Table 20: Clinical evidence profile: Comparison 1. Radiotherapy to the internal mammary nodes versus no radiotherapy to the internal mammary nodes

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (10 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1318/5082 (25.9%)	1434/5177 (27.7%)	HR 0.9 (0.83 to 0.97)	21 fewer per 1000 (from 6 fewer to 36 fewer)	HIGH	IMPORTANT
Treatment-related morbidity - acute radiation pneumonitis (within 3 to 6 months of completing radiotherapy)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	34/1249 (2.7%)	14/1293 (1.1%)	RR 2.7 (1.03 to 7.08)	18 more per 1000 (from 0 more to 66 more)	MODERATE	CRITICIAL
Disease-free survival - Whole sample (10 year follow-up)												
3	Randomised trials	No serious risk of bias	Serious[2]	No serious indirectness	No serious imprecision	None	1124/3590 (31.3%)	1196/3580 (33.4%)	HR 0.92 (0.85 to 1)	18 fewer per 1000 (from 35 fewer to 0 more)	MODERATE	CRITICIAL
Disease-free survival - 0 positive lymph nodes (10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	228/976 (23.4%)	269/979 (27.5%)	HR 0.82 (0.69 to 0.98)	38 fewer per 1000 (from 4 fewer to 68 fewer)	HIGH	CRITICIAL
Disease-free survival - 1-3 positive lymph nodes (10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	384/1637 (23.5%)	441/1646 (26.8%)	HR 0.85 (0.74 to 0.98)	31 fewer per 1000 (from 4 fewer to 55 fewer)	HIGH	CRITICIAL
Disease-free survival - 4+ positive lymph nodes (10 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute		
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	143/304 (47%)	140/292 (47.9%)	HR 0.89 (0.62 to 1.27)	29 fewer per 1000 (from 116 fewer to 60 more)	MODERATE	CRITICIAL
Disease-free survival - T stage: 1 (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	299/1205 (24.8%)	316/1203 (26.3%)	HR 0.93 (0.8 to 1.09)	14 fewer per 1000 (from 41 fewer to 17 more)	HIGH	CRITICIAL
Disease-free survival - T stage: 2 (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	268/716 (37.4%)	305/714 (42.7%)	HR 0.83 (0.7 to 0.97)	45 fewer per 1000 (from 7 fewer to 84 fewer)	HIGH	CRITICIAL
Disease-free survival - T stage: 3 (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	28/70 (40%)	30/71 (42.3%)	HR 0.9 (0.54 to 1.51)	25 fewer per 1000 (from 139 fewer to 102 more)	MODERATE	CRITICAL
Disease-free survival - Tumour position: medial (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	20/125 (16%)	34/136 (25%)	HR 0.6 (0.35 to 1.04)	83 fewer per 1000 (from 146 fewer to 7 more)	MODERATE	CRITICAL
Disease-free survival - Tumour position: lateral (10 year follow-up)												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Serious[1]	None	97/564 (17.2%)	122/578 (21.1%)	HR 0.77 (0.59 to 1.01)	40 fewer per 1000 (from 75	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute		
		risk of bias								fewer to 2 more)		
Treatment-related morbidity - secondary cancer (potentially radiation-induced; 10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	289/2815 (10.3%)	315/2871 (11%)	RR 0.95 (0.77 to 1.19)	5 fewer per 1000 (from 25 fewer to 21 more)	HIGH	CRITICAL
Locoregional recurrence (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	44/916 (4.8%)	71/916 (7.8%)	HR 0.59 (0.39 to 0.89)	30 fewer per 1000 (from 8 fewer to 46 fewer)	MODERATE	CRITICAL
Treatment-related morbidity - arm/shoulder function impairment (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	1/1922 (0.1%)	8/1944 (0.4%)	RR 0.13 (0.02 to 1.01)	4 fewer per 1000 (from 4 fewer to 0 more)	LOW	CRITICAL
Treatment-related morbidity – fatigue (3 month to 3 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	192/2815 (6.8%)	189/2871 (6.6%)	RR 1.05 (0.87 to 1.26)	3 more per 1000 (from 9 fewer to 17 more)	MODERATE	CRITICAL
Treatment-related morbidity - Grade 2+ acute pain (site not specified; within 3 months of completing radiotherapy)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	53/893 (5.9%)	40/927 (4.3%)	RR 1.38 (0.92 to 2.05)	16 more per 1000 (from 3 fewer to 45 more)	LOW	CRITICAL
Treatment-related morbidity - skin toxicity (3 month to 3 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	704/2815 (25%)	618/2871 (21.5%)	RR 1.17 (1.02 to 1.34)	37 more per 1000 (from 4	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute		
										more to 73 more)		
Treatment-related morbidity - lung toxicity (3 to 10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	89/2815 (3.2%)	36/2871 (1.3%)	RR 2.5 (1.7 to 3.67)	19 more per 1000 (from 9 more to 33 more)	MODERATE	CRITICAL
Treatment-related morbidity - cardiac toxicity (10 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	148/3487 (4.2%)	124/3533 (3.5%)	RR 1.2 (0.95 to 1.52)	7 more per 1000 (from 2 fewer to 18 more)	LOW	CRITICAL
Treatment-related morbidity - Grade 2+ lymphoedema (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	75/893 (8.4%)	42/927 (4.5%)	RR 1.85 (1.29 to 2.67)	39 more per 1000 (from 13 more to 76 more)	MODERATE	CRITICAL
Treatment-related morbidity - Grade 3+ morbidity on SOMA-LENT scale (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	None	21/672 (3.1%)	15/662 (2.3%)	RR 1.38 (0.72 to 2.65)	9 more per 1000 (from 6 fewer to 37 more)	LOW	CRITICAL
Treatment-related morbidity – mastitis (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	6/1922 (0.3%)	7/1944 (0.4%)	RR 0.87 (0.29 to 2.57)	0 fewer per 1000 (from 3 fewer to 6 more)	MODERATE	CRITICAL
Treatment-related morbidity - breast infection (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	3/1922 (0.2%)	4/1944 (0.2%)	RR 0.76 (0.17 to 3.38)	0 fewer per 1000 (from 2	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute		
										fewer to 5 more)		
Treatment-related morbidity – radionecrosis (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	1/1922 (0.1%)	2/1944 (0.1%)	RR 0.51 (0.05 to 5.57)	1 fewer per 1000 (from 1 fewer to 5 more)	MODERATE	CRITICAL
Treatment-related morbidity – osteonecrosis (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	None	27/1922 (1.4%)	22/1944 (1.1%)	RR 1.24 (0.71 to 2.17)	3 more per 1000 (from 3 fewer to 13 more)	LOW	CRITICAL
Treatment-related morbidity – oedema (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[7]	None	151/1922 (7.9%)	155/1944 (8%)	RR 0.99 (0.79 to 1.22)	1 fewer per 1000 (from 17 fewer to 18 more)	MODERATE	CRITICAL
Treatment-related morbidity - breast/chest wall pain (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	35/1922 (1.8%)	45/1944 (2.3%)	RR 0.79 (0.51 to 1.22)	5 fewer per 1000 (from 11 fewer to 5 more)	LOW	CRITICAL
Treatment-related morbidity - retrosternal pain (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	2/1922 (0.1%)	1/1944 (0.1%)	RR 2.02 (0.18 to 22.29)	1 more per 1000 (from 0 fewer to 11 more)	MODERATE	CRITICAL
Treatment-related morbidity – dysphagia (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	4/1922 (0.2%)	0/1944 (0%)	RR 9.1 (0.49 to 168.96)	-	MODERATE	CRITICAL

CI: Confidence interval; HR: hazard ratio; IM: internal mammary; RR: Risk ratio; RT: radiotherapy; SOMA-LENT: Subjective, Objective, Management, Analytic-Late Effects of Normal Tissues

[1] total events <300

[2] Significant heterogeneity (I2 = 73%) - not present in subsequent subgroup analysis

[3] total events <300 and 95% CI crosses both no effect (1) and minimally important difference based on GRADE default value (0.8)

[4] 95% CI crosses no effect (1) and minimally important difference based on GRADE default value (1.25)

[5] total events <300 and 95% CI crosses no effect (1) and minimally important difference based on GRADE default value (1.25)

[6] total events <300 and 95% CI crosses no effect (1) and minimally important differences based on GRADE default values (0.8 and 1.25)

[7] 95% CI crosses both no effect (1) and minimally important difference based on GRADE default value (0.8)

[8] total events <300; not downgraded based on 95% CI due to very small differences in absolute risk