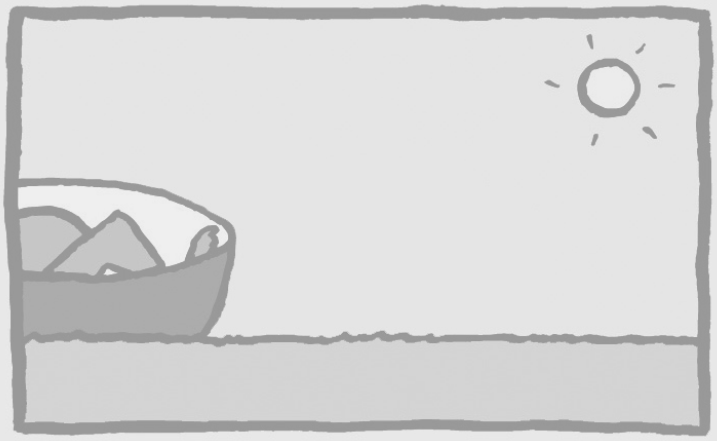
Patterns of care in Dutch postmenopausal patients with hormone-sensitive early breast cancer participating in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial



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Abstract

Background The Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial investigates the efficacy and safety of adjuvant exemestane alone and in sequence after tamoxifen in postmenopausal women with hormone-sensitive early breast cancer. As there was a nationwide participation in The Netherlands, we studied the variations in patterns of care in the Comprehensive Cancer Centre Regions (CCCRs) and compliance with national guidelines.

Methods Clinicopathological characteristics, carried out local treatment strategies and adjuvant chemotherapy data were collected.

Results From 2001 to January 2006, 2754 Dutch patients were randomised to the study. Mean age of patients was 65 years (standard deviation 9). Tumours were ≤ 2cm in 46% (within CCCRs 39%–50%), node-negative disease varied from 25% to 45%, and PgR status was determined in 75%–100% of patients. Mastectomy was carried out in 55% (45%–70%), sentinel lymph node procedure in 68% (42%–79%) and axillary lymph node dissections in 77% (67%–83%) of patients, all different between CCCRs ($p < 0.0001$). Adjuvant chemotherapy was given in 15%–70% of eligible patients ($p < 0.001$).

Conclusion In spite of national guidelines, breast cancer treatment on specific issues widely varied between the various Dutch regions. These data provide valuable information for breast cancer organisations indicating (lack of) guideline adherence and areas for breast cancer care improvement.

Introduction

In women with hormone-sensitive early breast cancer, adjuvant endocrine therapy improves disease-free survival (DFS) and overall survival (OS).[1] For many years, tamoxifen has been the gold standard in this setting. Third-generation aromatase inhibitors have shown superior efficacy compared with tamoxifen in postmenopausal women with metastatic/advanced breast cancer.[2] Therefore, many clinical trials have investigated the value of these drugs as adjuvant therapy in hormone-sensitive postmenopausal breast cancer.[3-8] The Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial (Netherlands Trial Register NTR267) is a randomised international trial comparing the efficacy and safety of 2.5–3 years of adjuvant tamoxifen followed by 2.5–2 years of exemestane versus 5 years of exemestane in postmenopausal women with hormone-sensitive early breast cancer. In The Netherlands, this trial has been activated in 76 of a total of 123 Dutch centres, both academic and community hospitals, throughout the country.

In line with international developments, an evidence-based/expert-based guideline on the treatment of breast cancer exists in The Netherlands, coordinated by the National Breast Cancer Organisation of The Netherlands (NABON). A multidisciplinary working party, consisting of representatives from different disciplines involved in breast cancer care, as well as from the patient advocacy group, is responsible for its contents as well as regular updates. The implementation process is being facilitated and stimulated by working parties in the nine Dutch Comprehensive Cancer Centre Regions (CCCRs). During the largest accrual period of the TEAM trial, the NABON guideline version 2002 was prevailing (www.oncoline.nl).

As adherence to the guideline is advised, differences with respect to breast cancer treatment may exist between hospitals and across different CCCRs. For The Netherlands, this has been reported in studies with respect to breast-conserving surgery (BCS), sentinel lymph node procedure (SLNP) and chemotherapy.[9-11] So far, data on adherence to the NABON guideline are scarce and were generated from retrospective population-based studies carried out in a particular CCCR, while no data are available on the variation in patterns of breast cancer care between all different CCCRs. As there was a nationwide participation, the TEAM trial of-

Table 1 Patient and tumour characteristics given in numbers and in percentage, unless otherwise mentioned.

	CCCR																				
	IKA		IKL		IKMN		IKN		IKO		IKR		IKST		IKW		IKZ		Total		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	*p*
Number of patients included	319	*12*	105	*4*	280	*10*	245	*9*	260	*9*	492	*18*	207	*8*	364	*13*	482	*18*	2754	*100*	
Age at randomisation (years)																					< 0.001, 0.297[a]
Mean	65		71		65		64		66		65		65		64		64		65		
Standard deviation	9		10		9		9		9		9		8		10		9		9		
Body Mass Index																					0.038
≤ 25	115	*39*	30	*35*	94	*36*	85	*37*	79	*34*	151	*33*	92	*47*	96	*34*	176	*42*	918	*38*	
26-30	110	*38*	31	*37*	111	*43*	82	*36*	93	*40*	176	*38*	73	*37*	107	*38*	147	*35*	930	*38*	
>30	68	*23*	24	*28*	56	*22*	62	*27*	59	*26*	132	*29*	32	*16*	76	*27*	93	*22*	602	*25*	
Tumour size																					0.200
≤ 2cm	155	*49*	41	*39*	140	*50*	104	*43*	124	*48*	220	*45*	89	*43*	149	*41*	227	*47*	1249	*46*	
> 2cm	163	*51*	64	*61*	139	*50*	139	*57*	136	*52*	271	*55*	118	*57*	215	*59*	254	*53*	1499	*55*	
Hormone receptor																					< 0.001
ER+ / PgR+	209	*66*	76	*72*	222	*79*	142	*58*	184	*71*	340	*69*	162	*78*	229	*63*	387	*81*	1951	*71*	
ER+ / PgR-	62	*20*	28	*27*	57	*20*	35	*14*	72	*28*	129	*26*	40	*19*	92	*25*	80	*17*	595	*22*	
ER+ / PgR not done	43	*14*	0	*0*	0	*0*	61	*25*	0	*0*	16	*3*	0	*0*	24	*7*	9	*2*	153	*6*	
ER- / PgR+	4	*1*	1	*1*	1	*0*	6	*3*	2	*1*	5	*1*	5	*2*	18	*5*	5	*1*	47	*2*	
Histology grade																					< 0.001
I	50	*17*	14	*14*	60	*26*	37	*15*	23	*10*	61	*13*	26	*13*	43	*13*	106	*24*	420	*16*	
II	142	*48*	49	*48*	101	*44*	126	*52*	113	*47*	221	*46*	110	*55*	143	*42*	213	*49*	1218	*47*	
III	104	*35*	39	*38*	68	*30*	79	*33*	103	*43*	201	*42*	64	*32*	159	*46*	120	*27*	937	*36*	
Nodal status																					< 0.001
pN0	90	*30*	31	*30*	70	*26*	60	*25*	114	*45*	137	*28*	80	*40*	116	*33*	137	*30*	835	*31*	
pN1-3	152	*50*	52	*50*	165	*60*	127	*53*	113	*44*	264	*54*	85	*42*	176	*50*	252	*55*	1387	*52*	
pN4-9	38	*13*	14	*14*	31	*11*	43	*18*	21	*8*	60	*12*	28	*14*	43	*12*	49	*11*	327	*12*	
pN≥10	22	*7*	7	*7*	9	*3*	8	*3*	8	*3*	29	*6*	9	*5*	18	*5*	21	*5*	131	*5*	

[a]Patients of IKL excluded. The numbers and percentage are calculated on available data. Missing data are not shown.
BMI body mass index; *CCCR* Comprehensive Cancer Centre Region; *ER* estrogen receptor; *IKA* Integraal Kankercentrum Amsterdam; *IKL* Integraal Kankercentrum Limburg; *IKMN* Integraal Kankercentrum Midden Nederland; *IKN* Integraal Kankercentrum Noord; *IKO* Integraal Kankercentrum Oost; *IKR* Integraal Kankercentrum Rotterdam; *IKST* Integraal Kanker Centrum Spectrum Twente; *IKZ* Integraal Kankercentrum Zuid; *PgR* progesterone receptor.

fered the opportunity to evaluate the differences in patterns of care regarding local treatment strategies and adjuvant chemotherapy between the various CCCRs and the adherence to the national guideline.

Patients and methods

Organisation of breast cancer care in The Netherlands

In The Netherlands, a nationwide programme offering biannual mammography to women aged 50–70 years (later on 75) was initiated in 1989. In case of suspicious changes or abnormalities, the general practitioner is informed and refers the patient to the surgical department of one of the regional hospitals. The diagnostic work-up and therapy of breast cancer are carried out routinely in all hospitals. However, the number of patients annually seen and treated per hospital varies. The guideline advises that planning of local and systemic therapy should be discussed preoperatively by a complete multidisciplinary breast cancer team. As during the period that the TEAM study was running, not all hospitals had a dedicated breast cancer team, not all patients were discussed preoperatively, whereas this occurred postoperatively in almost all patients.

The TEAM trial

The TEAM trial is an international randomised phase III trial and was originally designed to compare 5 years of exemestane (25mg/day) versus 5 years of tamoxifen (20mg/day). However, the published data of the Intergroup Exemestane Study (IES) showed a significantly improved DFS with exemestane following 2–3 years of tamoxifen as compared with the standard 5 years of tamoxifen treatment.[12] 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 2.5–2 years of exemestane. Primary end points of the core protocol are DFS at 2.75 and 5 years; secondary end points include OS, incidence of a new primary breast cancer and relative safety profiles.[13]

Eligibility criteria for the Dutch TEAM trial

Eligibility criteria were postmenopausal women with histologically confirmed invasive breast cancer, positive estrogen receptor (ER) and/or progesterone receptor (PgR) status, having undergone intentionally curative surgery and having an indication for adjuvant endocrine therapy according to the NABON guideline. Postmenopausal status was defined as follows: patients with intact uterus and natural amenorrhoea for > 1 year and history of bilateral surgical oophorectomy and no hormone replacement therapy. In case of doubt, follicle-stimulating hormone and estradiol concentrations had to be within the postmenopausal ranges. Adjuvant chemotherapy preceding the start of endocrine therapy was allowed. Radiotherapy was given according to the NABON guideline whereby no recommendation was given regarding the sequence of radiotherapy and chemotherapy. Endocrine treatment had to be started within 10 weeks after completion of definitive surgery or chemotherapy.

Patients were ineligible in case of inflammatory breast cancer, clinical skin ulceration/infiltration of local skin metastasis, positive supraclavicular lymph nodes, evidence of distant metastases, neoadjuvant chemotherapy, participation in another clinical trial interfering with the end points of the TEAM trial, other clinically relevant or serious illnesses, previous breast cancer or history of another malignancy within the preceding 5 years (except for adequately treated carcinoma in situ of the uterine cervix or basal squamous cell carcinoma). Hormone replacement therapy had to be stopped >4 weeks before randomisation.

Patients received oral and written information and provided informed written consent. The trial has been approved by the appropriate regulatory and ethics authorities of the different participating hospitals.

Data collection

From each patient, the following data were recorded: patient characteristics (age, length, weight, menopausal status and medical history), tumour characteristics (primary disease site, histological grade, Mitotic Activity Index score, tumour–node–metastasis stage and ER and PgR status), local therapy data (dates and type of surgery, SLNP, axillary lymph node dissection (ALND) and radiotherapy (to the breast or to the chest wall)) and chemotherapy data. Original pathology reports were centrally collected and checked for tumour

Table 2 Local and systemic treatment given in numbers and in percentages, unless otherwise mentioned.

	CCCR																	
	IKA		IKL		IKMN		IKN		IKO		IKR		IKST		IKW		IKZ		Total		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	*p*
Number of patients included	319		105		280		245		260		492		207		364		482		2754		
Local treatment[a]																					< 0.001
MST - radiotherapy	113	*35*	51	*49*	117	*42*	106	*43*	119	*46*	247	*50*	83	*40*	154	*40*	146	*30*	1127	*41*	
MST + radiotherapy	42	*13*	22	*21*	24	*9*	34	*14*	31	*12*	84	*17*	34	*16*	54	*15*	73	*15*	398	*15*	
BCS - radiotherapy	18	*6*	1	*1*	1	*0*	4	*2*	2	*1*	8	*2*	3	*1*	4	*1*	19	*4*	60	*2*	
BCS + radiotherapy	146	*46*	31	*30*	138	*49*	100	*41*	108	*42*	153	*31*	87	*42*	161	*44*	244	*51*	1168	*42*	
SLNP																					< 0.001
No	87	*27*	35	*33*	74	*26*	69	*28*	56	*22*	206	*42*	120	*58*	96	*26*	145	*30*	888	*32*	
Yes	230	*73*	70	*67*	206	*74*	176	*72*	204	*79*	286	*58*	87	*42*	268	*74*	337	*70*	1866	*68*	
ALND																					< 0.001
No	80	*25*	27	*26*	53	*19*	45	*18*	85	*33*	83	*17*	47	*23*	100	*28*	115	*24*	635	*23*	
Yes	239	*75*	78	*74*	227	*81*	200	*82*	175	*67*	409	*83*	160	*77*	264	*73*	366	*76*	2118	*77*	
Examined nodes in ALND																					< 0.001
Median	16		13		14		13		15		14		14		15		13		14		
Minimum	6		4		4		3		0		1		6		1		1		0		
Maximum	37		25		46		30		42		33		30		39		31		46		
Adjuvant chemotherapy[b]																					< 0.001
No	123	*58*	22	*50*	112	*59*	83	*46*	151	*85*	180	*53*	83	*60*	76	*30*	240	*70*	1070	*57*	
Yes	88	*42*	22	*50*	79	*41*	99	*54*	26	*15*	162	*47*	56	*40*	175	*70*	103	*30*	810	*43*	
Chemotherapy																					< 0.001
CMF	0	*0*	0	*0*	1	*1*	0	*0*	7	*27*	1	*1*	1	*2*	*4*	*2*	18	*18*	32	*4*	
FAC / FEC	28	*34*	2	*9*	16	*20*	28	*29*	13	*50*	34	*21*	10	*18*	*32*	*18*	51	*52*	214	*27*	
AC / EC	55	*66*	20	*91*	62	*79*	69	*71*	6	*23*	127	*78*	44	*80*	*138*	*79*	30	*30*	551	*69*	
Sequence																					< 0.001
Radiotherapy => CT	28	*43*	1	*7*	35	*69*	4	*6*	10	*83*	0	*0*	17	*50*	39	*33*	5	*7*	139	*27*	
Radiotherapy during CT	12	*19*	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*	1	*3*	5	*4*	16	*21*	34	*7*	
CT => Radiotherapy	25	*39*	14	*93*	16	*31*	60	*94*	2	*17*	90	*100*	16	*47*	74	*63*	55	*72*	352	*67*	

[a]Radiotherapy includes radiation to the breast or to the chest wall.
[b]Only patients <70 years. The numbers and percentage are calculated on available data. Missing data are not shown.
AC adriamycin and cyclophosphamide; *ALND* axillary lymph node dissection; *BCS* breast-conserving surgery; *CCCR* Comprehensive Cancer Centre Region (Table 1); *CMF* cyclophosphamide, methotrexate and 5-fluorouracil; *CT* chemotherapy; *EC* epirubicin and cyclophosphamide; *FAC* 5-fluorouracil, adriamycin and cyclophosphamide; *FEC* 5-fluorouracil, epirubicin and cyclophosphamide; *IKA* Integraal Kankercentrum Amsterdam; *IKL* Integraal Kankercentrum Limburg; *IKMN* Integraal Kankercentrum Midden Nederland; *IKN* Integraal Kankercentrum Noord; *IKO* Integraal Kankercentrum Oost; *IKR* Integraal Kankercentrum Rotterdam; *IKST* Integraal Kankercentrum Spectrum Twente; *IKZ* Integraal Kankercentrum Zuid; *MST* mastectomy; *SLNP* sentinel lymph node procedure.

characteristics. Central pathology review was not carried out for this analysis but will be carried out for all Dutch patients within the context of an ongoing international project.[14]

Statistics

All data were analysed using the statistical package SPSS for Windows 15.0 (SPSS Inc.; Chicago, IL). Descriptive data are given as mean (standard deviation (SD)) or median (range). Pearson's chi-square test was used to compare frequencies between groups. Differences of quantitative data between CCCRs were tested by one-way analysis of variance (ANOVA) or Kruskal–Wallis test. Univariate and multivariable analyses were carried out using logistic regression procedures. Significant factors at univariate analysis ($p < 0.10$) were included in a multivariable model. All testing was two tailed with 0.05 as level of significance.

Results

Patient and tumour characteristics

From 76 of a total of 123 Dutch centres (62%), 2754 postmenopausal breast cancer patients were enrolled in the TEAM trial from 16 July 2001 to 23 January 2006. Patients were included by surgeons (48%), medical oncologists (52%) and one radiotherapist. Patients' characteristics are presented in Table 1. The mean age at diagnosis was different between CCCRs (one-way ANOVA overall $p < 0.001$). *Post hoc* analysis with Bonferroni correction revealed that this difference was caused by the age of patients in one CCCR (Integraal Kankercentrum Limburg (IKL), mean age 71 years (SD 10)). Excluding patients from this CCCR, age at diagnosis of the other CCCRs was similar (mean age 65 years, SD 9, $p = 0.297$).

Overall, 46% of patients had a T1 tumour, ranging between 39% and 50% among the CCCRs ($p = 0.200$). The frequency of node-negative disease ranged from 25% in the Integraal Kankercentrum Noord (IKN) to 45% in the Integraal Kankercentrum Oost (IKO) ($p < 0.001$). As hormone sensitivity was an inclusion criterion for the TEAM trial, the ER status was available for all patients. The PgR status was not regularly assessed in five CCCRs, particularly in the Integraal Kankercentrum Amsterdam (IKA) and IKN region (PgR status not available in 14% and 25%, respectively). Human epidermal growth factor receptor 2 overexpression was not routinely assessed as at that time it did not have therapeutic consequences.

Local therapy

Overall, more women underwent a mastectomy compared with BCS (55% versus 45%, respectively; Table 2). Although tumour size was not significantly different between the various regions, the mastectomy rate ranged between 45% (Integraal Kankercentrum Zuid (IKZ)) and 70% (IKL) ($p < 0.001$). In all CCCRs, mastectomy was carried out more often for larger tumours. For T1 tumours, mastectomy rates ranged between 20% and 55% ($p < 0.001$, data not shown). Results of univariate analysis regarding type of surgery with age at diagnosis, tumour size, body mass index (BMI), CCCR and physician who included the patients (medical oncologist versus surgeon) as variables indicated that all factors except BMI were statistically significant (Table 3). In multivariable analysis, age, lower T stage and CCCR remained independent factors for BCS (Table 4). For the CCCR Integraal Kankercentrum Rotterdam (IKR), we separately investigated whether BCS rate was related to the travel distance to a radiotherapy facility. This could not be demonstrated (data not shown).

An SLNP was carried out in 68% of patients, ranging from 42% (Integraal Kanker Centrum Spectrum Twente (IKST)) to 79% (IKO) ($p < 0.001$; Table 2). All variables included in univariate analysis were significant (Table 3). In multivariable analysis, it was observed that favourable tumour stage, BCS and CCCR were associated with more SLNPs (Table 4). Almost 80% of the patients underwent an ALND (range 67%–83%), being different between the CCCRs ($p < 0.001$). On an average, 14 (range 0–46) lymph nodes were examined, being consistent with the guideline recommendation.

Radiotherapy to the breast (with/without boost) or chest wall was given in 57% of cases (Table 2). Ninety-five percent (1168of 1228) of the patients who underwent BCS received radiotherapy. The frequency of radiotherapy after mastectomy ranged between 17% and 33% ($p = 0.043$). In multivariable analysis, age, larger tumour stage, BCS and more positive lymph nodes were predictive for receiving radiotherapy (Table 4).

Table 3 Univariate logistic regression model for factors associated with type of surgery, SLNP, radiotherapy and chemotherapy.

		Type of surgery		SLN		Radiotherapy		Chemotherapy	
		OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
CCCR	IKA	1.00	< 0.001	1.00	< 0.001	1.00	0.001	1.00	< 0.001
	IKL	0.41 (0.26–0.66)		0.75 (0.47–1.21)		0.71 (0.46–1.11)		1.40 (0.73–2.68)	
	IKMN	0.93 (0.68–1.28)		1.04 (0.73–1.50)		0.96 (0.69–1.33)		0.99 (0.66–1.47)	
	IKN	0.70 (0.50–0.98)		0.96 (0.66–1.39)		0.86 (0.61–1.20)		1.67 (1.12–2.49)	
	IKO	0.69 (0.50–0.96)		1.37 (0.93–2.01)		0.80 (0.58–1.11)		0.24 (0.15–0.40)	
	IKR	0.46 (0.34–0.61)		0.52 (0.38–0.71)		0.65 (0.49–0.86)		1.26 (0.89–1.78)	
	IKST	0.73 (0.51–1.03)		0.27 (0.19–0.39)		0.98 (0.69–1.40)		0.94 (0.61–1.46)	
	IKW	0.78 (0.58–1.06)		1.05 (0.75–1.47)		1.01 (0.74–1.37)		3.22 (2.19–4.73)	
	IKZ	1.34 (0.86–1.51)		0.87 (0.64–1.19)		1.34 (1.00–1.79)		0.60 (0.42–0.86)	
Included by	Medical oncologist	1.00	0.001	1.00	0.839	1.00	0.765	1.00	< 0.001
	Surgeon	1.28 (1.10-1.49)		2.12 (0.84-1.15)		0.98 (0.84-1.14)		0.30 (0.25-0.36)	
Age	<50	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001
	50-59	3.04 (1.69–5.49)		1.44 (0.83–2.50)		1.45 (0.85–2.47)		0.29 (0.13–0.61)	
	60-69	2.72 (1.51–4.89)		1.33 (0.77–2.31)		1.21 (0.71–2.06)		0.04 (0.02–0.09)	
	≥70	1.22 (0.68–2.21)		0.84 (0.49–1.46)		0.65 (0.38–1.11)			
Tumour stage	T1	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001
	T2	0.36 (0.31-0.43)		0.45 (0.38–0.54)		0.52 (0.44–0.61)		1.58 (1.31–1.91)	
	T3 or T4	0.04 (0.02–0.07)		0.18 (0.13–0.24)		0.90 (0.65–1.24)		2.09 (1.40–3.14)	
BMI	≤25	1.00	0.758						
	>25-<30	1.01 (0.84–1.21)							
	≥30	1.08 (0.88–1.33)							
Surgery	MST			1.00	< 0.001	1.00	< 0.001	1.00	< 0.001
	BCS			4.18 (3.48–5.01)		55.12 (41.5–73.2)		0.72 (0.60–0.86)	
Nodal stage	pN0					1.00	< 0.001	1.00	< 0.001
	pN1 (1-3)					0.98 (0.83–1.17)		1.70 (1.36–2.13)	
	pN2 (4-9)					4.36 (3.19–5.96)		8.92 (6.16–12.9)	
	pN3 (≥10)					7.42 (4.26–12.93)		7.70 (4.60–12.9)	
Histology	Grade 1					1.00	0.901	1.00	0.006
	Grade 2					0.95 (0.76–1.19)		1.38 (1.04–1.84)	
	Grade 3					0.95 (0.75–1.20)		1.61 (1.20–2.15)	

An OR <1 indicates a decreased likelihood, an OR >1 an increased likelihood of BCS, an SLNP, receiving radiotherapy or chemotherapy. Patients >70 years are excluded from the chemotherapy analysis.

BCS breast-conserving surgery; *BMI* body mass index; *CI* confidence interval; *CCCR* Comprehensive Cancer Centre Region; *IKA* Integraal Kankercentrum Amsterdam; *IKL* Integraal Kankercentrum Limburg; *IKMN* Integraal Kankercentrum Midden Nederland; *IKN* Integraal Kankercentrum Noord; *IKO* Integraal Kankercentrum Oost; *IKR* Integraal Kankercentrum Rotterdam; *IKST* Integraal Kankercentrum Spectrum Twente; *IKZ* Integraal Kankercentrum Zuid; *MST* mastectomy; *OR* odds ratio; *SLN* sentinel lymph node; *SLNP* sentinel lymph node procedure.

Adjuvant chemotherapy

Adjuvant chemotherapy was given in 43% of women <70 years of age varying between the CCCRs ($p < 0.001$; Table 2). For the age groups <50, 50–59 and 60–69 years, this was 86%, 65% and 21%, respectively ($p < 0.001$, data not shown). In multivariable analysis, younger age at diagnosis, larger tumour stage, more positive nodes, worse histological grade, the physician who included the patient and CCCR were prognostic factors for administration of chemotherapy (Table 4). In most CCCRs (seven of nine), adriamycin and cyclophosphamide or epirubicin and cyclophosphamide was administrated in the majority of the patients receiving chemotherapy. More 5-fluorouracil, adriamycin and cyclophosphamide or fluoruracil, epirubicin and cyclophosphamide was administrated in the two CCCRs where cyclophosphamide, methotrexate and 5-fluorouracil also was given in ~20% patients.

Sequence of radiotherapy and chemotherapy

The sequence of administration of radiotherapy and chemotherapy, respectively, was different in the various CCCRs ($p < 0.001$; Table 2). Radiotherapy was almost always given after chemotherapy in the IKL, IKN and IKR region (>90%). In the Integraal Kankercentrum Midden Nederland and IKO region, the majority of patients received radiotherapy before chemotherapy (69% and 83%, respectively). This policy, however, was not consistent throughout the hospitals in these regions (data not shown). In the IKA and IKZ region, some patients received chemotherapy in combination with radiotherapy.

Discussion

To our knowledge, this is the first report describing variations in patterns of breast cancer care regarding local treatment strategies and adjuvant chemotherapy in all Dutch CCCRs. In view of the large number of included patients and the nationwide participation in the TEAM trial, the results of the current analysis may be considered as a reflection of the management of postmenopausal breast cancer patients in The Netherlands. We have no indication that patients within the TEAM trial were treated differently with respect to locoregional therapy and adjuvant chemotherapy compared with postmenopausal breast cancer patients outside the TEAM trial. Our results indicate that, despite the existence of a national breast cancer guideline, patterns of care varied widely throughout the country.

Age at diagnosis and tumour size were not significantly different in the various CCCRs, except for the IKL region, where due to a concurrent adjuvant chemotherapy trial, less young postmenopausal patients were included. In only 46% of cases, the tumour was < 2cm. This can be explained by the fact that during inclusion of the TEAM study, only larger tumours or small tumours with grade III or small tumours with positive nodes were candidates for endocrine therapy according to the pending guidelines. The observation that in some CCCRs, information on the PgR status was lacking despite the national recommendation to determine both ER and PgR status can be explained by the fact that some pathology laboratories only determined the PgR status in case of a negative ER status as with a positive ER status; knowledge on the PgR status had no consequences with respect to the type of adjuvant systemic therapy. This observation is in accordance with data from other aromatase inhibitor trials (Table 5).

More patients were treated with mastectomy compared with BCS. The choice concerning the type of breast surgery is known to be influenced by the preference of patients, doctors (especially the surgeon being a key player) and geographical factors.[15-20] Regarding the latter, the absence of a local radiotherapy unit as well as travel distance and facilities can play a role. The higher age of patients in the IKL region might explain the higher rate of mastectomies. In contrast, this does not explain the high rate of mastectomies in the IKR region (67%). Differences in surgical choice were also seen in the 'Anastrozole, Tamoxifen, Alone or in Combination' trial.[21] In this trial, nationality (United States versus UK versus rest of the world) was found to be an independent determinant of type of surgery; American women were more likely to undergo a mastectomy than women in the UK. In accordance with our findings, the accessibility to a radiotherapy facility was not found to be a major determinant for less or more extensive surgery.

According to the guideline, radiotherapy was

Table 4 Multivariable logistic regression model for factors associated with type of surgery, SLNP, radiotherapy and chemotherapy.

		Type of surgery		SLN		Radiotherapy		Chemotherapy	
		OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
CCCR	IKA	1.00	< 0.001	1.00	< 0.001	1.00	0.082	1.00	< 0.001
	IKL	0.52 (0.31–0.87)		1.09 (0.66–1.82)		2.35 (1.10–5.02)		1.38 (0.59–3.21)	
	IKMN	0.89 (0.62–1.26)		1.06 (0.72–1.57)		1.39 (0.77–2.51)		2.18 (1.23–3.87)	
	IKN	0.69 (0.47–1.00)		1.09 (0.73–1.62)		1.36 (0.75–2.47)		1.02 (0.58–1.78)	
	IKO	0.65 (0.46–0.93)		1.57 (1.05–2.37)		2.16 (1.20–3.89)		0.21 (0.11–0.39)	
	IKR	0.42 (0.31–0.58)		0.61 (0.44–0.85)		1.72 (1.03–2.86)		0.93 (0.57–1.50)	
	IKST	0.71 (0.48–1.04)		0.25 (0.17–0.37)		2.13 (1.13–4.03)		1.92 (1.05–3.50)	
	IKW	0.83 (0.60–1.16)		1.17 (0.81–1.68)		2.00 (1.15–3.47)		3.51 (2.08–5.93)	
	IKZ	1.17 (0.85–1.59)		0.82 (0.59–1.15)		2.20 (1.30–3.73)		0.79 (0.48–1.28)	
Included by	Medical oncologist	1.00	0.904					1.00	< 0.001
	Surgeon	1.01 (0.82-1.25)						0.25 (0.18-0.35)	
Age	<50	1.00	< 0.001	1.00	0.084	1.00	0.027	1.00	< 0.001
	50-59	3.15 (1.70–5.85)		1.10 (0.61–1.98)		0.61 (0.27–1.39)		0.37 (0.16–0.88)	
	60-69	2.80 (1.51–5.19)		1.04 (0.58–1.87)		0.45 (0.20–1.03)		0.03 (0.01–0.08)	
	≥70	1.37 (0.74–2.55)		0.84 (0.47–1.51)		0.40 (0.18–0.91)			
Tumour stage	T1	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001	1.00	0.004
	T2	0.38 (0.32-0.45)		0.58 (0.48–0.70)		0.99 (0.73–1.33)		1.55 (1.18–2.03)	
	T3 or T4	0.04 (0.02–0.07)		0.29 (0.20–0.41)		6.05 (3.80–9.65)		1.77 (0.96–3.25)	
Surgery	MST			1.00	< 0.001	1.00	< 0.001	1.00	0.840
	BCS			3.37 (2.76–4.12)		194 (135–279)		1.02 (0.78–1.34)	
Nodal stage	pN0					1.00	< 0.001	1.00	< 0.001
	pN1 (1-3)					1.38 (0.99–1.91)		2.33 (1.69–3.19)	
	pN2 (4-9)					33.5 (21.8–51.6)		14.9 (9.03–24.5)	
	pN3 (≥10)					58.2 (30.5–111)		16.3 (8.41–31.4)	
Histology	Grade 1							1.00	0.007
	Grade 2							1.35 (0.93–1.96)	
	Grade 3							1.87 (1.25–2.82)	

An OR <1 indicates a decreased likelihood and an OR >1 an increased likelihood of BCS, an SLNP, receiving radiotherapy or chemotherapy. Patients ≥70 years are excluded from the chemotherapy analysis.

BCS breast-conserving surgery; *CI* confidence interval; *CCCR* Comprehensive Cancer Centre Region; *IKA* Integraal Kankercentrum Amsterdam; *IKL* Integraal Kankercentrum Limburg; *IKMN* Integraal Kankercentrum Midden Nederland; *IKN* Integraal Kankercentrum Noord; *IKO* Integraal Kankercentrum Oost; *IKR* Integraal Kankercentrum Rotterdam; *IKST* Integraal Kankercentrum Spectrum Twente; *IKZ* Integraal Kankercentrum Zuid; *MST* mastectomy; *OR* odds ratio; *SLN* sentinel lymph node; *SLNP* sentinel lymph node procedure.

given after BCS in the majority of cases (95%). In previous studies, age appeared to be a stronger predictor than co-morbidity with respect to omitting radiotherapy, especially in the oldest age group.[22,23] In view of the growing proportion of the elderly for the next decades, this and other issues regarding elderly patients are worthwhile exploring.

In most CCCRs, SLNP was carried out in at least 70% of patients. Low percentages were in the IKST (42%) and IKR (58%) region, where in some hospitals, this procedure had only been introduced since 2003–2004. We expect that the differences in SLNP between the CCCRs will disappear over time because the SLNP has now been implemented nationwide. Whether a different percentage of clinically positive nodal disease at presentation might be another explanation is unclear as no information about this issue is available in our database. On an average, all regions fulfilled the national recommendation to examine at least 10 lymph nodes at ALND. Not all patients with a positive sentinel lymph node received an ALND, which in part may be explained by concomitant participation in the ongoing AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery?) trial.[24] In this trial, patients with clinically negative nodal disease and a positive SLNP were randomly allocated between ALND or radiotherapy to the axilla.

Despite the fact that most patients had node-positive disease, only a minority was treated with chemotherapy. This is in part a reflection of the NABON guideline of 2002, in which chemotherapy is only recommended for fit patients under the age 70 years with unfavourable tumour characteristics (≥ N2 disease). Remarkably, fewer patients received chemotherapy in the IKO region since in some hospitals, adjuvant chemotherapy was erroneously thought to be an exclusion criterion for this trial. Our data are in accordance with the findings of IES, showing substantial geographical differences in indications for and choice of adjuvant chemotherapy.[25] Differences regarding chemotherapy administration are also seen between the various aromatase inhibitor trials, although this can be partly explained by the different trial eligibility criteria (Table 5).

CCCR was, even after correction for relevant factors, an independent predictor for type of surgery, SLNP and adjuvant chemotherapy. This indicates that implementation of, and interpretation and adherence to the national guidelines varies between CCCRs. Different reasons have been reported for not adhering to guidelines including physician-related factors, patient's age, patient/doctor preferences, comorbidity burden, number of patients seen and type of hospital, organisation of and access to health insurance, trial participation, ethnical, cultural and geographical location, factors and the use of specialist/nonspecialist care (breast cancer team).[15,17,26-28] Because of the retrospective nature of this analysis, it was not possible to study the impact of most of these factors. However, in view of the ultimate goal of national and international guidelines and of the strong evidence that treatment in accordance to guidelines results in improved outcome for breast cancer patients, attention for improvement of guideline adherence is necessary.[29] In addition, these variations in locoregional and adjuvant chemotherapy policies might influence the end points of adjuvant studies with hormonal agents in postmenopausal women. This could be relevant as, in general, the benefit of aromatase inhibitors is small compared with antiestrogens.

One way to address this issue further is focussing on the implementation of breast cancer teams. These multidisciplinary teams intend to coordinate, standardise and ameliorate breast cancer care and outcome. It has been demonstrated that 43% of patients advised and treated by a multidisciplinary team received a different treatment than when they were treated by a single specialist.[30] Also, the advice given by the multidisciplinary team was more in line with good clinical practice guidelines as compared with advices given by a single specialist, which particularly reflected their own discipline. Patients reported that physicians' recommendations greatly influenced their treatment decisions.[31] The implementation of newer adjuvant systemic therapies was strongly dependent on the activation of a multidisciplinary team resulting in an improved survival for respective patients.[28] Due to the lack of data concerning the availability of Dutch breast cancer teams, it was not possible to evaluate its effect in this analysis.

Table 5 Patient characteristics in aromatase inhibitor trials (given in percentages, unless otherwise mentioned).

Trial	Dutch TEAM	ATAC[5]	ARNO95 ABCSG8[7]	ITA[3]	IES[4]	BIG 1-98[8]	MA-17[6]
Number of patients	2754	9366	3224	448	4742	8010	5157
Age							
Mean (SD)	65 (9)	64 (9)			64 (8)		
Median (range)	64 (38-96)		62 (41-80)	63(38-77)		61 (38-90)	62
Tumour size							
≤ 2cm	46	64	70	47		62	
> 2cm	55	36	30	48		37	
Hormone receptor							
ER+/PgR+	71		78		55	63	
ER+/PgR-	22		17		15	20	
ER+/PgR nc	6		0		11	14	
ER-/PgR+	2		2		2	2	
Grade							
I	16	21	70	65 (including		30	
II	47	47	24	grade II)		52	
III	36	24	5	22		18	
Nodal status							
N0	31	61	74	0	51	57	50
N+	69	35	25	100	44	41	46
0	31	61	74	0	51		
1-3	52	24	21	63	30		
>3	17	11	4	36	14		
Surgery							
Mastectomy	55	48	23	53	52	43	57
BCS	45	52	77	47	47	57	50
Adjuvant CT							
No	57	79	100	33	67	75	54
Yes	43	21	0	67	32	25	46

ABCSG8 Austrian Breast and Colorectal Cancer Study Group 8; *ARNO95* 'Arimidex'–'Nolvadex 95'; *ATAC* Anastrozole, Tamoxifen, Alone or in Combination; *BCS* breast-conserving surgery; *BIG 1-98* Breast International Group 1-98; *CT* chemotherapy; *ER* estrogen receptor; *IES* Intergroup Exemestane Study; *ITA* Italian Tamoxifen Anastrozole; *nc* not carried-out; *PgR* progesterone receptor; *SD* standard deviation; *TEAM* Tamoxifen Exemestane Adjuvant Multinational.

In conclusion, our data show that, despite a national breast cancer treatment guideline, major regional differences in treatment exist. These differences must be taken into account when evaluating a certain element of the therapy for breast cancer, for example, endocrine therapy comparing aromatase inhibitors with antiestrogens in postmenopausal women. In our opinion, in attempting to improve breast cancer care, it is important to increase and further evaluate adherence to guidelines.

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