

Appendix D – Major Protocol Deviations in the ICE3 Study

Table 15. Protocol deviations in the Full Analysis Set (N=206) of the ICE3 study, categorized as major deviations by IceCure Medical. Subjects indicated with an asterisk (*) are those who were excluded from the Primary Analysis Set by the DSMB due to their protocol deviations and withdrawn from further follow-up.

Major deviations		
Deviation category	Patient code	Reason for deviation
Inclusion/Exclusion Deviations	(b) (6)	Nuclear grade 3
		Nuclear grade 3; patient was recommended to be withdrawn by DMSB for further follow up, but does not appear to have been excluded from the primary analysis set
		Nuclear grade 3; probe was malpositioned during the cryoablation
		Prior lumpectomy and radiation in addition to baseline multifocal tumor; patient withdrawn by DMSB for further follow up
		Baseline tumor size 2.3 x 1.1 cm per DSMB radiology expert re-measuring the index lesion; patient withdrawn by DMSB for further follow up
		On baseline pathology, DCIS 40%; patient withdrawn by DMSB for further follow up
		Initial lesion size prior to biopsy were 1.7 x 1.2 x 0.6 cm per ultrasound and 1.36 cm in the longest dimension parallel to the chest wall per baseline mammography. Realtime measurements on the day of the procedure measured the lesion to be 1.2 x 8.4 x 0.6 cm. Since the cryoprobe will be inserted along the long axis it is anticipated the entire lesion would be engulfed with 30x24mm including 10mm margins around the lesion (based on probe selection brochure guide).
		Patient age is 63
		Nuclear grade 3
		Lesion size 1.7 x 1.4 x 1.5 cm; patient withdrawn by DMSB for further follow up
		Lesion size 1.5 x 1.7 x 1.7 cm; patient withdrawn by DMSB for further follow up
		Patient age is 62
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		Patient age is 64
		Ki-67>14%, Luminal B
		Lesion measurements per MIR 1.7 x 1.1 x 1.0 cm
		Ki-67>14%
Lesion measurements 1.8 x 1.5 x 1.4 cm; patient withdrawn by DMSB for further follow up		
Patient was reported as Luminal B after cryoablation treatment. DSMB reassessed as Luminal A in the absence of Ki-67 data.		

(b) (6)

Lesion measured on mammography as 1.6 cm. Patient was treated with neoadjuvant hormone blockage. The lesion was reevaluated before cryoablation treatment as 1.1 x 0.8 cm; patient withdrawn by DMSB for further follow up
Lesion measured as 1.9 cm on sonography. Patient was treated with neoadjuvant hormone blockage. The lesion was reevaluated before cryoablation treatment as 1.2 x 0.9 x 1.1 cm; patient withdrawn by DMSB for further follow up
Mammogram measurement was 1.8 x 0.97 cm
Ki-67 22%
Two small proximal lesions <1.5 cm treated as one lesion
Larger lesion size on mammography (size not specified); patient withdrawn by DMSB for further follow up
Lesion size measured on MRI as 1.6 x 0.8 x 1.0 cm; lesion size measured on ultrasound as 9.8 x 9.4 x 12.8 mm
Prior lumpectomy and axillary node dissection of the right breast plus chemo and radiation. Presence of prior or concurrent neoadjuvant chemotherapy for breast cancer
Positive lymph node (N=1). Patient received whole breast radiation and endocrine treatment. No axillary dissection.
Patient is 57 years old
Prior lumpectomy. Presence of en bloc open surgical biopsy and/or lumpectomy for diagnosis/treatment of the index breast cancer
Prior lumpectomy. Presence of en bloc open surgical biopsy and/or lumpectomy for diagnosis/treatment of the index breast cancer
Ki-67 65-75%, Luminal B
Nuclear polymorphism 3; overall Nottingham grade 2
Overall Nottingham grade 2; pathologist felt the nuclear grade was 2-3 based on the majority of cells with nuclear grade 2 but some cells with nuclear grade 3
Nuclear grade is 2-3 but mitotic score is 1 and Ki-67 is low.
Overall Nottingham grade 2; nuclear score 3
Overall Nottingham grade 2; nuclear score 3
Overall Nottingham grade 2; nuclear score 3. High suspicion of Luminal B
Overall Nottingham grade 2; nuclear score 3
Overall Nottingham grade 2; nuclear score 3
Overall Nottingham grade 2; nuclear score 3 (Ki-67 40%)
Nuclear grade 3, all other criteria met. Discordance with histologic grade between very low mitotic score and high nuclear score could be related to specimen size
Prior partial mastectomy. Presence of prior en bloc open surgical biopsy and/or lumpectomy for diagnosis/treatment of the index breast cancer.
Prior partial mastectomy. Presence of prior en bloc open surgical biopsy and/or lumpectomy for diagnosis/treatment of the index breast cancer.

	(b) (6)	Prior mastectomy with chemo. Presence of prior en bloc open surgical biopsy and/or lumpectomy for diagnosis/treatment of the index breast cancer.
Informed Consent Deviations		Spanish ICF was not available (the patient consented using an English Form). Spanish ICF completed 31-May-2018 Site is missing the original ICF on file
Procedural deviations		Mammogram evaluation not done at the 48 month follow-up 60 month mammogram was not performed. The next mammogram was scheduled after site closure.
Other		Inadequate procedure time: 5x5x5 instead of 9x8x9
		Extremely short treatment protocol that could not cover the lesion; patient withdrawn by DMSB for further follow up
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		Core biopsies used for eligibility do not include the degree of tubular formation, nuclear grade, and mitotic activity.
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		Machine malfunction. The patient received only freezing cycle of 9:15 F1, 8:00 Thaw, 2:24 second freeze cycle
		Site did not perform FISH analysis on HER2