

# Approaches to postmastectomy radiotherapy (PMRT) in the Intergroup Exemestane Study (IES)

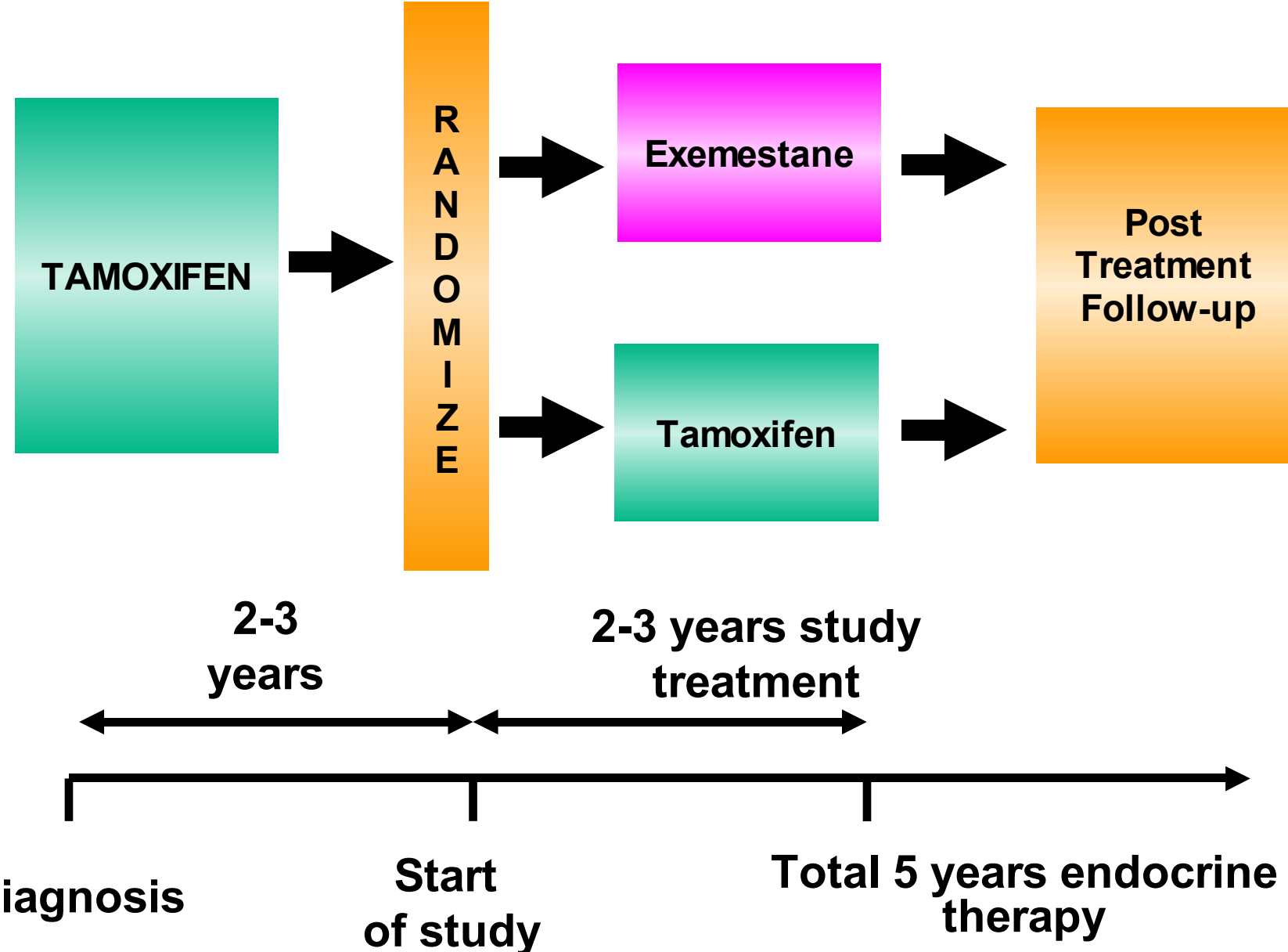
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## INTRODUCTION

Within the IES we have previously shown that the use of mastectomy versus breast conserving therapy (BCT) varies greatly between countries (EJC Suppl. 2004; 2: 163). Whereas tumour excision in early breast cancer is typically followed by radiotherapy (RT), indications for PMRT use are still debatable. In the present study we analysed the factors affecting PMRT use according to geographical region to gauge within the patients receiving mastectomy, differences within clinically defined prognostic subgroups.

## IES STUDY DESIGN

Fig. 1. Study design



Postmenopausal patients with ER positive/unknown, adequately treated unilateral breast cancer, who remained disease-free after 2-3 years of tamoxifen, were randomised to continue tamoxifen (20 mg/day) or switch to exemestane (25 mg/day) for a further 2-3 years to complete a total of 5 years adjuvant endocrine therapy (Fig. 1). According to protocol all patients who received BCT should have received RT. However, use of RT following mastectomy was optional and therefore administered according to local centre policy. Main study results have previously been reported (N Engl J Med 2004; 350: 1081-92; J Clin Oncol 2006; 24 (Suppl 18S), Abstract LBA527).

## METHODS

The trial was coordinated by the International Collaborative Cancer Group (ICCG), Imperial College London, via 20 cooperative groups under the auspices of the Breast International Group (BIG).

Multivariate logistic regression was used to investigate the use of PMRT adjusting for clinical characteristics and region. Odds ratios greater than 1 indicate increased odds of receiving PMRT relative to the reference groups.

Country grouping was by geographical locations and regions of specific interest. One country (Hong Kong) did not fall within any defined category and so is not included in the analyses by regional group (n=6).

## PATIENT CHARACTERISTICS

A total of 4,724 eligible patients were randomised into the trial from 366 sites in 37 countries between February 1998 and February 2003. 4646 patients received adequate local therapy (78 patients were excluded from these analyses because they received BCT without RT or RT and/or surgical variables were missing). Nodal status and oestrogen receptor status were well balanced between the randomised treatment groups. The mean age at study entry was 64.2 years (95% confidence interval: 63.9 – 64.4).

Table 1. Baseline characteristics by local treatment

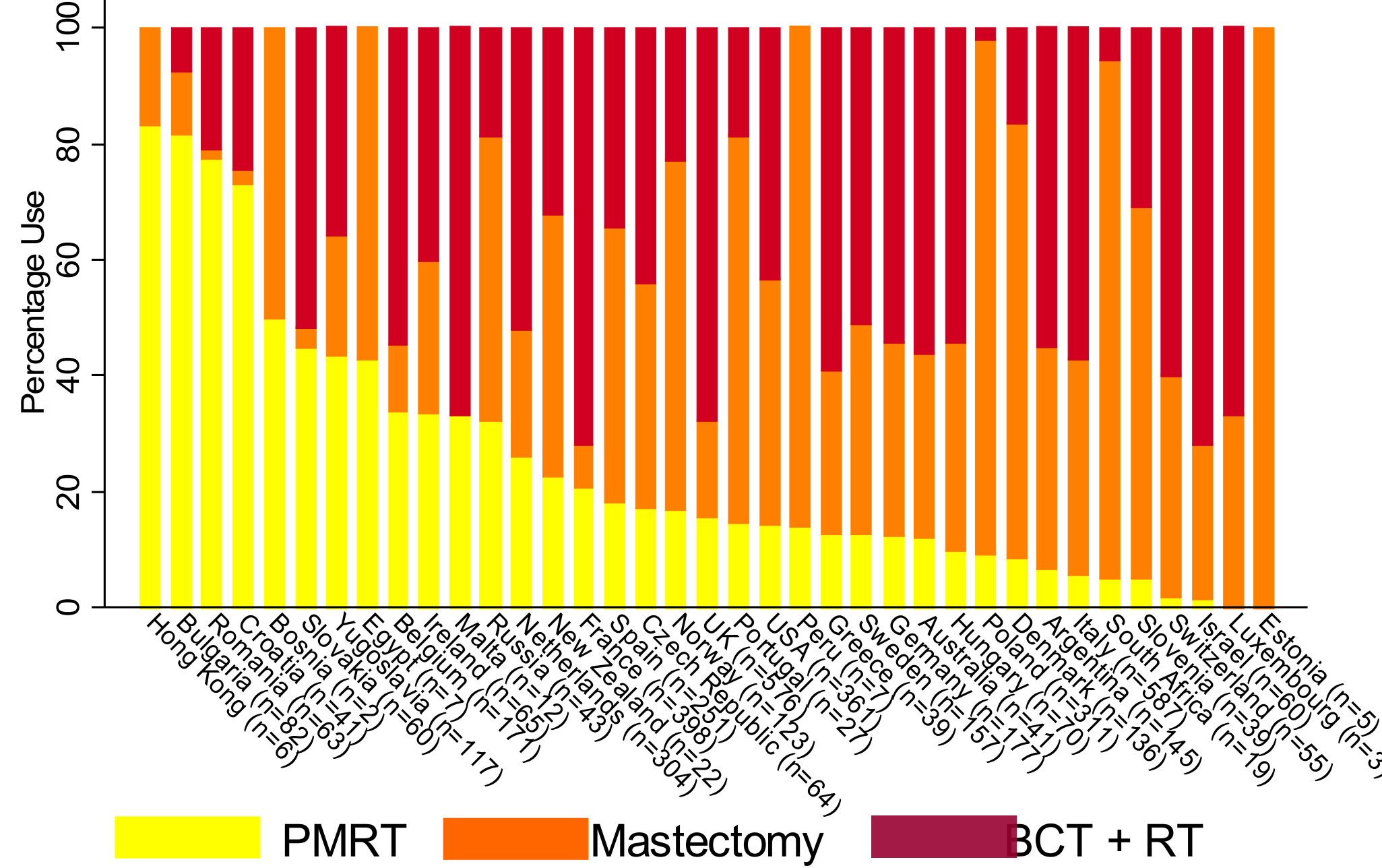
		PMRT (N = 872)		BCT (N = 2173)		Mastectomy (N = 1601)	
		n	row %	n	row %	n	row %
Age (years)	<50	44	31.0	56	39.4	42	29.6
	50-54	64	16.1	229	57.5	105	26.4
	55-59	194	20.0	474	49.0	300	31.0
	60-64	177	16.4	537	49.9	363	33.7
	65-69	180	19.6	418	45.4	322	35.0
	70-74	132	19.4	290	42.5	260	38.1
	≥75	81	17.6	169	36.8	209	45.5
Nodal status	Negative	250	10.4	1307	54.2	855	35.4
	1-3 N+	317	22.5	557	39.4	538	38.1
	≥4 N+	295	45.3	185	28.4	171	26.3
	Unknown/Missing	10	5.8	124	72.5	37	21.6
Tumour size	<2cm	226	10.3	1367	62.1	608	27.6
	2-5 cm	566	25.3	770	34.5	897	40.2
	>5cm	80	37.7	36	17.0	96	45.3
Histological grade	G1	85	11.2	458	60.2	218	28.6
	G2	354	18.1	946	48.3	659	33.6
	G3	172	19.6	399	45.4	307	35.0
	G4	16	38.1	16	38.1	10	23.8
	GX	27	26.5	21	20.6	54	52.9
	Unknown/Not Assessed/Missing	218	24.1	333	36.8	353	39.0
Chemotherapy	Yes	455	29.8	562	36.8	510	33.4
	No	417	13.4	1611	51.7	1091	35.0
Region	USA	52	14.4	156	43.2	153	42.4
	UK	90	15.6	389	67.5	97	16.8
	Central & Eastern Europe	288	32.1	194	21.6	415	46.3
	Rest of Europe	415	16.1	1323	51.4	834	32.4
	Southern Hemisphere	22	9.4	111	47.4	101	43.2
	Other	5	63.3	0	0.0	1	16.7

## RESULTS

Of the 4646 analysed patients, 2173 (47%) underwent BCT followed by RT, 2473 (53%) underwent mastectomy, of these 872 (35%) underwent PMRT (Table 1).

The use of local treatment varied greatly across country (Fig 2). This can be looked at firstly in terms of the differing use of BCT and mastectomy, and secondly the differing use of PMRT in mastectomy patients.

Fig. 2. Use of local treatment by country



The proportion of mastectomy patients who receive PMRT constitute a very different group of patients in different countries, for example, overall, similar proportions of patients in the UK and USA received PMRT (16% and 14%, respectively), however mastectomy patients were, approximately twice as likely to receive PMRT in the UK compared to the USA (48% and 25%, respectively).

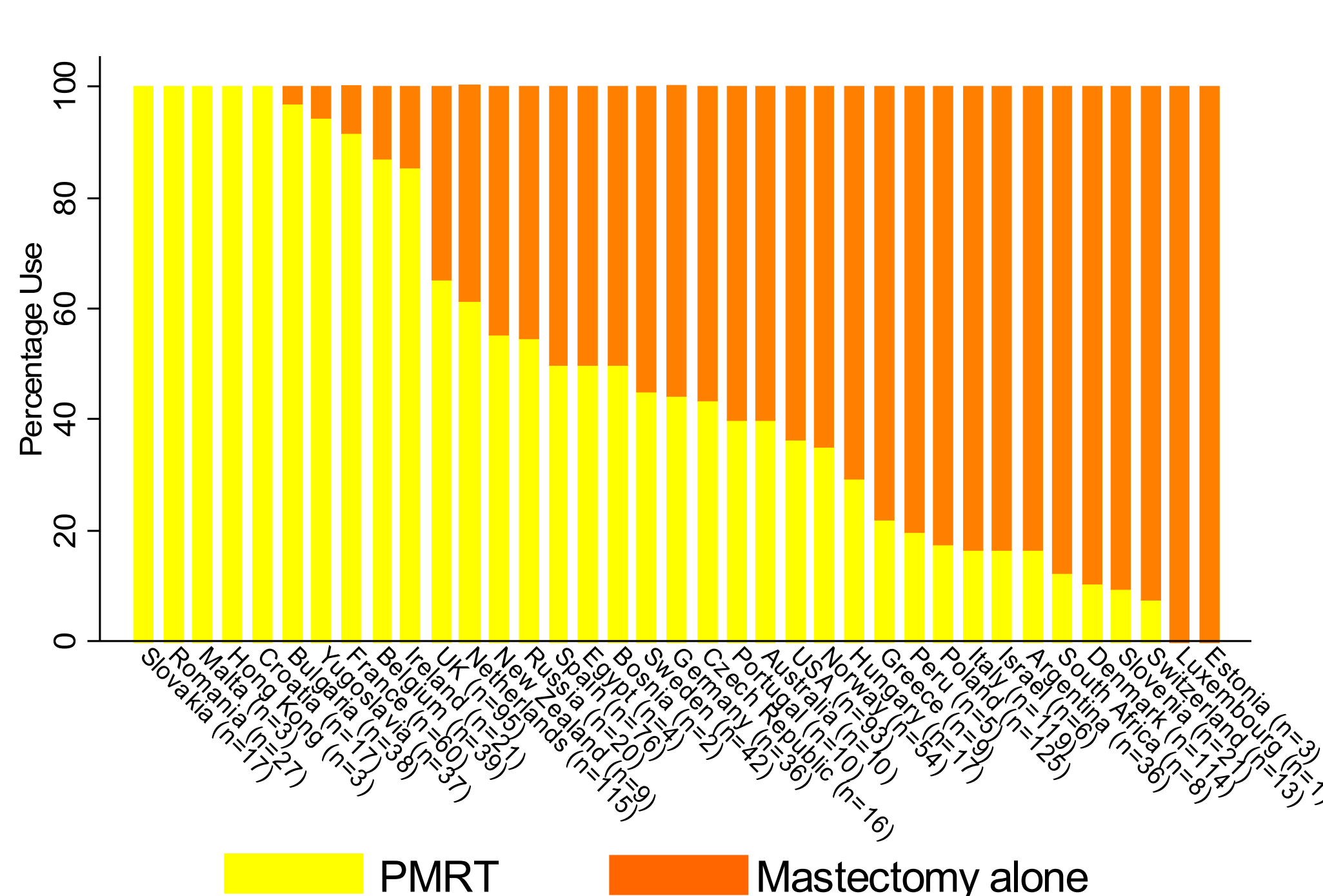
Table 2: Multivariate odds ratio for use of PMRT

Multivariate odds of receiving PMRT				
	N	Odds ratio	95% CI	P-value
Node negative	1102	1	-	-
1-3 Node Positive	853	1.85	(1.50, 2.28)	<0.001
≥4 Node Positive	464	4.77	(3.69, 6.17)	<0.001
Tumour size <2cm	815	1	-	-
Tumour size 2-5cm	1432	1.40	(1.14, 1.72)	0.001
Tumour size >5cm	172	1.54	(1.06, 2.23)	0.023
Grade G1	292	1	-	-
Grade G2	993	1.09	(0.80, 1.48)	0.586
Grade G3	468	1.13	(0.80, 1.60)	0.484
Grade G4	24	3.55	(1.42, 8.91)	0.007
Grade GX/Unknown/Not assessed/Missing	642	1.16	(0.83, 1.61)	0.380
No chemotherapy to breast	1472	1	-	-
Chemotherapy to breast	947	1.69	(1.38, 2.05)	<0.001
ER & PgR unknown	346	1	-	-
ER+/PgR+	1295	1.56	(1.16, 2.10)	0.003
ER+/PgR- or PgR unknown	693	1.48	(1.09, 2.01)	0.013
ER-	85	0.97	(0.56, 1.67)	0.905
USA	203	1	-	-
UK	182	4.11	(2.51, 6.71)	<0.001
C & E Europe	688	2.73	(1.83, 4.07)	<0.001
Rest of Europe	1229	1.59	(1.10, 2.31)	0.014
Southern Hemisphere	117	0.54	(0.29, 0.99)	0.045

Multivariate logistic regression (Table 2) shows that in mastectomy patients:

- Use of PMRT is independently related to nodal status, tumour size, chemotherapy and region.
- Patients with tumour size 2-5 cm and >5 cm were 1.4 and 1.5 times more likely, respectively, to undergo PMRT than mastectomy patients with tumour size <2 cm.
- Patients who received chemotherapy to the breast were 1.7 times more likely to also receive PMRT than mastectomy patients who did not receive chemotherapy.
- Patients in UK and Central Europe were approximately 4 and 3 times more likely, respectively, to receive PMRT than mastectomy patients in the USA.
- 1-3 and ≥4 node positive (N+) patients were approximately 2 and 5 times more likely, respectively, to receive PMRT than mastectomy patients with negative node status.

Fig. 3. Use of PMRT by country in node positive mastectomy patients



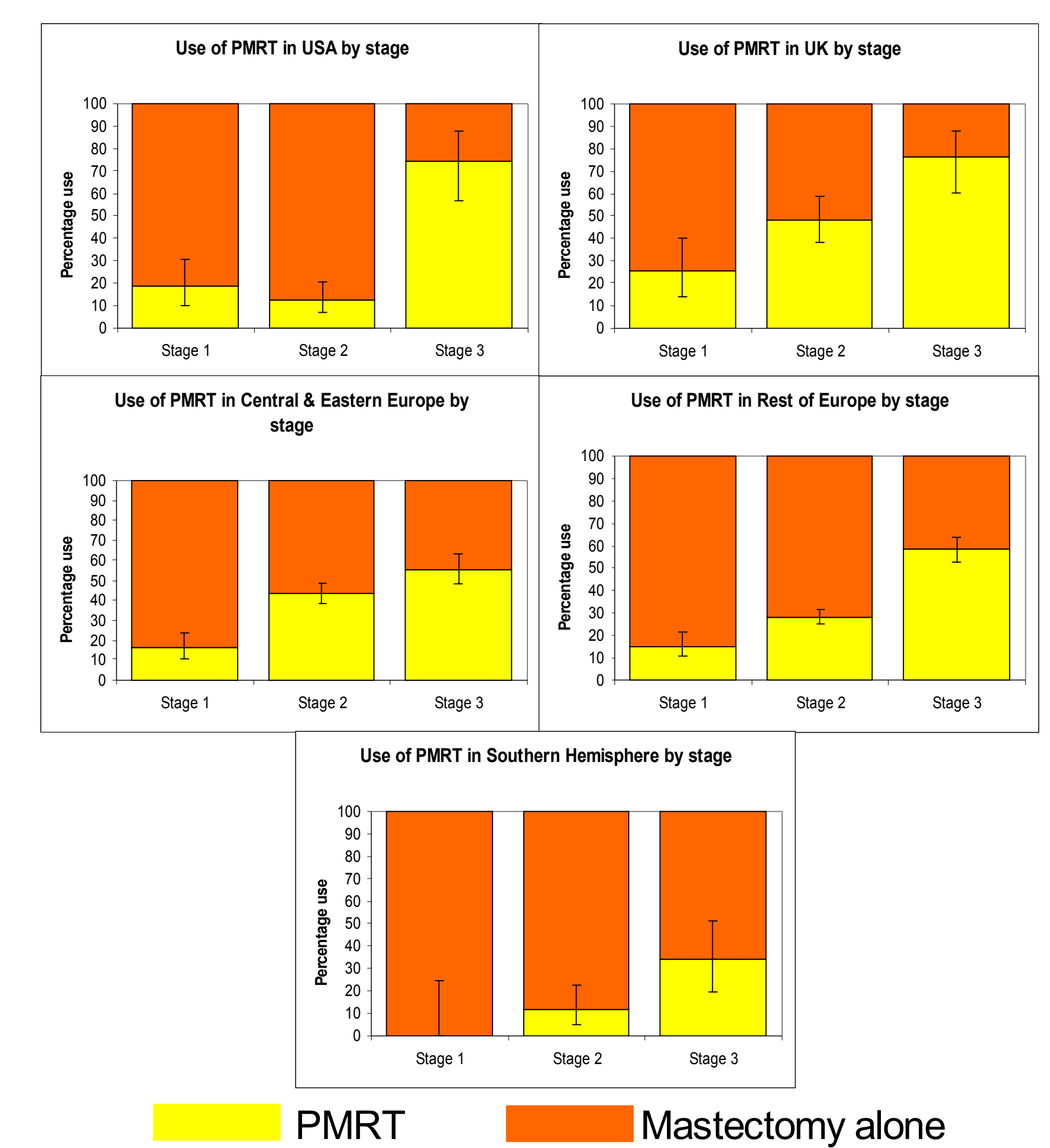
There were large differences in PMRT use between countries. For example, the proportion of node positive mastectomy patients who received PMRT was as follows: UK 65%, Netherlands 62%, Spain 50%, USA, 37%, Poland 18%, Italy 17%, Denmark 11% (Fig. 3).

When the use of PMRT was investigated between countries in the separate N+ groups (1-3 and ≥4), PMRT rates were higher in the ≥4 N+ mastectomy patients compared to the 1-3 N+ mastectomy patients. Although overall rates appeared to be higher in the ≥4 N+, there is still considerable variation between countries (data not shown).

Stage is often used as a selection factor for PMRT, the stage variable combines node status (node negative, 1-3 N+, ≥4 N+) and tumour size (<2 cm, 2-5 cm, >5 cm):

- Stage I (n=450):** Tumour size <2 cm and node negative
- Stage II (n=1392):** Tumour size <2 cm and 1-3 N+  
Or  
Tumour size 2-5 cm, and node negative or 1-3 N+
- Stage III (n=588):** Tumour size >5 cm and/or ≥4 N+
- Stage X (n=43):** Missing nodal status / tumour size (excluded from subsequent analysis)

Fig. 4. Use of PMRT within stage by region



In the UK, Europe and the Southern Hemisphere, PMRT use appeared to increase with stage. Although PMRT use was high for stage III patients in the USA, there was little difference between its use in stage I and II patients.

## Comparison of results to PMRT guidelines

The ASCO guidelines for PMRT (JCO 2001; 19 (5): 1539-1569) recommend the use of PMRT in patients with 4 or more positive axillary lymph nodes and suggest the use of PMRT in patients with T3 or stage III tumours.

The corresponding percentage of ≥4 node positive mastectomy patients to receive radiotherapy in IES was: USA=76%, UK=83%, Central and Eastern Europe=64%, Rest of Europe=62%, Southern Hemisphere=31%.

## CONCLUSIONS

The use of PMRT in breast cancer patients varies between countries and geographical regions. This is at least in some part due to large differences in the use of mastectomy vs BCT. Simple comparison of PMRT rates internationally may therefore be confounded by differing use of mastectomy.

Although the majority of patients in IES with ≥4 positive nodes in the USA, UK and other European countries received PMRT, more emphasis needs to be placed on using PMRT in this subgroup of patients worldwide.

## ACKNOWLEDGEMENTS

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