IMPORT HIGH trial: Dose escalated simultaneous integrated boost radiotherapy in early breast cancer

Purpose/Objective

IMPORT HIGH is a randomised phase 3 trial testing dose escalated simultaneous integrated boost (SIB) against sequential boost using intensity modulated radiotherapy and image guided radiotherapy (IGRT) for early stage breast cancer with high local relapse risk. We report results of primary efficacy analyses and 5-year adverse effects (AE).

Material/Methods

Women aged ≥18 after breast conservation surgery for pT1-3pN0-pN3aM0 invasive carcinoma were randomised (1:1:1) between 40Gy/15F to whole breast (WB) + 16Gy/8F sequential photon boost to tumour bed (40+16Gy; control), 36Gy/15F to WB, 40Gy to partial breast + 48Gy (48Gy) or + 53Gy (53Gy) in 15F SIB to tumour bed. In all patients, boost planning target volume (PTV) was the clip-defined tumour bed + 5mm. AE were assessed annually by clinicians (all patients) and in a planned sub-set (n=840) by photographs at 3 & 5 years and by patients at 6, 12, 36 and 60 months. Primary endpoint was ipsilateral breast tumour relapse (IBTR). Protocol-specified non-inferiority (α=0.025) for IBTR defined as 3% absolute excess in test groups based on expected 5% 5-year rate for 40+16Gy. 95% confidence intervals (CI) are shown. Primary comparison for AE was between 53Gy and 48Gy.

Results

2617 women consented from 03/2009-09/2015 from 76 UK centres. Median age 49 (IQR 44-56); 9%, 38% & 53% were tumour grade 1, 2 & 3 respectively; 30% were N+. 66% received chemotherapy and 73% endocrine therapy. Median boost PTV was 13cm^3 (IQR 7, 22) 5-year follow-up was available for 2335/2411 (96.8%) expected (not died or withdrawn). After median follow-up of 74.0 months (IQR 73.4, 75.6), 76 IBTR events had occurred (40+16Gy: 20, 48Gy: 21, 53Gy: 35). Estimated 5-year IBTR incidence was 1.9% (95%CI 1.2, 3.1) for 40+16Gy, 2.0% (1.2, 3.2) for 48Gy, 3.2% (2.2, 4.7) for 53Gy. Hazard ratios vs 40+16Gy were 1.04 (0.56, 1.92) for 48Gy, 1.76 (1.02, 3.04) for 53Gy. Estimated absolute differences in 5-year IBTR incidence vs 40+16Gy were 0.1% (-0.8, 1.7) for 48Gy, 1.4% (0.03, 3.8) for 53Gy. Since the upper 95%CI limit for 48Gy versus 40+16Gy was <3%, non-inferiority according to pre-specified absolute difference criteria is shown for the 48Gy treatment group.

5-year AE data were available for 1894 clinician assessments, 513 photographs and 708 patient assessments; prevalence of marked AE was low overall (Table). Rates of 5-year moderate/marked AE were broadly similar between each test group and control with higher risk of clinically-assessed breast induration, breast distortion and patient-assessed breast hardness/firmness for 53Gy versus 48Gy.

Conclusion

IBTR event incidence is low in this higher risk breast cancer group treated with small boost PTVs and IGRT, whether the boost is delivered sequentially or simultaneously with the 95%CI excluding the 5-year 5% rate originally predicted for the control group. Rates of 5-year moderate/marked AE are low. SIB is a safe treatment with reduced patient visits and further escalation of boost dose does not appear advantageous.

Adverse effects (AE) at 5 years	**40+16Gy** n (%)	**48Gy** n (%)	**53Gy** n (%)
Clinician assessments			
Any AE in breast[1]; N	606	656	632
None	260 (43)	321 (49)	261 (41)
Mild	241 (40)	249 (38)	258 (41)
Moderate	93 (15)	78 (12)	90 (14)
Marked	12 (2)	8 (1)	23 (4)
P-value[2]	-	0.041[4]	0.823[5]
		0.011[6]	
Breast induration; N	600	653	627
None	420 (70)	482 (74)	405 (65)
Mild	144 (24)	137 (21)	166 (26)
Moderate	31 (5)	33 (5)	48 (8)
Marked	5 (1)	1 (<1)	8 (1)
P-value[2]	-	0.623[4]	0.065[5]
		0.006[6]	
Breast shrinkage; N	600	652	626
None	371 (62)	433 (66)	411 (66)
Mild	166 (28)	171 (26)	157 (25)
Moderate	58 (10)	44 (7)	49 (8)
Marked	5 (<1)	4 (1)	9 (1)
P-value[2]	-	0.058[4]	0.503[5]
		0.129[6]	
Breast distortion; N	601	651	625
None	409 (68)	473 (73)	419 (67)
Mild	149 (25)	147 (23)	154 (25)
Moderate	38 (6)	28 (4)	41 (6)
Marked	5 (1)	3 (<1)	11 (2)
P-value[2]	-	0.092[4]	0.457[5]
		0.007[6]	
Patient assessments			
Change in breast appearance; N	235	231	242
None	37 (16)	45 (19)	45 (19)
Mild	107 (46)	113 (49)	111 (47)
Moderate	51 (22)	54 (23)	51 (21)
Marked	36 (16)	20 (9)	30 (13)
P-value[2]	-	0.205[4]	0.442[5]
		0.335[6]	
Breast hardness / firmness; N	232	230	237
None	88 (38)	113 (49)	105 (44)
Mild	79 (34)	82 (36)	74 (31)
Moderate	39 (17)	22 (9)	41 (17)
Marked	26 (11)	13 (6)	17 (7)
P-value[2]	-	0.001[4]	0.402[5]
		0.008[6]	
Photographic assessments			
Change in breast appearance; N	163	172	178
None	103 (63)	130 (76)	129 (72)
Mild	51 (31)	35 (20)	41 (23)
Marked	9 (6)	7 (4)	8 (5)
P-value[3]	-	0.014[4]	0.085[5]
		0.294[6]	

Denominators may vary due to missing AE assessments. [1] Any AE in breast includes distortion, shrinkage, induration (index quadrant), telangiectasia, oedema; [2] comparing moderate/marked vs none/mild; [3] comparing mild/marked vs none; [4] 48Gy vs 40+16Gy (2-sided p-value); [5] 53Gy vs 40+16Gy (2-sided p-value); [6] 53Gy vs 48Gy (1-sided p-value)