Factors predicting lymphoedema development after 1 months' and 6 months' analysis

Two analyses were performed: one looked at the situation described above (lymphoedema after 6 months and up to 2 years), and the other looks at the time to first lymphoedema including all follow-up data (1 month visit was excluded as per the protocol [version 5.2] and the NIHR programme grant response letter). Both RAVI (>10%) and sleeve application were considered in these analyses.

Lymphoedema development after 6 months surveillance (i.e. 6 months up to 2 years and the time to first lymphoedema within that time period). Patients with lymphoedema at 3 or 6 months are excluded because the inclusion of the RAVI variable, which is determined at 6 months, means there would need to be a ≥10% category RAVI variable but this is also used as the outcome event. In addition, excluding these patients is part of the study protocol (version 5.2) and the NIHR programme grant response letter.

For RAVI >10 univariate analysis revealed BMI (p<0.002), number of nodes involved (Median 2(range 0-41 (p<0.001)), and largest RAVI change by six months (p<0.001: (HR = 5.58 for ≥5%-<10% vs <3%, 95% CI 3.61 – 8.62)) and BIS >10% (p<0.001) all predicted lymphoedema development from six months up to two years.

The multivariable analysis included RAVI change by six months (p<0.001: (HR = 5.22 for ≥5%-<10%, 95% CI 3.22-8.47)) along with number of nodes involved (HR 1.05, 95% CI 1.02 – 1.07), adjuvant chemotherapy HR = 1.61 (1.01-2.55), BMI >30 (HR 1.87, 95% CI 1.16 – 3.02) and BIS >10% (p=0.069) in the model for predicting lymphoedema development after six months up to two years

TABLE 92: Univariate and multivariable analyses of predictors of lymphoedema (defined by perometry) after 6 months

	Univariate		Multivariable	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year increase)	1.01 (0.99-1.02)	0.31	-	-
BMI at baseline (ref ≤25)		0.002		0.008
>25-≤30	0.81 (0.48-1.36)	0.42	0.96 (0.56-1.67)	0.90
>30	1.78 (1.13-2.79)	0.013	1.87 (1.16-3.02)	0.010
ER negative	1.27 (0.79-2.05)	0.33	-	-
Nodes positive (per node increase)	1.05 (1.03-1.08)	<0.001	1.05 (1.02-1.07)	<0.001
Adjuvant CT (yes)	1.24 (0.81-1.88)	0.32	1.61 (1.01-2.55)	0.044
Adjuvant RT (yes)	1.43 (0.80-2.55)	0.23	-	-
Previous SN biopsy	0.68 (0.44-1.03)	0.069	-	-
Arm measurements – 6 months (ref <3%inc)		<0.001		<0.001
≥3<5% inc		0.030		0.041
≥5<10% inc	1.88 (1.06-3.33)	<0.001	1.87 (1.03-3.41)	<0.001
	5.58 (3.61-8.62)		5.22 (3.22-8.47)	
– BIS at 6 months (ref <3% inc)		<0.001		0.069
				0.22
>3<5% inc	1.48 (0.74-2.95)	0.26	1.54 (0.77-3.11)	0.44
>5<10% inc	1.37 (0.79-2.39)	0.26	1.25 (0.70-2.24)	0.010
>10% inc	3.70 (2.30-5.95)	<0.001	1.98 (1.18-3.33)	

Smoking, type of surgery, weight gain and histological tumour type were ns
[N=1100: those with lymphoedema ≤6 months have been excluded]

TABLE 93: Time to lymphoedema from after 6 months to 24 months (excluding lymphoedema to 6 months) - Clinical lymphoedema/appropriately applied sleeve

Variable	Univariate		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year increase)	1.00 (0.99-1.01)	>0.99	-	-
BMI at baseline (ref ≤25)		0.76	-	-
>25-≤30	1.09 (0.72-1.65)	0.67		
>30	1.18 (0.77-1.80)	0.45		
ER negative	0.63 (0.38-1.05)	0.076	0.51 (0.30-0.86)	0.012
Nodes positive (per node increase)	1.04 (1.02-1.06)	<0.001	-	-
Adjuvant CT (yes)	1.78 (1.19-2.66)	0.005	1.92 (1.24-2.96)	0.003
Adjuvant RT (yes)	2.23 (1.23-4.03)	0.008	2.03 (1.11-3.71)	0.021
Previous SN biopsy	0.93 (0.65-1.33)	0.68	-	-
Arm measurements – perometer at 6 months (ref <3% inc)		<0.001		<0.001
≥3-<5% inc	1.94 (1.15-3.26)	0.013	1.57 (0.92-2.69)	0.099
≥5-10% inc	3.84 (2.47-5.96)	<0.001	3.13 (1.97-4.98)	<0.001
≥10% inc	12.56 (7.84-20.14)	<0.001	7.90 (4.78-13.06)	<0.001
Arm measurements – BIS at 6 months (ref <3% inc)		<0.001		<0.001
≥3-<5% inc	1.27 (0.60-2.67)	0.53	1.48 (0.69-3.14)	0.31
≥5-10% inc	2.39 (1.47-3.89)	<0.001	2.51 (1.50-4.20)	<0.001
≥10% inc	5.65 (3.63-8.79)	<0.001	4.06 (2.51-6.58)	<0.001

TABLE 94: FACT-B at 6, 12, 18 and 24 months respectively

Lymphoedema at...	Perometer >10%		
	Mean (SD)		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (660:58)	107.4 (21.5)	101.0 (21.4)	P=0.030
At 12 months (628:55)	112.0 (21.1)	103.7 (22.8)	P=0.005
At 18 months (566:59)	113.6 (20.2)	106.2 (21.5)	P=0.008
At 24 months (541:68)	114.1 (20.1)	108.0 (25.3)	P=0.059
	Sleeve application		
Lymphoedema at...	Mean (SD)		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
By 6 months (683:60)	107.1 (21.5)	99.6 (23.5)	P=0.011
By 12 months (577:121)	112.9 (20.4)	104.6 (24.3)	P=0.001
By 18 months (518:124)	114.1 (19.9)	107.3 (21.6)	P=0.001
By 24 months (466:151)	114.8 (19.8)	108.5 (23.8)	P=0.003

TABLE 95: FACT-B TOI at 6, 12, 18 and 24 months respectively

Lymphoedema at...	Perometer >10%		
	Mean (SD)		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (690:63)	64.7 (15.5)	58.0 (16.1)	P=0.001
At 12 months (585:123)	70.0 (14.2)	63.6 (17.0)	P<0.001
At 18 months (523:128)	70.9 (14.0)	65.6 (14.6)	P<0.001
At 24 months (472:152)	71.5 (13.7)	67.0 (16.5)	P=0.003
	Sleeve application		
Lymphoedema at...	Mean (SD)		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (669:59)	65.0 (15.4)	58.1 (15.3)	P=0.001
At 12 months (637:56)	69.3 (14.6)	62.9 (16.2)	P=0.002
At 18 months (570:63)	70.4 (14.2)	64.6 (14.2)	P=0.002
At 24 months (546:70)	71.1 (13.9)	65.2 (17.8)	P=0.009

TABLE 96: Lymphoedema symptoms at 6, 12, 18 and 24 months respectively

Perometer 10%			
Lymphoedema at....	% (no.) with swelling		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (601:55)	31% (186)	91% (50)	P<0.001
At 12 months (591:53)	37% (219)	91% (48)	P<0.001
At 18 months (524:61)	36% (187)	89% (54)	P<0.001
At 24 months (525:70)	35% (185)	87% (61)	P<0.001
Sleeve application			
Lymphoedema at....	% (no.) with swelling		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
By 6 months (620:60)	30% (189)	90% (54)	P<0.001
By 12 months (540:119)	31% (167)	89% (106)	P<0.001
By 18 months (473:127)	28% (134)	88% (112)	P<0.001
By 24 months (449:153)	28% (126)	80% (123)	P<0.001

	Perometer 10%		
Lymphoedema at...	% (no.) with numbness		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (643:56)	78% (500)	77% (43)	P=0.87
At 12 months (631:53)	77% (483)	75% (40)	P=0.86
At 18 months (557:60)	75% (419)	80% (48)	P=0.41
At 24 months (535:68)	74% (394)	78% (53)	P=0.45
Sleeve application			
Lymphoedema at....	% (no.) with numbness		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
By 6 months (663:60)	78% (514)	77% (46)	P=0.88
By 12 months (581:119)	75% (435)	84% (100)	P=0.032
By 18 months (507:128)	74% (375)	83% (106)	P=0.037
By 24 months (465:146)	73% (338)	77% (113)	P=0.26

Perometer 10%			
Lymphoedema at....	% (no.) with heaviness		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
At 6 months (620:57)	38% (233)	67% (38)	P<0.001
At 12 months (590:53)	40% (237)	66% (35)	P<0.001
At 18 months (523:59)	39% (202)	85% (50)	P<0.001
At 24 months (516:67)	40% (208)	73% (49)	P<0.001
Sleeve application			
Lymphoedema at....	% (no.) with heaviness		
Time (n=no, n=yes)	Lymphoedema -No	Lymphoedema -Yes	
By 6 months (640:60)	37% (239)	68% (41)	P<0.001
By 12 months (544:112)	37% (203)	67% (75)	P<0.001
By 18 months (477:121)	35% (169)	74% (90)	P<0.001
By 24 months (441:149)	37% (164)	64% (95)	P<0.001

Conclusions

- Post-operative monitoring will allow early intervention and treatment of arm swelling in patients with ≥3%-<10% RAVC.
- Perometer RAVC≥10% is the optimal diagnostic and monitoring test.
- Arm measurements from baseline after axillary surgery necessary and increases greater than 3% should lead to further surveillance to prevent lymphoedema development.
- Perometer RAVC≥10% is the optimal diagnostic and monitoring test.
- Arm measurements from baseline after axillary surgery necessary and increases greater than 3% should lead to further surveillance to prevent lymphoedema development.
- Perometer measurement is the optimal technique for measuring and predicting the development of lymphoedema.
- Baseline BMI, no. of involved nodes, and relative arm volume increase ≥3% are