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## Irreversible Electroporation (IRE): Standardization of Terminology and Reporting Criteria for Analysis and Comparison

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**Background:**

Irreversible electroporation (IRE) as newer ablation modality has been introduced and its clinical niche is under investigation. At present just one IRE system has been approved for clinical use and is currently commercially available (NanoKnife® system). In 2014, the International Working Group on Image-Guided Tumor Ablation updated the recommendation about standardization of terms and reporting criteria for image-guided tumor ablation. The IRE method is not covered in detail. But the non-thermal IRE method and the NanoKnife System differ fundamentally from established ablations techniques, especially thermal approaches, e.g. radio frequency ablation (RFA).

**Material/Methods:**

As numerous publications on IRE with varying terminology exist so far – with numbers continuously increasing – standardized terms and reporting criteria of IRE are needed urgently. The use of standardized terminology may then allow for a better inter-study comparison of the methodology applied as well as results achieved.

**Results:**

Thus, the main objective of this document is to supplement the updated recommendation for image-guided tumor ablation by outlining a standardized set of terminology for the IRE procedure with the NanoKnife Sytem as well as address essential clinical and technical informations that should be provided when reporting on IRE tumor ablation.

**Conclusions:**

We emphasize that the usage of all above recommended reporting criteria and terms can make IRE ablation reports comparable and provide treatment transparency to assess the current value of IRE and provide further development.

**MeSH Keywords:**

**Ablation Techniques • Current Procedural Terminology • Electroporation • Irreversible Electroporation • Reference Standards • Research Design • Therapy, Soft Tissue**

**PDF file:**

<http://www.polradiol.com/abstract/index/idArt/896034>

### Background

Focal ablation therapy is playing an increasingly important role in oncology and may reduce risks and toxicity of current surgical and radiation treatments while achieving complete tumor destruction with an adequate oncologic outcome. Newer ablation modalities, such as

irreversible electroporation (IRE), have been introduced and their respective clinical niches are under investigation [1–6]. IRE causes cell death through the repeated application of short-duration high-voltage electrical pulses that create irreversible damage to cell membranes by electrical breakdown of the cell membrane [7]. While there may be some hyperthermic ablative changes with

high-power applications, the mechanism of cell death with IRE is thought to be predominantly non-thermal [7,8]. Nonthermal ablative irreversible electroporation has been proposed to be “tissue-selective” by leading to apoptosis without affecting the extracellular matrix with potential advantages compared with current thermal-ablation technologies or radiotherapy. Therefore matrix-based tissue borders and surrounded structures can be preserved [7,8]. At present only one IRE system has been approved for clinical use and is currently commercially available (NanoKnife® system; AngioDynamics Inc.). In 2007, NanoKnife® received a 510(k) medical product clearance for surgical ablation of soft tissue by the U.S. FDA. However, it has not been cleared for the treatment of any specific disease or condition and the treatment parameters have been mostly developed in *ex vivo* models, particularly the liver model [9]. Thus far there are no adequate tumor entity-specific proofs of its effectiveness, and its clinical application has hitherto been confined to very small patient cohorts.

In 2014, the International Working Group on Image-Guided Tumor Ablation updated the recommendation about standardization of terms and reporting criteria for image-guided tumor ablation [10]. The main objective of this document is to improve precision in communication in the field of image-guided tumor ablation, leading to a more accurate comparison of technologies, results, and ultimately to improved patient outcomes. Herein, they outlined a standardized set of general terminology to be used and essential clinical and technical information that should be provided when reporting on tumor ablation. The IRE method is not covered in detail. As numerous publications on IRE with varying terminology exist so far – with numbers continuously increasing – standardized terms and reporting criteria of IRE are needed urgently. The use of standardized terminology may then allow for a better inter-study comparison of the methodology applied as well as results achieved. Hence, parameters for successful ablation may be identified and undesired side effects such as reversible electroporation or thermal ablation may be detected when performing a meta-analysis and looking at larger patient collectives.

## Material and Methods

Whereas the NanoKnife-System manual explains general conditions for use, the efficacy of several service parameters has not been studied extensively in prospective clinical studies [11]. Additionally, the specific terminology used does not comply entirely with the updated recommendations of the International Working Group on Image-Guided Tumor Ablation and dedicated reporting criteria are completely missing. Last but not least, the IRE method and the NanoKnife System differ fundamentally from established ablation techniques, especially thermal approaches (e.g. RFA) [12,13]. Otherwise, IRE efficacy will be compared with thermal ablation techniques, mainly RFA, as the most prevalent technique [12,13].

Thus, the main objective of this document is to supplement the updated recommendation for image-guided tumor ablation [10] by outlining a standardized set of terminology for the IRE procedure with the NanoKnife System as well

as address essential clinical and technical information that should be provided when reporting on IRE tumor ablation.

## Results

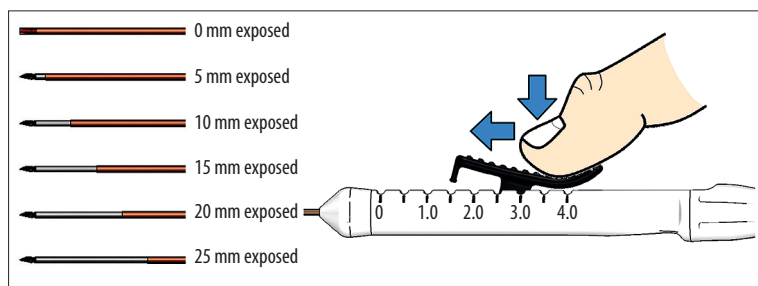
### General terminology for IRE ablation

According to the proposal for standardization of terms and reporting criteria for image-guided tumor ablation by the International Working Group on Image-Guided Tumor Ablation [10], classifying terminology for IRE is defined:

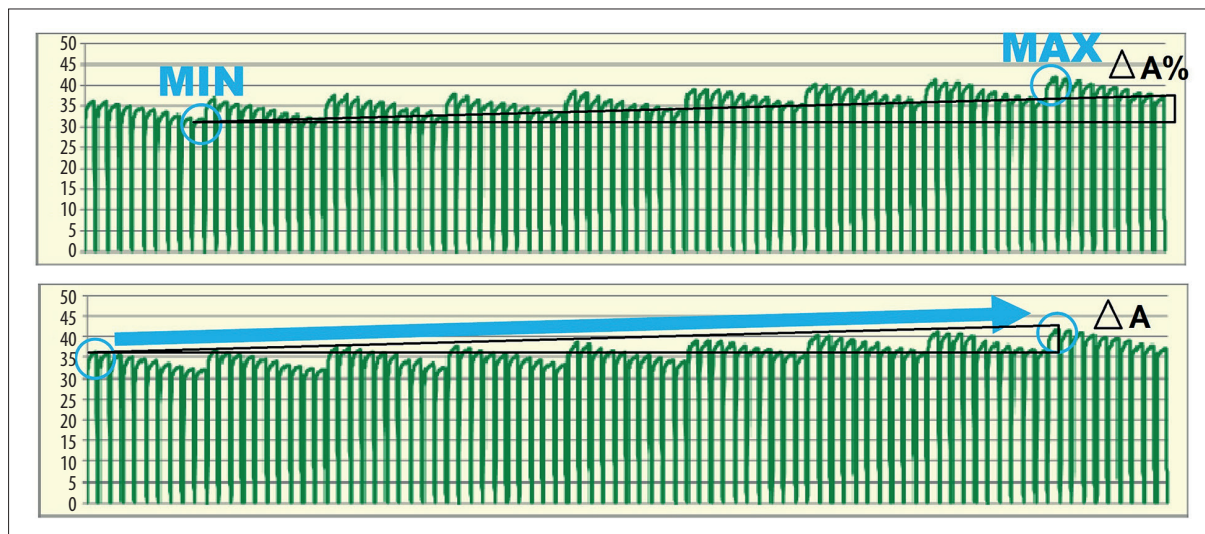
IRE as '**energy-based ablation method**' is used as '**focal therapy**' (FT) for localized soft '**tissue ablation**' (TA), usually under image guidance. IRE or '**IRE ablation**' is based on a '**nonthermal ablation mechanism**'. Decisive of that is the '**electrical conductivity**' of the target tissue that mainly depends on the tissue entity, tissue homogeneity and anatomical structures. In case of tumor ablation '**malignant tissue**' and '**non-malignant tissue**' can be treated. IRE ablation of malignant tumor mainly focused on debulking should be classified as treatment with '**debulking intent**' compared to treatment with '**curative intent**' or '**palliative (symptomatic) intent**'. IRE, with debulking intent (tumor downsizing) could be used as '**neo-adjuvant pre-surgical treatment**' to achieve negative resection margins (R0 resection, curative intent), especially close to vital structures that have to be preserved [5,14,15].

The specific tumor which is supposed to be treated with IRE is called '**target tumor**'. The term '**targeting**' is used to describe the step during an IRE ablation procedure that involves placement of the electrodes into the tumor. The applicators for IRE are electrodes and should be addressed as such; the term 'probes' of the NanoKnife system manual [11] should not be used. The term '**needle-like electrodes**' needs to be further specified with respect to diameter (in '**Gauge**' [G]) and length (in centimeters [cm]). IRE can be performed with one '**bipolar (single) electrode**' applicator or with two to six '**monopolar (single) electrode**' applicators, whereby two electrodes constitute one '**monopolar electrode pair**'. The length of the '**exposure**' of the monopolar IRE NanoKnife system electrodes can be manually changed and should be described as the '**active tip length**' (Figure 1).

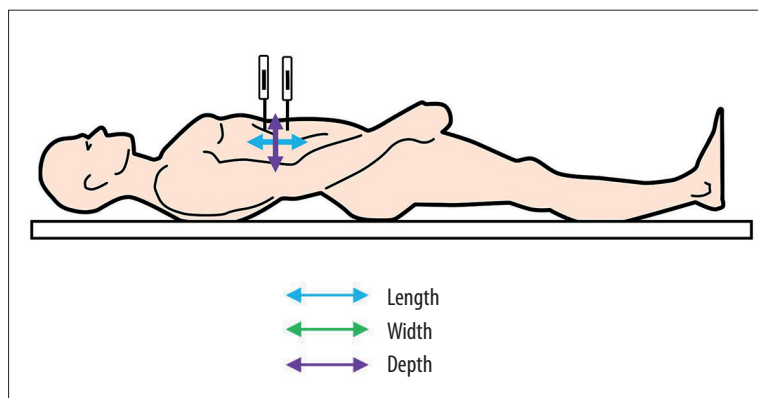
The monopolar electrodes are usually placed in '**multipolar applicator insertions**'. One 'IRE procedure' as a single event (operation) is counted as one '**IRE session**' (number of procedures = number of IRE sessions). If more than one 'IRE ablation' is performed during one IRE session, this series of IRE ablation is called '**IRE course of treatment**'. Monitoring of IRE ablation by imaging, the process by which the IRE therapy effects with its definitive extent and effectiveness are viewed during the procedure, is not yet available. The term '**intraprocedural modification**' is used to describe the intraprocedural tools and techniques that are used to perform intraprocedural modification of the ablation treatment. Up to now there is only one approved NanoKnife system-based tool to monitor the IRE treatment by reviewing the IRE current graphs to determine the overall current draw after each completed IRE course (see also Reporting Criteria and Figure 2). An



**Figure 1.** The active tip length of the monopolar IRE electrodes of the NanoKnife system can be manually changed in exposure.



**Figure 2.** Output of current graphs with 9 clusters of 10 pulses each of 1 electrode pair for 1 IRE round. Marking the bottom and the peak of one cluster of 10 pulses. One can deduce a successful IRE ablation by reviewing the current graphs for an overall upward trend for each probe pair and for a slightly angled upwards cluster plateau (blue arrow in Figure 2). 1 Cluster of 10 pulses – small bracket. 1 session of 1 electrode pair with 9 clusters resp. 90 pulses – 1 burst – large bracket.

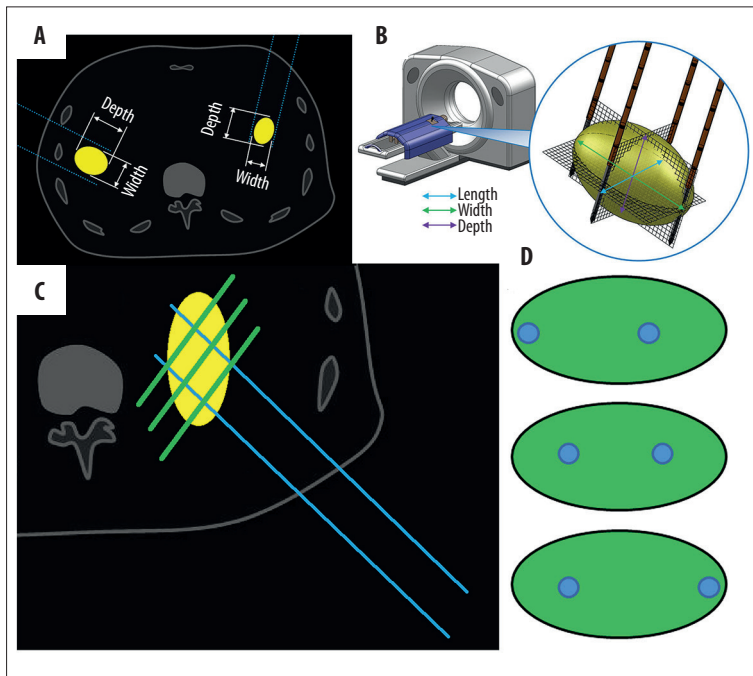


**Figure 3.** Specification of the tumor size in three anatomical dimensions of the patient's body (sagittal – depth, transversal – width and longitudinal – length) in order to make follow-up measurements systematically comparable.

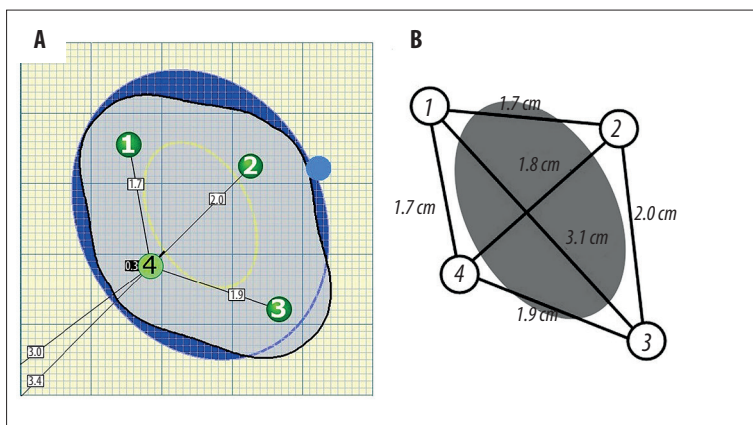
automated system that automatically terminates the ablation at a critical point in the IRE procedure is still not available.

The preferred term for the initially identified tumor prior to IRE ablation is 'index tumor'. The term 'lesion' should not be used. CT and MRI are the best currently available and reproducible methods to measure target lesions (tumor) selected for response assessment [16]. When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. In diagnostics and follow-up of oncologic patients, CT or MRI are the commonly used methods that enable 3D

measurements of the targets, even if IRE is not performed under CT guidance but sonography guidance. The WHO (1979) and RECIST (2000) criteria were introduced to unify and standardize therapy response or course of disease in the studies [16]. The WHO criteria use 2D and RECIST 1D measurements. However, widespread use of multidetector CT, MR imaging, and post-imaging processing procedures enables to view targets from any arbitrary plane and even to measure the volume three-dimensionally (3D measurement) [16]. To evaluate studies of the new and very complex Nanoknife IRE ablation technique, a 3D measurement should be adopted. The IRE ablation zone diameters depend on the individual IRE electrode and ablation settings (number and



**Figure 4.** (A, B): The sketch of description of the IRE electrode-based tumor dimensions. Idealized coaxial IRE electrode placement in elliptic tumors. Green line in Figure 4A – IRE treatment planning sectional plane (2D) according to Figure 3. (C, D): Required oblique-angled IRE electrode placement in an elliptic tumor. Green lines in Figure 4C – different IRE treatment planning sectional planes (2D) in Figure 4D according to Figure 3 depending on the sectional plane level.



**Figure 5.** The sketch of monopolar IRE ablation with all interelectrode spacings and spacings between the electrodes (numbered green dots) and the shortest distance to the tumor margin (targeted edge, yellow circle).

position of electrodes, active tip/ exposure, voltage setting, overlapping ablation) in all three dimensions. Therefore, in IRE trials and publications, the actual tumor sizes should be specified in three anatomical dimensions of the patient's body (sagittal, transversal and longitudinal) as well as in their maximum diameter in order to make follow-up measurements systematically comparable (Figure 3).

Moreover, the IRE ablation index tumor size should be reported in one dimension coaxial to the IRE electrode direction and in the other two vertical dimensions in order to make the extent of the index tumor compared to the 2D visualization of the estimated 'ablation zone' comprehensible (see also Reporting Criteria and Figures 4, 5). The NanoKnife manual and software terminology uses the term 'estimated ablation zone' (Figure 6) to describe the treatment zone that is visualized in 2D only. The term 'ablation zone' should be used after ablation of the target index tumor. Therefore, the term 'estimated ablation zone' should be replaced by 'planned treatment zone' (PTV). The IRE index tumor should be classified according to the Standardization of Terms and Reporting Criteria

for Image-Guided Tumor Ablation by the International Working Group on Image-Guided Tumor Ablation in the following scale: tumors <3 cm as 'small', tumors of 3–5 cm as 'intermediate', and tumors >5 cm as 'large'.

The 'planned treatment volume (PTV)' consists of the 'target volume' (= tumor) and the circumferential 'ablative margin' that should be described separately. The term 'ablative IRE margin' ('margin'), analogous to the surgical margin, is used to describe the region around the target that should ideally be ablated. At present, the ideal peritumoral IRE margin size is still under investigation and thus no definite recommendation can be made. Guidelines for (thermal) ablation methods recommend that the target tumor should be completely covered by the ablation zone that includes at least a 5–10-mm margin all around the expected tumor margin, in order to be considered successful ablation. The presence of micrometastases around the index tumor has to be taken into account [17]. As long as no specific data for IRE exist, this recommendation should be adopted at the minimum likewise. The thickness of that margin around the tumor can be adjusted per NanoKnife system



**Table 1.** Recommended IRE electrode settings for different tumor sizes based on calculations of IRE treatment planning using the PC-based NanoKnife® planning software demo tool (ProcedureManager-2\_2\_0\_23 for Windows, AngioDynamics) for spherical masses and an approx. 5-mm safety ablation margin orthogonal to the electrodes. The ablation margin longitudinal to the electrodes (depth) is 5 mm as specified by the manufacturer [11].

Index tumor size [mm]	8	10	13	15	18	20	23	25	28	30	33	35	38	40
Margin circumferential (example) [mm]	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Width of target zone, orthogonal to probes [mm]	18	20	23	25	28	30	33	35	38	40	43	45	48	50
Probe configuration	2	3	3	3	3	3	4	4	4	6 (pentagonal with center) (DIE FACE-5)	6 (pentagonal with center) alternative: 5 + OL (mirrored trapezoid)	5 + OL (mirrored trapezoid) alternative: 6 (pentagonal with center)	5 + OL (mirrored trapezoid)	5 + OL (mirrored trapezoid)
Active tip, electrode exposure [mm], Pull-back (PB)	10, no PB	10–15, no PB	15, no PB	15–20, no PB	20, no PB	20–25, no PB	25, no PB	15, 1xPB	15, 1xPB	20, 1xPB	20, 1xPB	20, 1xPB	20–25, 1xPB	20–25, 1xPB
Depth of target zone, longitudinal to probes [mm]	20	20–25	25	25–30	30	30–35	35	Variable due to PB	Variable due to PB	Variable due to PB	Variable due to PB	Variable due to PB	Variable due to PB	Variable due to PB

Ablation zones reach a more or less spherical shape depending on the electrode count, probe configuration, tissue conductivity and technical conditions. PB – pull-back of the probes. OL – overlapping ablation.

software (Figure 6). This setting just serves the visualization of NanoKnife IRE treatment planning (target zone, margin zone) and orientation for IRE electrode configuration only. It differs from the estimated ablation zone depending on the electrode setting (Figure 6). The aim of IRE ablation is a complete coverage of the tumor zone (yellow) and as far as possible of the margin zone (blue) by the estimated ablation zone (grey). The coaxial dimension to the IRE electrode direction is named 'depth' of the target zone and is not visualized in the NanoKnife system planning software.

The ideal electrode configuration depends on the tumor size and aimed ablation margin. Fixed IRE electrode configuration settings for tumor categories in 5–10-mm increments are not practicable. Due to the complex and parallel image-guided IRE electrode placement, the aim is to receive complete tumor ablation with the smallest possible ablation margin and as few as possible electrodes. The following table (Table 1) provides recommended IRE electrode settings according to the NanoKnife System Manual and the NanoKnife System Treatment planning software.

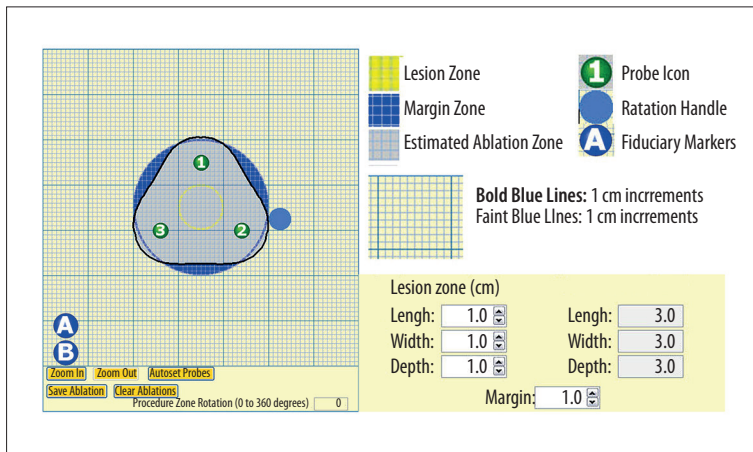
**IRE ablation method reporting criteria**

As treatment criteria the 'operating room time (OR)', the 'operating time (OT)' between first electrode insertion and last electrode removal, the IRE 'electrode placement time (EPT)', the 'application time (AT)' of the IRE pulse

application, the general anaesthesia or intubation time between the beginning and ending should be reported separately. In the complex setting of IRE ablation the anaesthesia, the electrode placement time (EPT) and the duration of intraprocedural modification or treatment planning take up most of the time of the operation room time (ORT) and operating time (OT) compared to the IRE pulse application time.

The IRE pulse application speed (pulse per minute = ppm) has to be mentioned according to the eligible options 90 ppm, 240 ppm or ECG-triggered, whereas the heart rate for ECG triggering has to be reported. A pulse frequency of 240 ppm is not recommended anymore (unpublished data) due to possible thermal ablation effects (unpublished data, no official distributor statement).

The IRE ablation index tumor size (yellow ellipsoid) should be reported in one dimension coaxial (depth) to the IRE electrode direction (blue dotted lines) and in the other two vertical dimensions (width and length) in order to make the extent of the index tumor compared to the ablation zone comprehensible according to Figure 6 (Figure 4A, 4B). Figure 4A and 4B show idealized situations whereby the longest diameter of an elliptic tumor is parallel/coaxial to the IRE electrodes. It is getting more difficult if placement of an oblique-angled IRE electrode is required (Figure 4C, 4D). Different diameter and distances have to be taken into account.



**Figure 6.** The planning margin (blue area) around the tumor ('lesion zone', yellow circle) can be adjusted initially per NanoKnife software (right down) for visualization of NanoKnife IRE treatment planning (grey triangular area) and orientation for IRE electrode configuration (numbered green spots). The named term 'lesion' should not be used; the term 'tumor' should be used instead. The discrepancy between the term 'lesion' of the NanoKnife system manual and the recommended term 'tumor' by the International Working Group on Image-Guided Tumor Ablation may result from the received clearance for surgical ablation of soft tissues in general but not for tumor exclusively.

The electrode positions and the treatment planning (target) zone have to be reported reproducibly in relation to the tumor location to analyze possible incomplete tumor ablations (positive margin or skip lesions). That complex situation is getting obvious for IRE application per monopolar IRE electrodes: For the use of monopolar IRE electrodes, all electrodes have to be numbered, whereas the IRE activator electrode should be labeled as IRE electrode 1. For monopolar IRE ablation all inter-electrode spacings have to be mentioned (Figure 5). Moreover, all spacings between the electrodes and the shortest distance to the tumor margin (targeted edge) have to be documented (Figure 5). All these parameters should be reported in a figure (Figure 5).

A basic problem of the visualization of the IRE treatment planning (Figures 5, 6) is the depiction of the transverse plain (just 2D) to the IRE electrodes by the NanoKnife System Software only. The depth of the target and the active tips of the electrodes are not depicted.

The term '**IRE ablation zone**' can be used to describe the radiologic region or zone of induced treatment effect. Reporting of the ablation zone should be made in the transversal plain of the electrode axis with relation to the target tumor and planned treatment zone, if possible. According to the ablation zone, ablation should be classified as complete or partial, whereas the report on the degree (percentage) of partial ablation should be avoided. Intermediate or large targets can be treated with overlapping IRE ablations. The term '**overlapping IRE ablation**' is used for the creation of a complex overlapping ablation zone in the transversal plane of the electrode axis (Figure 7A). The term '**pull-back IRE ablation**' is used for the creation of a complex overlapping ablation zone in the coaxial axis of the electrodes by using ablation zones behind one another with pulling the electrodes back stepwisely and applicating IRE ablation again (Figure 7B). Pull-back IRE ablation seems to be very intricate and not very practicable even with electrode length markings, especially in cases of small margins and small overlapping ablation zones.

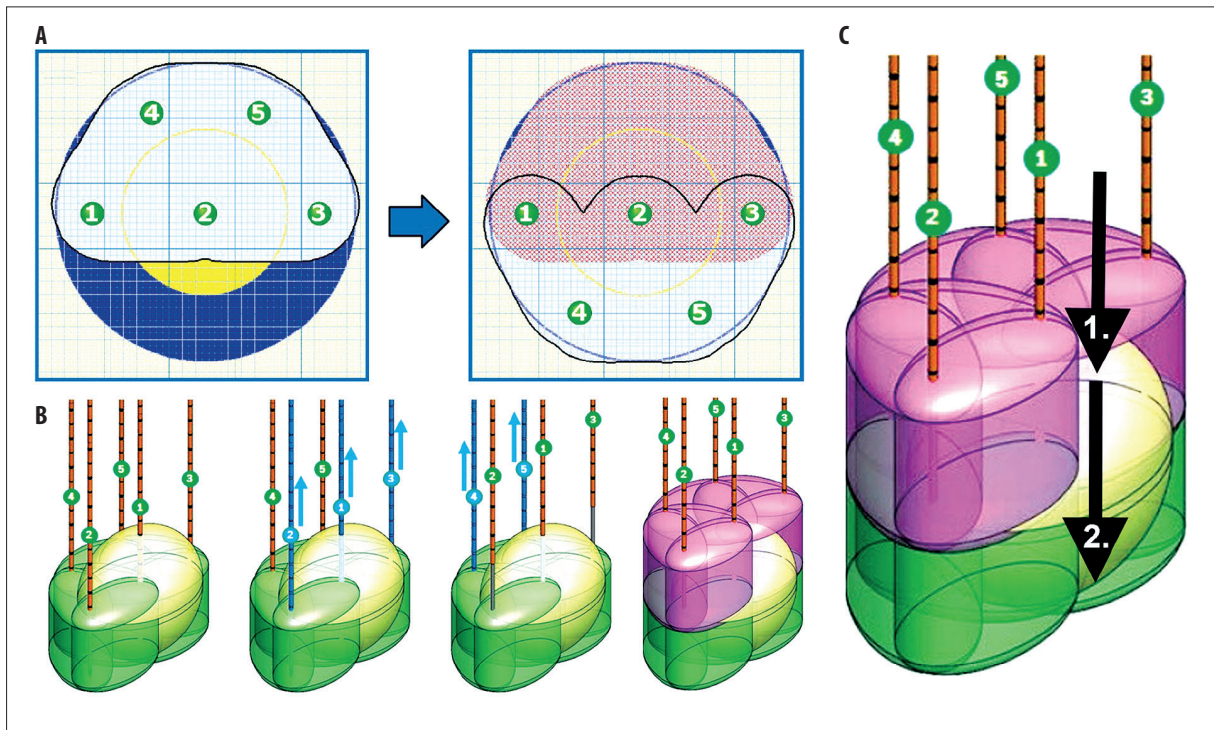
Needle tract seeding has thus far been described by Ricke et al. [4] after IRE of lung tumors and by Fredericks et al. [18] after IRE of colorectal carcinomas. A higher rate of needle tract seeding after IRE than after RFA

is under discussion. The risk of seeding is reduced in RFA by thermal ablation of the needle tract, a technique that IRE cannot utilize [18]. In IRE with the NanoKnife system, the cover is pulled back at the electrode (as an active tip) in the tumor before insertion. The tip should be covered again on withdrawal. However, it is unclear whether this would reduce the risk of seeding [4]. A higher needle tract tumor seeding for pull-back IRE ablation should be discussed. If a complex IRE ablation with coaxial overlapping in the electrode axis is necessary, we propose a '**push-forward IRE ablation**' instead of the pull-back ablation to reduce the hypothetical risk of needle tract tumor seeding (Figure 7C).

Micrometastases close to the primary index tumors or macrometastases have been observed in different entities that had been seeded from the primary index tumor or originated from the macrometastatic lesions as satellite lesions [17].

For different IRE sessions in one IRE course of treatment different electrode pairs can be selected as an intraprocedural modification (Figure 8). Here, for example, only 3 IRE electrode pairs can be selected for IRE ablation in spite of 4 inserted IRE electrodes and 6 possible IRE electrode pairs. IRE electrode pairs should be recorded as a cathode (P-) and anode (P+) analogous to the pulse parameter table (Figure 8). Before starting IRE ablation the user can set the number of pulses in the pulse parameter table. The NanoKnife system tests automatically each electrode pair with one '**test pulse**' application with reduced voltage. We recommend applying each 10 test pulses (1 '**test run**') with the aimed planning voltage set in the pulse parameter table in order to check for a high current risk within that planning voltage setting (Figure 8). The number of IRE pulses can be adjusted in a group of ten pulses (decadic), where 10 pulses count as 1 '**IRE pulse cluster**' (10 pulses = 1 cluster). The number of clusters can be set up to nine for one session per pair (9 clusters = 90 pulses) (Figure 2). The terms 'burst' and 'train' are not common for IRE description. But the term 'IRE cluster' is similar to 'RFA train'. All clusters of one IRE session for one electrode pair can be described as one '**IRE burst**', analogous to 'RFA burst'.

Up to now, there has been only one approved NanoKnife-based tool to monitor the IRE treatment for



**Figure 7.** Overlapping IRE ablation (A). Pull-back IRE ablation (B). Push-forward IRE ablation (C).

	P+	P-	Voltage	Pulse length	Num Pulses	V/cm	Distance
	1	2	2550	90	70	1500	1.7
▶	1	3	3000	90	70	1500	3.1
	2	3	3000	90	70	1500	2.0
	3	4	2850	90	70	1500	1.9
	4	1	2550	90	70	1500	1.7
	2	4	3000	90	70	1500	2.0

+     -     Adjust Dist     Apply

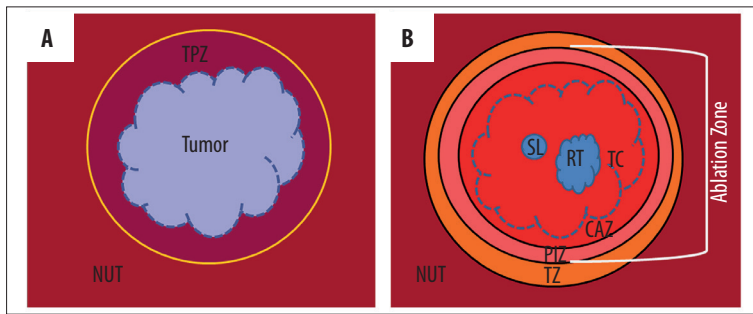
**Figure 8.** IRE NanoKnife pulse parameter table.

Cathode (P-) and anode (P+). The current direction between the IRE electrodes can be adjusted for each electrode pair during IRE treatment planning (table column anode [P+] and cathode [P-]). The relevance between the current direction and the grade of IRE ablation has not been still examined systematically – especially for overlapping ablations and centrifugal plus peripheral-concentric ablation for 5–6 electrodes with one central electrode.

intraoperative modification by reviewing the 'IRE current graphs' to determine the overall current draw after each completed IRE course (Figure 2). Reviewing the 'IRE result graphs' is recommended upon the completion of each IRE ablation before removing or repositioning the IRE electrodes. The result graphs should be assessed for abnormalities which may require an additional ablation session. An automated system that automatically terminates the ablation at a critical point in the IRE procedure is still not available. The graphs display the voltage output and the current output of each pulse delivered between all probe pairs (Figure 2). For a successful IRE ablation an output of uniform voltage graphs within each probe pair's results should be reported. By reviewing the current graphs for an

overall upward trend for each probe pair and for a slightly angled upwards cluster plateau (blue arrow in Figure 2), one can deduce a successful IRE ablation. This indicates a decrease in soft-tissue resistance throughout the pulse delivery. A flat trend does not indicate an unsuccessful pulse delivery (only the area may have been previously ablated within this course of treatment). Current draws exceeding 45 Amps may lead to high current conditions during a subsequent ablation with undesirable thermal ablation.

The range of minimum and maximum current of each IRE electrode pair for each session ('session pair current range') should be reported as IRE ablation method



**Figure 9.** Pre-IRE description (A): NUT – natural untreated tissue, TPZ – treatment planning zone. Post-IRE description (B): NUT – natural untreated tissue, TZ – transition zone, PIZ – peripheral inflammation zone, CAZ – central ablation zone, TC – tumor contour, RT – residual tumor, SL – skip lesion, CAZ + PIZ – ablation zone.

**Table 2.** IRE method reporting criteria with reporting data example (fictive) of 1 IRE ablation in 1 IRE session/course of treatment for 1 target with intraprocedural modification.

Patient	Tumor/target	Ablation	Round	No. of electrode	Intra-procedural modification	Active tip [mm]	Sketch electrode configuration	Electrode configuration	Electrode – tumor-margin distance [mm]	Electrode end/tip – tumor margin distance [mm]	Electrode pairs	Current flow direction [-> +]	Inter-electrode space [mm]	Voltage setting [V/cm]	Voltage Setting Total [V]	Pulse length [µs]	No of pul-ses	Application-speed [bpm]	E [kV]	ΔA burst [A]	ΔA% burst [A]		
1	1	1	0	1	Test	20		Trapezoid/square	1-R: +3	1T-R: +1	1-2	1+>2-	20	1500	3000	90	10	HR	X	-	-		
				2	20	2-R: +2			+1	2-3	2+>3-	17	1700	2890	90	10	HR	X	-	-			
				3	20	3-R: 0			2T-R: +2	3-4	3+>4-	15	1800	2700	90	10	HR	X	-	-			
				4	20	4-R: 0			3T-R: 0	1-3	1+>3-	21	1450	3000	90	10	HR	X	-	-			
			1	1	1	1	Pulse Count	20		Trapezoid/square	1-R: +3	1T-R: +1	1-2	1+>2-	20	1500	3000	90	70	HR	X	X	X
											2-R: +2	+1	2-3	2+>3-	17	1700	2890	90	70	HR	X	X	X
											3-R: 0	2T-R: +2	3-4	3+>4-	15	1800	2700	90	70	HR	X	X	X
											4-R: 0	3T-R: 0	1-3	1+>3-	21	1450	3000	90	70	HR	X	X	X
			2	1	1	1	Pull-Back	20		Trapezoid/square	1-R: +5	1T-R: -14	1-2	1+>2-	20	1500	3000	90	70	HR	X	X	X
											2-R: +3	-14	2-3	2+>3-	17	1700	2890	90	70	HR	X	X	X
											3-R: +2	2T-R: -13	3-4	3+>4-	15	1800	2700	90	70	HR	X	X	X
											4-R: +2	-13	1-3	1+>3-	21	1450	3000	90	70	HR	X	X	X
Total (3 rounds):	1	1	1	4	Pull-Back	20	Trapezoid/square	Min: +Max:	+Max: -15	6	-	Min: 15	Min: 1300	Min: 2700	90	900	HR	X	X	X			
								0Max: +5	-Max: -15			Max: 22	Max: 1800	Max: 3000									
												Med: 19	Med: 1540	Med: 2900									

reporting criteria. Moreover, the difference between the maximum current of the first cluster and the maximum current of the last cluster of each IRE electrode pair of each session (blue arrow in Figure 2) should be reported ('**session pair current delta**'). Due to the claimed increase, this difference of each burst should be reported in case of a positive increase (+) or a negative decrease (-), as well as reported as delta Ampere [**ΔA burst**] and delta of percentage [**ΔA% burst**] of the current graph plateaus (Figure 2). The value of this delta may allow for drawing conclusions on IRE ablation success [4,11].

For IRE ablation method reporting, the following table with the mentioned variables should be reported in each publication (Table 2).

The NanoKnife system includes no automatically prepared report of the applied energy (Joule [J]) for each ablation. This makes the comparison with the applied energy of other ablation modalities impossible. A detailed, clinically oriented calculation of the electric energy of the electric field seems to be not practicable, but it is approximately possible. In a simplified case of a constant voltage per



electrode pair and constant current (level of current result graphs), the electric energy [E] can be calculated by the multiplication of the applied voltage [U], the applied current [I] and the total pulse length of all applied pulses [t]:

Example for 6 used IRE electrode pairs of one IRE session:  
 $E_{total} = E1-2 + E2-3 + E3-4 + E1-4 + E2-4 + E1-3$   
 $= [(U_{1-2}) \times (I_{1-2}) \times \text{number of pulses}_{1-2} \times \text{pulse length}_{1-2}] +$   
 $[(U_{2-3}) \times (I_{2-3}) \times \text{number of pulses}_{2-3} \times \text{pulse length}_{2-3}] +$   
 $[(U_{3-4}) \times (I_{3-4}) \times \text{number of pulses}_{3-4} \times \text{pulse length}_{3-4}] +$   
 $[(U_{1-4}) \times (I_{1-4}) \times \text{number of pulses}_{1-4} \times \text{pulse length}_{1-4}] +$   
 $[(U_{2-4}) \times (I_{2-4}) \times \text{number of pulses}_{2-4} \times \text{pulse length}_{2-4}] +$   
 $[(U_{1-3}) \times (I_{1-3}) \times \text{number of pulses}_{1-3} \times \text{pulse length}_{1-3}].$

### IRE pre-treatment and outcome reporting criteria

The difference between pathological findings and imaging findings of IRE ablation must be stressed by an appropriate selection of terminology. For ablation therapy, given that many tumors undergo central necrosis without ablation therapy, the term 'coagulation' is preferred over the use of 'necrosis', as it denotes that the ablation intervention actively leads to tumor destruction. The term '**coagulation**' should also be used to describe pathological findings caused by newer ablation technologies, such as microwave ablation and IRE, as well. The more generalized term 'coagulation' is preferred over the term '**coagulative necrosis**', as the latter has a well-defined meaning within the pathology literature including the absence of visible nuclei within the dead cells. When histopathological evaluation of the ablation zone is performed, tumor cells identified in morphologic stains (hematoxylin-eosin) should undergo additional evaluation with specialized immunohistochemical stains to determine the viability or irreversible cell death. The optimal method for specialized immunohistochemical stains for IRE coagulation has not been evaluated conclusively.

For histopathological description of the IRE ablation zone the terminology '**central ablation zone**' and '**peripheral inflammation zone**' should be used (Figure 9). This should be differentiated from the thickness of the IRE ablation '**transition zone**', which describes how much spatial zone resides between coagulative necrosis or dead tissue and normal/unaffected tissue (Figure 9). The true correlation and imaging of these zones have not been evaluated for imaging methods after IRE ablation conclusively. Residual tumor zones and skip lesions should be reported separately. The dimensions and locations of these zones or lesions are of special interest (Figure 9).

IRE ablation zones may show shrinkage of the ablation volume after IRE. The term '**involution**' should be used to describe this process over weeks to months. It is important to note that the lack of or minimal involution after IRE does not imply treatment failure. This is a finding that has been described for multiple thermal ablation modalities and IRE as well. Finally, a successful IRE ablation zone will be significantly larger than the target tumor and therefore traditional Response Evaluation Criteria in Solid Tumors, or RECIST, do not address successful ablation. Cicatrization may accompany involution, where nearby normal tissue is retracted toward the IRE treatment zone. The amount of contraction varies with ablation time.

Finally, zones of IRE coagulation often demonstrate spherical shapes, but can show variations in the cross-sectional axis which can introduce variability in ablation size measurements. A three-dimensional, or whenever possible, volumetric evaluation, should be performed to measure the IRE ablation zone according to both above mentioned measuring methods (Figures 3, 4).

The optimal follow-up imaging method after IRE ablation seems to be multiparametric MRI whenever possible. Previous IRE reports used different follow-up terms for outcome inhomogenously, especially for short-term imaging or histopathological data.

According to the proposal for standardization of the International Working Group on Image-Guided Tumor Ablation (a) technical success and early safety data should have a 6-month follow-up, (b) clinical outcome results up to 1 year of follow-up should be named as preliminary or short-term, (c) 1-5-year follow-up as intermediate-term, (d) and at least 5-year (and ideally longer) follow-up as long-term.

The '**primary IRE efficacy rate**' is defined as the percentage of target tumors successfully eradicated following the initial or IRE treatment (adequate ablation, '**local control**'). The '**secondary or assisted IRE efficacy rate**' is defined as including tumors that have undergone successful repeat IRE ablation following identification of '**local tumor progression**' ('**retreatment**').

The term '**IRE (technical) success**' should be used to report whether the tumor was treated according to the protocol. A tumor that is treated according to the protocol and covered completely (i.e. ablation zone completely overlaps or encompasses the target tumor with the ablative margin), as determined at the time of the procedure, is 'technically successful'.

The term '**IRE (technique) efficacy**' should be used to report whether the tumor was ablated effectively (local control). IRE efficacy can only be demonstrated with appropriate clinical follow-up, and should therefore refer to a prospectively-defined time point at which point 'complete ablation' of macroscopic tumor, as evidenced by imaging follow-up or histopathological analysis of a resection specimen or biopsies.

For IRE ablation outcome reporting, the following table with the mentioned variables of pre-treatment variables and outcome variables should be reported in each publication (Table 3).

### Complication reporting

Complications should be stratified on the basis of the outcome by using the most recent version of the unified standardized SIR grading system of the Society of Interventional Radiology (SIR) [10,19]. The SIR grading system is the most commonly used complication-reporting system for interventional radiological procedures according to the severity of the complications. Alternative classifications exist, and can be used if a compelling reason is provided [10]. The

**Table 3.** Tabular IRE pre-treatment and outcome reporting criteria.

	Patient X
<b>Pre-IRE data</b>	
No. targets	
Tumor location/anatomy	
Pre-IRE tumor size, index tumor size [mm × mm × mm]	Length × width × depth
Pre-IRE tumor volume, index tumor volume [ccm]	Ellipsoid formula
Index tumor shape and class	
Biopsy histopathology	
Index tumor texture	Homogeneity?, solid?, cystic?, calcifications?
TNM	
Planned treatment zone size [mm × mm × mm]	Length × width × depth
Planned treatment zone volume [ccm]	Ellipsoid formula
<b>Post-IRE data (histological)</b>	
Ablation zone size [mm x mm x mm]	Length × width × depth
Ablation zone volume [ccm]	Ellipsoid formula
Post-IRE tumor contour/ structure size [mm × mm × mm]	Length × width × depth
Post-IRE tumor contour/ structure volume [ccm]	Ellipsoid formula
Tumor ablation degree	'Complete ablation' or 'partial ablation' (incomplete)
Regression grade (if available)	
Residual tumor zones	Number? location?
Post-IRE volume of histologically residual tumour [ccm]	Ellipsoid formula
Assessment method of viability of tumor tissue	
Skip lesions in the ablation zone	Number? location?
Difference of pre-post-IRE tumour volume [ccm]: Post – Pre	Negative value demonstrates involution with size reduction
Difference of pre-post-IRE tumour volume [%]: Post – Pre	Negative value demonstrates involution with size reduction
Difference of treatment planning zone volume and ablation zone volume [ccm]	

Common Terminology Criteria for Adverse Events (CTCAE) v4.0 of the National Cancer Institute [20] and the Clavien-Dindo Classification system [21] are commonly used systems in oncological and surgical practice. The CTCAE is the most detailed system for each symptom and organ system.

IRE, as a new treatment modality, will not be compared with different interventional procedures only, but with surgical therapies as well. Therefore, we propose using simultaneously the SIR grading system, the Clavien-Dindo Classification system and the CTCAE system [19–21].

## Discussion

The original intent of this standardization of IRE terminology was to provide an appropriate vehicle for reporting the various aspects of image-guided IRE ablation therapy. Our intent continues to be to provide such a framework which

would facilitate the clearest communication between investigators, and enable the greatest flexibility in comparisons in IRE ablation technology. We encourage all of our colleagues to adopt the terminology and reporting strategies outlined in this updated proposal to facilitate worldwide communication on scientific advances in IRE.

## Conclusions

We would like to emphasize that using all the above recommended reporting criteria and terms can make IRE ablation reports comparable and provide treatment transparency to assess the current value of IRE and provoke further development.

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