Magnetic Resonance Imaging Findings After Percutaneous Irreversible Electroporation of Liver Metastases

A Systematic Longitudinal Study

Alexandra Barabasch, MD, Martina Distelmaier, MD, Philipp Heil, MD, Nils Andreas Krämer, MD, Christiane K. Kuhl, MD, and Philipp Bruners, MD

Objective: The aim of this study was to systematically investigate the course of magnetic resonance (MR) signal intensity (SI) changes that occur in noncirrhotic livers after irreversible electroporation (IRE) of liver metastases.

Methods: This study is an institutional review board–approved prospective longitudinal follow-up study on 27 patients with 37 liver metastases who underwent computed tomography–guided percutaneous IRE and a standardized follow-up protocol by serial hepatic MR imaging studies that consisted of a gadobutrol-enhanced dynamic series, axial T2-weighted (T2w) turbo spin echo, and diffusion-weighted imaging (b = 0/50/800), acquired before, within 2, and at 24 hours after IRE; at 1, 2, 4, 6, 8, and 12 weeks after IRE; and every 3 months thereafter for a follow-up of at least 12 months.

Results: The ablated target lesion remained visible within the ablation zone in 23 (62%) of 37 of cases for a mean time of 21 ± 20 weeks (median, 12 weeks). The ablation zone appeared homogeneously hypointense on T2w turbo spin echo images on the day of IRE in 37 of 37 cases. By 24 hours after IRE, the ablation zone inverted its SI in 35 of 37 cases to intermediate hypointensity, with a rim of T2w bright SI that exhibited arterial phase enhancement; this persisted for 7 ± 5 weeks (median, 4 weeks). The rim resolved in 35 (95%) of 37 cases within 3 months. The ablation zone increased slightly over the first 48 hours, then shrank progressively. Complete healing of the ablation zone was observed in 57% (21/37) after an average of 14 ± 5 weeks (median, 8 weeks).

Average apparent diffusion coefficient values of the ablation zone decreased from 0.74 ± 0.36 × 10−3 mm²/s pre-IRE to 0.63 ± 0.27 × 10−3 mm²/s within the first 24 hours (P < 0.05), followed by a progressive normalization to 0.91 ± 0.30 × 10−3 mm²/s at 2 months.

Conclusions: Knowledge of the broad spectrum of MR imaging findings after IRE is important to avoid diagnostic errors in the follow-up of patients after IRE.

Key Words: electroporation, ablation techniques, magnetic resonance imaging, treatment outcome

MATERIALS AND METHODS

This institutional review board–approved prospective longitudinal observational diagnostic study was performed at an academic comprehensive cancer center.

Inclusion Criteria and Study Protocol

We included consecutive patients who underwent percutaneous CT-guided IRE for ablation of liver malignancies over a 3-year period (2012 through 2015). Our institution has an established clinical service for several ablative methods, including RFA, MWA, and IRE. The decision to perform hepatic tumor ablation was made for each patient by a multidisciplinary tumor board attended by hepatobiliary surgeons, gastroenterologists, oncologists, radiation therapists, and radiologists, with inclusion criteria that correspond to international practice guidelines as follows:

- no surgical candidate,
- without prognostically relevant extrahepatic tumor burden, and
- with preserved liver function, normal coagulation status (quick >50%), and Eastern Cooperative Oncology Group 0/1 status.

The choice between the different ablative techniques is at the discretion of the interventional radiologist and follows internal

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IRE Procedure

Irreversible electroporation was performed in close accordance with recommended practice standards under general anesthesia and deep relaxation. Depending on lesion size and shape, between two and five 19-gauge, unipolar IRE probes (NanoKnife; AngioDynamics, Amsterdam, the Netherlands) with an active tip length of 1.5 to 2.5 cm were placed strictly parallel under CT guidance. Before pulse application, a CT scan covering the target lesion was acquired to validate correct electrode positioning. Irreversible electroporation was performed with 70 pulses per electrode pair, a pulse length of 70 to 90 μs, and a maximum voltage of 3000 V with electrocardiographic gating.

Image Analysis

All MRI scans of each patient were systematically analyzed by 5 readers with 20, 11, 10, 9, and 5 years of experience in local ablation techniques and liver MRI. Parameters assessed were:

- Qualitative (visual) metrics:
  - Visibility of the ablation zone on T2-weighted (T2w) MRI
- Quantitative metrics:
  - Volume of the IRE ablation zone on T2w MRI scans
  - Apparent diffusion coefficient (ADC) values of the target lesion before IRE and of the ablation zone (which includes the target lesion) after IRE

Statistical Analysis

Continuous variables (tumor and ablation zone volumes and ADC values) are expressed as mean values ± standard deviation. For comparison of target lesion sizes, the unpaired Wilcoxon test was used. For comparison of ADC values at different time points, the paired Wilcoxon test was used. All test results were analyzed in an explorative way; thus, P values of P ≤ 0.05 were regarded as statistically significant. All statistical analyses were conducted using the Statistical Analysis System (SAS Version 9.2; SAS Institute, Cary, NC) and R (R Version 2.11.1. Copyright 2010 The R Foundation for Statistical Computing).

**TABLE 1. MRI Pulse Sequences**

| Type of scanner | 1.5 T Achieva; Philips Healthcare, Best, the Netherlands | Multielement 16-channel coil (Sense Torso XL) |
|-----------------|----------------------------------------------------------|---------------------------------------------|
| Type of contrast agent | Gadobutrol-enhanced liver MRI (Gadovist; Bayer Schering Pharma AG, Berlin, Germany) | 0.1 mmol/kg body weight |
| Dose of contrast agent | 304 × 233 | 380 mm |
| Pulse sequence type | Dynamic series T1-weighted 3D gradient echo | 2D turbo spin echo |
| TR/TE | 4.3 ms/1.3 ms | 2500 ms/80 ms |
| Orientation | Axial | Axial |
| Acquisition matrix | 330 mm | 7 mm |
| Field of view | 268 × 174 | Respiratory triggering and breath-hold |
| Section thickness | 8 mm | 2 |
| Breath compensation | Breath-hold | Respiratory triggering |
| Sense factor | 2 | NA |
| B values | NA | 0, 50, 800 |
| No. dynamics | 3 precontrast, 3 postcontrast with bolus tracking (arterial, portal venous, equilibrium phase) | |

MRI indicates magnetic resonance imaging; SE EPI, spin echo echo planar imaging; TR/TE, repetition time/echo time.
RESULTS

Patient and Target Lesion Characteristics

Twenty-seven patients with a total of 37 secondary liver malignancies were included (Table 2). The mean age was 62 ± 11 years (range, 46–68; median age, 64 years). The primary tumors were colorectal cancer in 15 patients; breast in 4; pancreatic and esophageal cancer in 2 each; and gastrointestinal stromal tumor, malignant melanoma, mesothelioma, and renal cell cancer in 1 patient each. Mean follow-up time is 23 ± 11 months.

Mean target lesion volume measured on preinterventional T2w turbo spin echo (TSE) images was 6.4 ± 11.4 mL (range, 0.1–45.0 mL; median, 1.5 mL). Target lesions were located immediately adjacent to major hepatic veins (n = 15), portal vein branches (n = 12), both (n = 10), and therefore were regarded not suitable for RFA or MWA.

MRI Patterns After IRE

Typical patterns of the temporal evolution of T2w-TSE and T1w-DCE imaging findings after IRE are provided in Figures 1, 2, and 3. Results of the temporal evolution of changes of the ablation zone size and of the ablation zone average ADC values are depicted in Figures 4 and 5.

Early Postinterventional Period (Day of IRE Until 1 Week After IRE)

On the day of the IRE, the ablation zone was visible as an immediately and homogeneously hyperintense area compared with normal liver parenchyma on T2w TSE images in all 37 of 37 cases. In 3 (8%) of 37 ablations on the day of IRE, the hyperintense rim of the ablation zone did not cover the entire target lesion.

One day after IRE, in 35 of 37 cases, the SI of the ablation zone on T2w imaging inverted to become immediately hypointense compared with normal parenchyma and exhibited a hyperintense rim that was visible around the ablation zone. This hyperintense rim exhibited strong enhancement on arterial phase imaging.

In this early post-IRE period, the ablated tumor (target lesion) remained visible within the ablation zone, with unchanged SI compared with the preinterventional MRI, in 62% of ablation zones (23/37). In the remaining 38% (14/37), the target lesion was not visible within the ablation zone. Target lesions that were still visible after IRE tended to be larger than those that were not visible (8.5 ± 9.3 mL vs 2.2 ± 1.3 mL; \( P < 0.05 \)).

On the day of IRE, the mean size of the ablation zone measured 26.6 ± 11.3 mL; referenced to the size of the respective target lesion, the ablation volume was 417% larger than the volume of the target lesion.

One day after IRE, the size of the ablation zone volume increased to measure 53.3 ± 33.5 mL on average, that is, 836% of the volume of the respective target lesion.

One week after the ablation, the ablation zones showed a slight decrease in size measuring 39.8 ± 37.0 mL.

For the analysis of the temporal evolution of ADC values, data sets of 3 patients needed to be discarded due to inconsistent diffusion-weighted imaging image quality, and in another 3 patients due to signs of incomplete ablation on the MRI performed immediately after IRE.

| Study Population (n = 27) | Age y 62 ± 11 | Sex Female/male 14/13 |
|---------------------------|---------------|-----------------------|
| **Demographic details**   |               |                       |
| Primary tumor             |               |                       |
| Breast cancer             | 4             | 4                     |
| Colorectal cancer         | 15            | 23                    |
| Pancreatic cancer         | 2             | 2                     |
| Melanoma                  | 1             | 1                     |
| Mesothelioma              | 1             | 1                     |
| Esophageal carcinoma      | 2             | 2                     |
| RCC                       | 1             | 3                     |
| GIST                      | 1             | 1                     |
| **Lesion characteristics**|               |                       |
| Total                     | 27            | 37                    |
| Mean size mL ± SD         | 6.4 ± 11.39   |                       |
| Lesion adjacent to         |               |                       |
| Portal vein branches      | n             | 12                    |
| Hepatic veins             | n             | 15                    |
| Both                      | n             | 10                    |
| **IRE procedure**         |               |                       |
| Median count of electrodes used | n (range) | 3 (2–5) |
| Pulses per electrode pair | n             | 70–90                 |
| Pulse length μs           | 70–90         |                       |
| Maximum voltage V         | 3000          |                       |
| Median electrode interval mm (range) | 15 (10–20) | 20 (10–25) |
| Median length of active tip mm (range) | 23 | 18 |
| Necessity of electrode replacement | n | 5 |
| Pull back technique       | n             | 18                    |
| New electrode placement   | n             | 5                     |

RCC indicates renal cell carcinoma; GIST, gastrointestinal stromal tumor; IRE, irreversible electroporation.

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For the remaining 31 of 37 patients, the average ADC of the ablation volume decreased from $0.74 \pm 0.36 \times 10^{-3}$ mm$^2$/s pre-IRE to $0.68 \pm 0.18 \times 10^{-3}$ mm$^2$/s immediately after IRE, reaching an average minimum of $0.63 \pm 0.27 \times 10^{-3}$ mm$^2$/s 24 hours after IRE ($P < 0.05$). Thereafter, ADC values showed a slight increase 1 week after IRE ($0.70 \pm 0.30 \times 10^{-3}$ mm$^2$/s).

Intermediate Post-IRE Changes (Week 2–8 Post-IRE)

The ablation zone remained intermediately hypointense with a hyperintense rim that exhibited arterial enhancement. This hyperintense rim exhibited a continuous SI decrease and disappeared within 1 week in 2 of 37, within 2 weeks in 7 of 37, within 4 weeks in 10 of 37, within 6 weeks in 2 of 37, and within 8 weeks in 9 of 37 cases. In the remaining 7 of 37 cases, the hyperintense rim persisted for more than 8 weeks, that is, persisted until the late post-IRE phase.

Of the 23 target lesions that were still visible within the ablation zone immediately after IRE, this persisted for a variable period. In detail, the lesion remained visible for 1 week in 1, for 2 weeks in 1, for 4 weeks in 2, for 6 weeks in 1, and or for 8 weeks in 3 cases, respectively. In the remaining 15 cases, the ablated target lesion remained visible for more than 8 weeks, but exhibited lower SI on T2w imaging compared with preinterventional baseline.

The average volume of the ablation zone decreased continuously from $39.8 \pm 37.0$ mL to $5.1 \pm 5.2$ mL.
The ablation zone disappeared completely within the first 8 weeks after IRE in 13 (35%) of 37 cases and persisted in 24 (65%) of 37. Such complete resolution was observed within 2 weeks in 1, within 4 weeks in 4, and within 8 weeks in 8 of 37 cases.

Average ADC of the ablation zone increased continuously during this period for the evaluable 31 cases from $0.77 \pm 0.25 \times 10^{-3} \text{mm}^2/\text{s}$ 1 week after IRE to $0.91 \pm 0.30 \times 10^{-3} \text{mm}^2/\text{s}$ 8 weeks after IRE ($P < 0.05$).

Late Post-IRE Changes (12 Weeks to 12 Months)

In 24 cases, the ablation zone was still visible 8 weeks after IRE. Of these, 8 resolved completely—4 by 3 months, 2 by 6 months, and 2 by 12 months.
A hyperintense rim with arterial contrast enhancement was visible in 7 cases around the 24 ablation zones and persisted for 3 months in 5 and for 6 months in 2 of the 7 cases. In 15 cases (15/37), the ablated target lesion was still visible within the ablation zone 8 weeks after IRE; this persisted for a quite variable time interval, that is, for 3 months after IRE in 6, for 6 months in another 6, for 9 months in 2, and for over 15 months in 1 case.

In the 24 ablation zones that were still visible beyond 8 weeks, the average volume decreased continuously from $5.6 \pm 11.0 \text{ mL}$ to $2.1 \pm 4.9 \text{ mL}$ after 12 months.

The average ADC of the ablation volume increased further from $0.91 \pm 0.33 \times 10^{-3} \text{ mm}^2/\text{s}$ at 3 months after IRE to $0.96 \pm 0.24 \times 10^{-3} \text{ mm}^2/\text{s}$ 12 months after IRE ($P > 0.05$).

**DISCUSSION**

Although recent studies have shown that tumor destructive effects induced by IRE are not exclusively nonthermal, it is true to state that the main principle of cell destruction by IRE is induction of controlled apoptosis. Therefore, whereas after successful radiofrequency or MWA, a clear-cut scar is visible on CT or MRI, and the detection of local recurrence is quite straightforward, the situation is more complex, and apparently more difficult after hepatic IRE. In accordance with the quite distinct mode of action of IRE compared with thermal local ablative techniques, the normal course of the ablation zone after IRE differs considerably from the normal course after thermal methods. We believe that knowledge of typical MRI appearance of the IRE ablation zone and its changes over time is important to avoid diagnostic errors in the follow-up of patients after IRE.

This study on 27 patients with 37 hepatic metastases from solid tumors demonstrates that hepatic IRE of noncirrhotic livers induces a broad spectrum of complex SI changes on MRI, with quite variable course over time. However, compared with MRI effects observed after IRE of HCC in cirrhotic livers, we were able to identify a somewhat more homogeneous pattern of imaging findings. In most cases, the following pattern was observed:

The ablation zone appeared homogenously hyperintense on T2w images on the day of IRE, then reversed its SI within the first 24 hours after IRE to become immediately hypointense, with a circular peripheral rim of T2w bright SI that exhibited arterial enhancement. This appearance persisted for a median 4 weeks after IRE. The hyperintense rim and its enhancement resolved within 3 months after IRE in 95% of cases (35/37). After IRE for HCC in patients with cirrhotic livers, the hyperintense rim as well as the increased contrast enhancement in the arterial phase persisted for a longer period. We propose that the faster resolution of the hyperintense rim and the increased arterial contrast enhancement observed in our cohort is explainable by the superior regenerative capacity of the noncirrhotic liver parenchyma. The described changes on T2w images may be local cytotoxic edema due to the ion leakage caused by the irreversible membrane defects. Furthermore, a local vascular dilatation and congestion as well as an inflammatory reaction as described in animal studies occurring at 7 to 15 days after IRE may also contribute to this imaging finding.

The peripheral hyperemia around the ablation zone is probably more problematic for the diagnosis of residual or recurrent tumor in patients with HCC but may also cause diagnostic difficulties in patients treated for hypervascular metastases.

It is likely that the T2w hyperintense, hypervascular rim represents an area of incomplete, that is, reversible electroporation. In principle, it is conceivable to exploit these therapy-induced changes to boost the efficacy of local transarterial treatment strategies such as transarterial chemoembolization after IRE. For the design of possible future combined IRE plus transarterial treatment approaches, the quite variable normal time course of the hypervascular rim after IRE in patients with cirrhotic versus noncirrhotic livers needs to be taken into account.

The ablation zones resolved completely in just over half of the cases (57%, 21/37), by an average of 14 weeks after IRE. In the other half (43%, 16/37), the ablation zone did not resolve for over 15 months of follow-up. We can only speculate why ablation zones do or do not disappear, in other words, why some patients exhibit a complete healing, whereas others do not. Confounding factors may be variable vascular supply and/or vascular or biliary drainage of the treated liver area, and/or variations of the regenerative capacity of livers that may exist after courses of systemic chemotherapy.

However, in all 34 cases with complete ablation, the ablation zone exhibited a progressive shrinkage over time. After a small temporary volume increase within the first 24 hours after IRE, the ablation zones shrank progressively over the follow-up period, although with different pace: The shrinkage was steeper in the first 2 weeks after IRE, followed by a moderate shrinkage in the following months. Since this was observed in all 34 cases with complete ablation, any increase in size of the ablation zone should raise the suspicion of local recurrence.

Probably due to the absence of coagulation necrosis, the ablated target lesion remained visible within the ablation zone, with unchanged SI compared with its preinterventional MRI appearance, in 62% of the cases (23/37); this was observed for a median of 3 months and could persist for 15 months after the ablation. Persistent visibility of the treated target lesion was more likely to be seen with larger targets than with smaller ones.

Average ADC values of the ablation volume decreased within the first 2 days after IRE, followed by a progressive normalization of ADC that was on average reached within 2 months after IRE in all cases with successful ablation.

In 3 patients, in whom the hyperintense rim depicted on the MRI study performed within 24 hours after was incomplete and did not include the full volume of the target lesions, follow-up imaging confirmed that the ablation had been incomplete. Accordingly, if doubt exist with regards to the local completeness of the procedure after CT-guided IRE, MRI on the day after IRE is useful. For the long-term follow-up, we suggest to start at 3 months after the procedure because by that time, signs of inflammation (hyperintense rim and strong contrast enhancement), at least in noncirrhotic liver, have subsided.

Our study has a number of limitations. We dealt with a relatively small group of patients who have various tumor types with different histological aspects in their appearance and may have been treated with different types of systemic therapy before, which may influence the “treatment response,” and may, in principle, influence the MRI appearance of the liver. However, none of our patients exhibited signs of chemotherapy-associated steatohepatitis clinically or on MRI. Moreover, we did not investigate the effects of IRE on other imaging methods such as CT or (contrast enhanced) ultrasound. Further studies are needed to establish the process of post-IRE healing in these imaging methods.

We can conclude that IRE treatment of secondary liver tumors induces quite variable effects. Knowledge of the expectable SI changes and their time course induced by IRE is essential to avoid diagnostic errors, especially misdiagnosing signs of local recurrence, and to design further local treatment approaches.

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