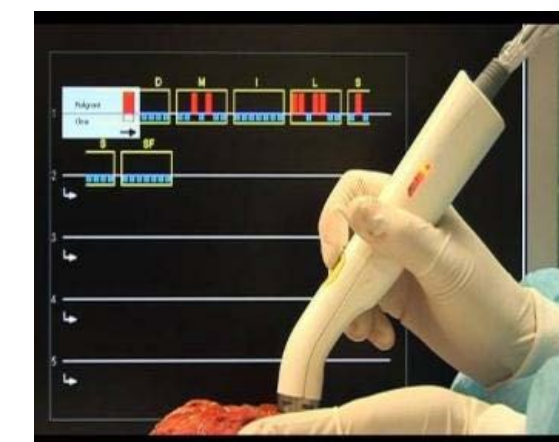


Introduction

The current techniques for intra-operative margin assessment of the lumpectomy specimen during breast conservation surgery is less than ideal. Additionally, there is much controversy defining what constitutes a positive margin with no clear consensus MARGINPROBE (Dune Medical Devices, Boston, MA) was developed to provide real-time assessment of lumpectomy specimens to evaluate for the presence of disease at the surgical margins (Figure 1). A Multi-center international pivotal study was conducted to determine if adjunctive use of MarginProbe can enhance surgeons' ability to identify positive margins intraoperatively, resulting in fewer patients who require (are candidates for) re-excision procedures.

Figure 1: The MARGINPROBE System



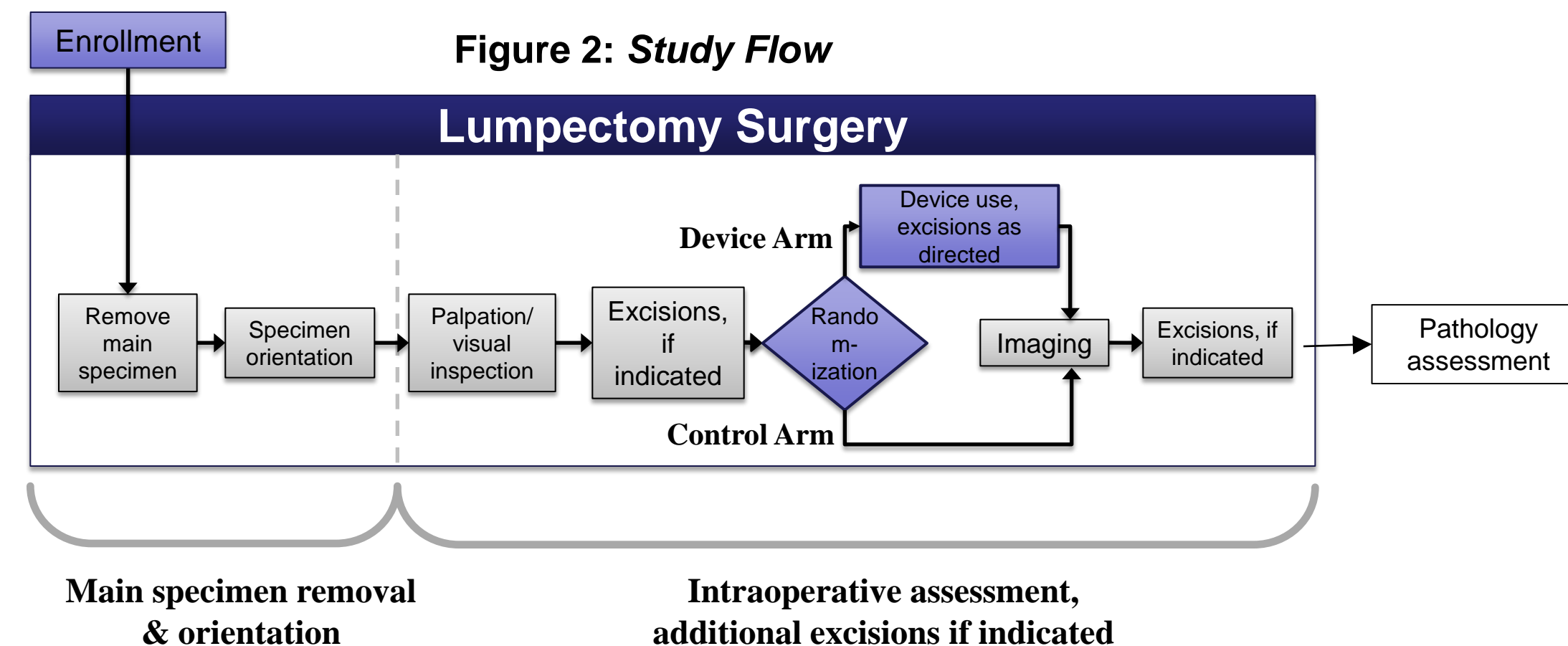
MARGINPROBE measures the electrical properties of tissue within the immediate vicinity of the probe tip.

By comparing a measurement to the electric properties of known tissue types, the system classifies the reading as either benign or malignant.

Within the framework of this study we evaluated the resulting positive margins across a 0-5mm spectrum of thresholds as analyzed by permanent pathology of the specimens and shavings removed during the lumpectomy procedure.

Methods

A total of 596 patients were randomized (1:1) in a prospective, international multicenter (n=21) study. Randomization occurred in the operating room, following standard of care lumpectomy. The device was used only on the main lumpectomy specimen. See Figure 2 for study flow and randomization. Pathologists were blinded to study arm. Margins were recorded with a 1 mm resolution, up to 10 mm.



Results

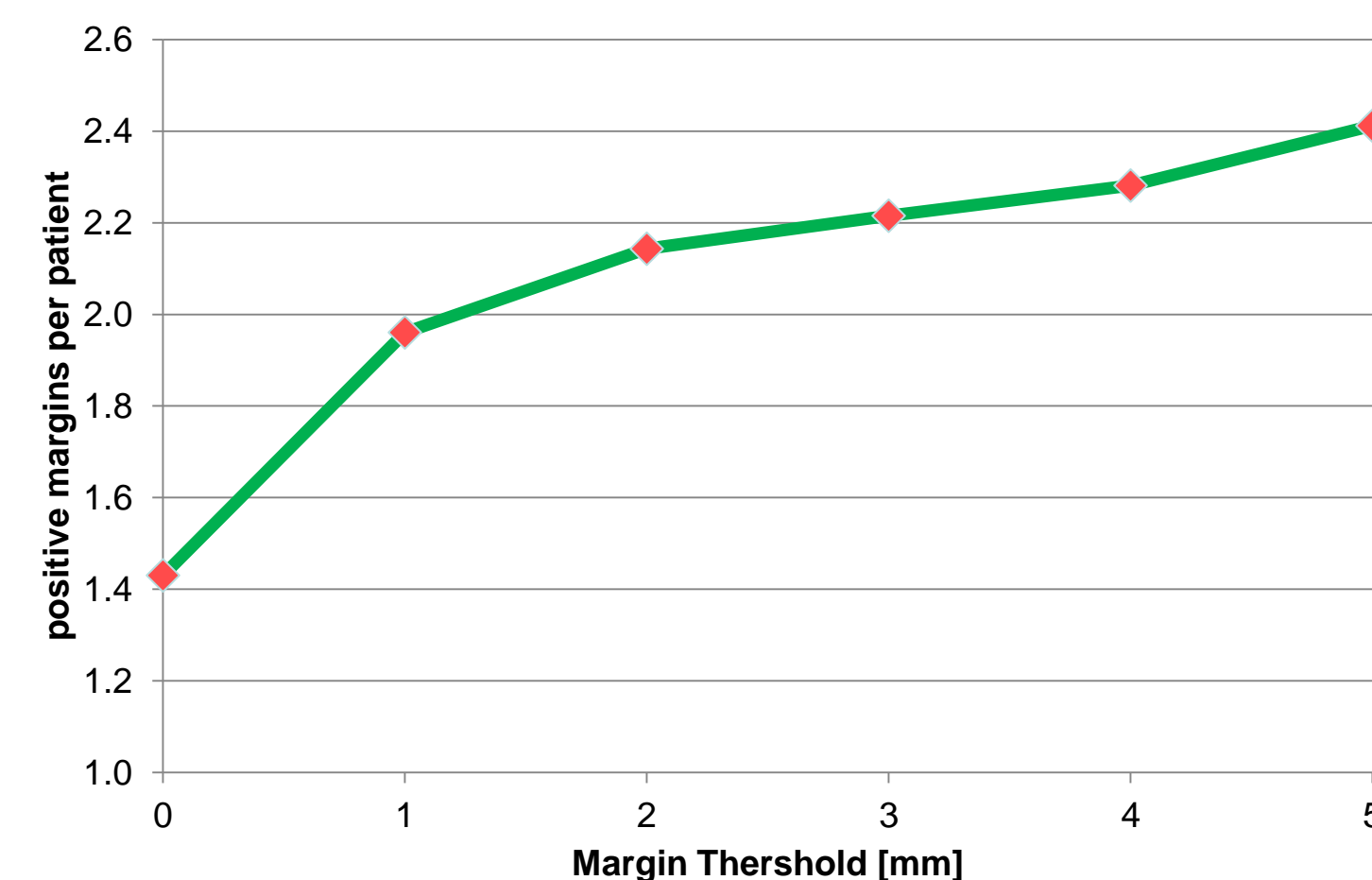
Since per protocol, the device was strictly measuring the main initial lumpectomy specimen and not the new resection surface of any shavings, we focus on this parameter first. Table 1 shows the dependence of the main (Initial lumpectomy) specimen positivity on margin threshold definition. The rate was balanced between the arms, as this measure relates to the status before randomization)

Table 1: Patients with positive main specimen

Margin Threshold [mm]	Device [%,(n)] (N=298)	Control [%,(n)] (N=298)
0	24% (71)	20% (61)
1	55% (163)	49% (147)
2	65% (194)	62% (185)
3	73% (217)	70% (209)
4	78% (232)	75% (224)
5	83% (247)	80% (238)

Additionally, as shown in Figure 3, the event of a positive margin in a patient increases as the depth threshold increases. As all positive margins on the main specimen need to be identified in order to achieve a clinical benefit, the deeper thresholds represent an increasing challenge.

Figure 3: Average number of positive margins on main specimen per positive patient



Adjunctive use of MARGINPROBE resulted in an increase, compared to Standard of Care alone, in identification of all positive margins of the main specimen, see Table 2. The improvement was observed for all margin threshold values.

Table 2: Clearance (shaving performed where a margin is positive) of All Margins from Main Specimen (for Patients with Positive Margins on Main Specimen; excluding fascia/skin)

Margin Threshold [mm]	Device [%,(#)]	Control [%,(#)]	P-value	Improvement [%]
0	73% (52/71)	34% (21/61)	<0.0001	113%
1	72% (117/163)	22% (33/147)	<0.0001	220%
2	65% (127/194)	20% (37/185)	<0.0001	227%
3	58% (125/217)	19% (39/209)	<0.0001	209%
4	53% (123/232)	18% (40/224)	<0.0001	197%
5	52% (128/247)	17% (40/238)	<0.0001	208%

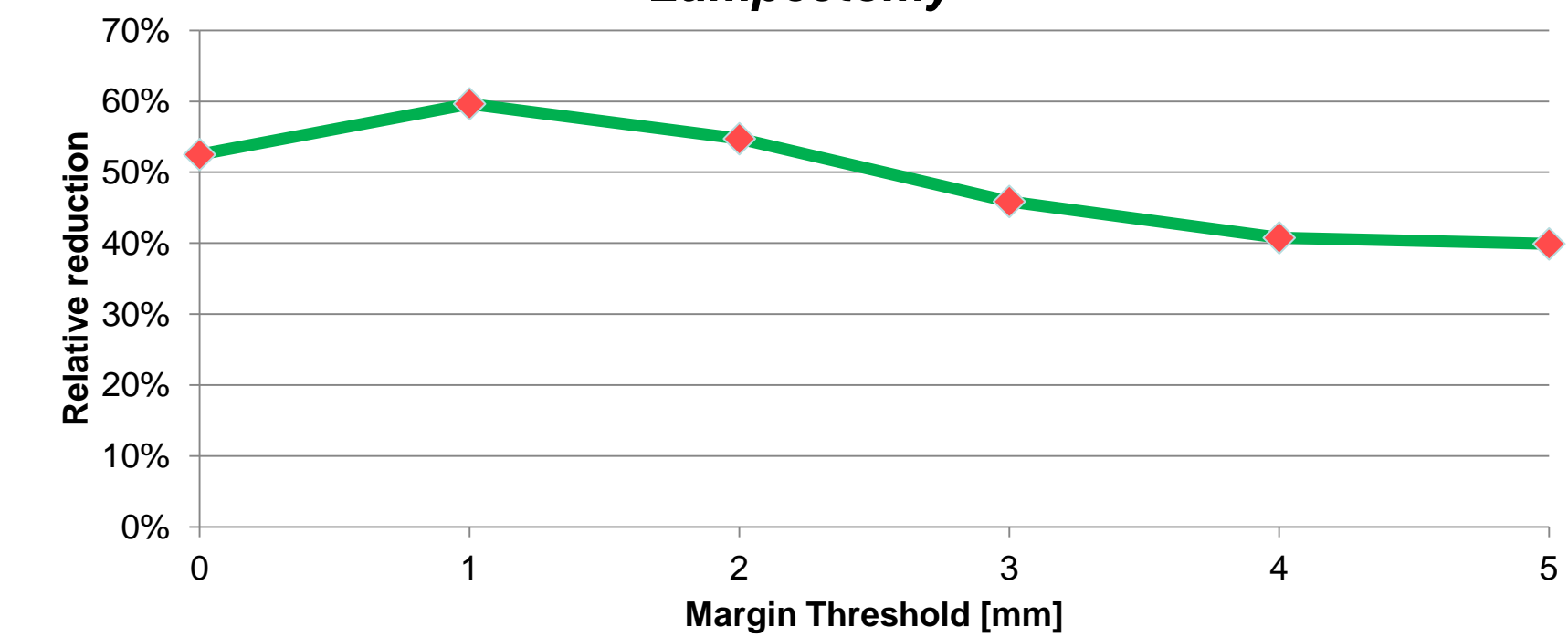
Consequently, use of MARGINPROBE led to a decrease in the rate of patients with positive margins after initial lumpectomy procedure. Again, this improvement was not dependent on the margin threshold definition. See Table 3 & Figure 4. The improvement was observed across all margin threshold values.

Table 3: Patients with remaining positive margins of main specimen, (excluding positive margins on additional shavings, which the device was not "allowed" to measure).*

Margin Threshold [mm]	Device [%,(n)] (N=298)	Control [% (n)] (N=298)	P-value	Improvement [%]
0	6% (19)	13% (40)	0.0057	53%
1	15% (46)	38% (114)	<0.0001	60%
2	22% (67)	50% (148)	<0.0001	55%
3	31% (92)	57% (170)	<0.0001	46%
4	37% (109)	62% (184)	<0.0001	41%
5	40% (119)	66% (198)	<0.0001	40%

* Excluding fascia /skin

Figure 4: Reduction Rate in Positive Margins after the Initial Lumpectomy



Positive margins after initial lumpectomy procedure, including positive margins originating from shavings, were reduced as well, independently of margin threshold definition. As the device was not used on any additional shavings, the combined reduction is less pronounced since it is diluted by a high rate of positive margins in the additional reshavings. See Table 4.

Table 4: Patients with positive margins after Initial lumpectomy, including margins originating from shavings

Margin Threshold [mm]	Device [%,(n)] N=298	Control [% (n)] N=298	P-value	Improvement [%]
0	12% (37)	15% (46)	0.34	20%
1	31% (92)	42% (124)	0.008	26%
2	41% (121)	53% (157)	0.004	23%
3	48% (143)	61% (181)	0.002	21%
4	54% (160)	65% (193)	0.007	17%
5	57% (169)	69% (207)	0.0017	18%

Conclusions

The rate of positive margins increases with the threshold definition.

The number of involved margins per patient on a positive specimen also increases with the threshold definition, and on average exceeds 2 for margin definition >=1

Adjunctive use of MARGINPROBE provided a significant contribution irrespective of the margin threshold definition.

The rate of positive margins patients / candidates for re-excision was significantly reduced with use of margin probe, irrespective of the margin threshold definition.