Technical efficacy and local recurrence after stereotactic radiofrequency ablation of 2653 liver tumors: a 15-year single-center experience with evaluation of prognostic factors

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ABSTRACT

Purpose: To assess the technical outcome and local tumor control of multi-probe stereotactic radiofrequency ablation (SRFA) in a large series of patients. Furthermore, to determine factors accounting for adverse outcomes.

Material and methods: Between 2003 and 2018, 865 patients were treated by SRFA for 2653 primary and metastatic liver tumors with a median tumor size of 2.0 cm (0.5 – 19 cm). Primary technical efficacy (PTE) and local recurrence (LR) were evaluated, and possible predictors for adverse events analyzed using uni- and multi-variable binary logistic regression.

Results: Overall, 2553 of 2653 tumors were successfully ablated at initial SRFA resulting in a PTE rate of 96.2%. Predictors of lower PTE rates were age > 70 years, tumor size > 5 cm, number of probes, location close to liver capsule/organs and segment II. LR occurred in 220 of 2653 tumors (8.3%) with the following predictors: age, tumor type/size, conglomerates, segments I/IVa/IVb, number of probes and location close to major vessels/bile duct. Multivatiable analysis revealed tumor size > 5 cm (odds ratio [OR] 3.153), age > 70 years (OR 1.559), and location in segment II (OR 1.772) as independent prognostic factors for PTE, whereas tumor location close to major vessels (OR 1.653) and in segment IVb (OR 2.656) were identified as independent prognostic factors of LR.

Conclusions: Stereotactic RFA is an attractive option in the management of primary or metastatic liver tumors with good local tumor control, even in large tumors. The presented prognostic factors for adverse local oncological outcome might help to stratify unfavorable tumors for ablation.

Abbreviations: HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; LR: local recurrence; PTE: primary technical efficacy; RF: radiofrequency; SRFA: stereotactic radiofrequency ablation; TACE: transcatheter arterial chemoembolization

Introduction

Radiofrequency ablation (RFA) has gained wide acceptance in the management of hepatocellular carcinomas (HCCs), intrahepatic cholangiocarcinoma (ICC) and liver metastases from colorectal cancer, breast cancer and neuroendocrine tumors [1–3]. In patients with early HCC [4], RFA has comparable overall survival to hepatic resection (HR) paired with lower morbidity rates due to its minimally invasive nature. However, HR often remains the treatment of choice in the context of preserved liver function. This is mainly attributed to relatively high rates of local recurrence (LR) reported in the RFA literature, varying from 10 to 39.1% within 5 years – depending on tumor size and number [5,6]. To minimize the chances of undertreatment, it is critical to establish a sufficient safety margin surrounding the tumor completely by at least 5 mm of ablation zone in all dimensions [7]. However, adequate treatment margins may be particularly challenging for tumors > 3 cm or in situations when the target is either difficult to visualize, awkward to access, or situated adjacent to vulnerable structures. To increase the size of the ablation zone, multiple RF electrode techniques or more efficient thermal ablation devices, such as microwave may be used [8–11]. However, conventional US- or CT-fluoroscopic guidance lacks reliability for accurate three-dimensional probe placement. Stereotaxy, already widely used in radiotherapy and surgical procedures, represents a useful way of precisely transposing pre-defined three-dimensional plans to the patient in order to enable more complex or challenging interventions.

The purpose of this study was to assess the technical outcome and local tumor control of multi-probe SRFA in a large
series of patients and to determine risk factors accounting for adverse outcomes.

**Materials and methods**

**Study population**

This retrospective, single-center study was approved by the Institutional Review Board (study number: AN4357). Written informed consent for SFRA was obtained from the entire study population. All treatment plans were approved by consensus in multidisciplinary tumor board meetings. The tumor board at our institution consists of hepatologists, oncologists, liver surgeons, radiation therapists and interventional radiologists. Between June 2003 and June 2018, 943 consecutive patients were treated by SFRA for primary or secondary liver tumors. Inclusion criteria for SFRA comprised: i) fit for general anesthesia ii) liver confined HCC/ICC or iii) liver dominant metastatic disease. A total of 78 patients with extended tumor spread and subsequent palliative intention to treat (n = 55) and benign liver tumors (n = 23), were excluded (Figure 1).

Contraindications for SFRA are: i) prothrombin activity < 50%, ii) platelet count < 50,000/mm³ and iii) tumor location within 1 cm of the central biliary structures. Due to the stereotactic approach, there are no limitations in terms of tumor size or number as long as sufficient functional liver remnant can be guaranteed.

Tumor diagnosis was based on classic tumor enhancement patterns on multiphasic contrast MRI or CT, with histopathological validation for inconclusive cases.

This patient cohort has been partially described in some of our previous works as summarized in a recent narrative review [12].

**Multi-probe SRFA**

The rationale of multi-probe RF ablation is to create multiple overlapping ablation zones for complete coverage of the tumor volume including a sufficient safety margin (Figure 2). For safe and complete necrosis between two RF probes, the maximum distance should not exceed 2 cm [13]. Thus, compared with single-probe techniques, multi-probe SRFA allows the creation of much larger ablation volumes. Stereotactic technique relates the position of targets within the scanned body to a Cartesian coordinate system, enabling reliable planning and execution of complex interventional procedures.

SRFA represents also an effective minimal-invasive treatment option for pediatric patients with liver tumors of different etiologies, as described in a recent, retrospective study [14].

**SRFA procedure**

Each SRFA procedure is either carried out independently or supervised by an experienced IR (with > 2 years SRFA experience). The exact method of SRFA has been previously described elsewhere [15-17]. Briefly, the crucial steps are as follows:

i. Patient fixation: Immobilization is obtained using a single vacuum fixation technique (Bluebag, iSys Medizintechnik, Kitzbühel, Austria) and by general anesthesia with deep muscle relaxation.

ii. Planning: A contrast-enhanced CT (CECT) (Siemens SOMATOM Sensation Open, sliding 82 cm gantry, Siemens AG, Munich, Germany) is acquired with a 3 mm slice thickness in arterial and portal-venous phases and subsequently transferred to an optical navigation system (Stealth Station Treon plus, Medtronic Inc., Dublin, Ireland). After that, needle trajectories are planned on multiplanar and 3D reconstructed images using the navigation system software.

iii. Coaxial Needle Insertion: Coaxial needles sized 15G x 17.2 cm (Bard Inc., New Providence, NJ; Covington) are inserted through the ATLAS aiming device (Elekta PSC Medical Intelligence Inc., Schwabmünchen, Germany), allowing a navigated alignment of the planned trajectories without real-time imaging. The coaxial needles serve as guides for the RF probes. The endotracheal tube is temporarily disconnected during imaging and for each stereotactic needle placement to prevent respiratory movements and to immobilize the liver. To verify correct needle placement, a non-enhanced CT is obtained and superimposed onto the planning CT with the possibility of manual re-adjustment. If needed, a 16G biopsy sample can be obtained via one of the coaxial needles (e.g., in patients with inconclusive imaging).

iv. Thermal ablation: Thermal ablation is performed using a unipolar RF generator (Cool-tip, Medtronic) including the Cool-tip RF switching controller. For serial tumor ablation, up to three 17G RF-electrodes at a time (Cool-tip, Medtronic, 25 cm length with 3 cm exposure) are introduced through the coaxial needles. The standard ablation time for three electrodes is 16 minutes. If the impedance increases (so-called ‘roll-off effect’), the ablation process is considered complete. Needle track ablation is performed before repositioning and during final removal of every needle in order to prevent bleeding and potential tumor seeding.

v. Completion: Finally, a post-interventional CECT-scan in arterial and portal venous phases is acquired and fused with the planning CT-scan to assess treatment success in three dimensions (i.e., complete coverage of the tumor with necrosis zone including an adequate safety margin). In case of incomplete ablation (i.e., residual tumor, lack of sufficient safety margin) the intervention may be continued in the same session by additional placement of coaxial needles with subsequent serial ablation.

Example images from a multiprobe SRFA are shown in Figure 3.
Technical improvements over time

The first SRFA in its current form was performed in 2003. To improve local tumor control, the SRFA was adapted with increasing experience by several technical modifications: i) despite initial attempts at bile duct cooling, it was decided to avoid treatment of tumors close to central biliary structures; ii) ‘no-touch’ or ‘partial touch’ needle distribution to cut off blood supply in case of a location close to heat-sensitive structures (diaphragm and organs) [18]; iii) acquisition of MR images prior to the intervention with intraoperative image fusion in order to increase the visibility of ‘CT-invisible’ lesions and for better delineation of tumor boarders; iv) planning of the intervention with the aim to achieve a three-dimensional ablation margin with a minimum of 5 mm.

Study endpoints

The primary endpoints of this study were primary/secondary technical efficacy and LR rate. Follow-up contrast-enhanced CT or MR scans were performed at 1 and 3-month intervals after SRFA for two years, and 6-month intervals thereafter. Two experienced abdominal radiologists examined the imaging results by consensus (BR and PES). Primary technical efficacy rate (PTE) was evaluated for each tumor nodule, defined as the absence of residual vital tumor tissue at 1-month follow-up imaging. Secondary technical efficacy rate was defined as the absence of residual vital tumor tissue after repeat ablation. Appearance of new nodules within or directly adjacent to the ablation zone was defined as LR. New nodules with their center distant from and discontinuous with the ablation zone were defined as new or distant recurrence.

Major complications were defined according to the Society of Interventional Radiology (SIR) Standards of Practice Committee classification [19]. Perioperative mortality was defined as death within 30 d after SRFA.

Definitions of risk factors

A distance of $< 1$ cm was defined as ‘close to’ in terms of diaphragm, liver capsule, organ, major vessel, central bile duct or gall bladder. A major vessel was defined as one with a diameter $> 3$ mm. Non-critical location was defined as a location without adjacent vulnerable structures. Conglomerate was defined as closely grouped tumors.

Statistical analysis

The statistical analysis was performed using SPSS version 27 (SPSS Inc., Chicago, IL). Data were expressed as total numbers, median and range.

Differences between categorical variables and independent continuous variables were evaluated using the $\chi^2$ test or the Mann–Whitney U test, respectively. Binary logistic regression was used to compare factors of categorical outcome (PTE, LR). The variables of interest ($p < .1$) identified in the univariable analysis were further analyzed in a multivariable model.

A $p$ value $< .05$ was considered as statistically significant.
Results

Patient characteristics

A total of 865 patients (259 (29.9%) females and 606 (70.1%) males), with a median age of 64 years (0.3 – 88) underwent SRFA for 422 (48.7%) HCCs, 35 (4.0%) ICCs and 408 (47.3%) metastatic tumors. The majority (61.1%) of metastatic disease originated from colorectal cancer. Forty-eight of 408 (11.8%) patients with liver metastasis had also extrahepatic manifestation at the time of the intervention. At initial SRFA, median tumor size was 3.0 cm (range, 0.5 – 18 cm). A median of 2 tumors (1–29) were treated per patient in a total of 1325 ablation sessions. At the beginning of treatment, 475 (55.0%) patients had a solitary liver tumor, 205 (23.7%) had two tumors, 89 (10.3%) had three tumors and 95 (11.0%) patients had more than three tumors (multiple nodules). A total of 421 (48.7%) patients had tumors < 3 cm, 294 (34%) between 3 and 5 cm and 149 (17.2%) > 5 cm, respectively. Liver cirrhosis was diagnosed in 379 (43.8%) patients, whereby 290 (76.5%) classified as Child–Pugh A, 82 (21.6%) Child–Pugh B and 7 (1.8%) Child–Pugh C. Prior to SRFA, 40 patients (4.6%, 21 for LR) underwent conventional “freehand” US- or CT-guided RF ablation, 82 patients (9.5%, 58 for LR) underwent TACE and 130 patients (15.0%, 37 for LR) underwent HR, respectively.

An overview is shown in Table 1.
Of 30-d mortality was 0.7% (9/1341 ablations) and major perioperative complication rate was 7.9% (106/1341 ablations). Four deaths occurred from major hemorrhage, two from acute liver failure on a background of advanced cirrhosis, two due to sepsis and one as a consequence of acute-on-chronic renal failure. The most common major complications were peri-/intra-hepatic hemorrhage in 34 (2.5%), major pleural effusion in 15 (1.1%), and pneumothorax in 17 (1.2%) patients – managed with angiographic coiling, thoracocentesis and chest tube insertion, respectively.

### Technical efficacy
A total of 2553 of 2653 tumors were successfully ablated at initial SRFA, resulting in a PTE rate of 96.2%. Of all residual tumors, 58/78 was successfully retreated, resulting in a secondary technical efficacy rate of 99.2% (2611/2631). The remaining 22 residual tumors were not retreated due to extensive tumor progression or loss to follow-up. In median 3 (range, 1–31) coaxial needles were used per tumor.

Univariable logistic regression analysis showed that age ($p < .018$), tumor size ($p < .001$), number of RF probes ($p < .001$), location close to the liver capsule ($p = .029$) or to hollow viscera ($p = .001$), or location in segment II ($p = .007$) were predictors of lower PTE. Non-critical intrahepatic location was associated with a higher PTE rate ($p = .003$).

In the significant model ($\chi^2 (7) = 49.681; p < .001$) of the multivariable analysis, tumor size ($p < .001$, Odds ratio [OR] $= 3.153$), location in segment II ($p = .042$, OR $= 1.772$) and age ($p = .043$, OR $= 1.559$), were found to be independent prognostic factors with significantly lower PTE rates.

An overview of the uni- and multi-variable logistic regression analyses of factors affecting PTE is shown in Table 2. ORs of the multivariable analysis are displayed as a forest plot in Figure 4.

### Local recurrence
Overall, LR occurred in 220 of 2653 tumors (8.3%). Of those, 78/220 (35.4%) were successfully retreated in an additional session, resulting in 2511/2653 (94.6%) completely ablated tumors in 1325 ablation sessions.

Univariable logistic regression analysis showed that age ($p = .008$), tumor type ICC ($p = .028$), tumor size $> 5$ cm ($p < .001$), close proximity to major vessels ($p < .001$) or central bile ducts ($p = .002$), tumor conglomerates ($p = .042$), location in segment I ($p = .001$), IVa ($p = .034$), IVb ($p < .001$) and number of RF probes ($p < .001$) were risk factors for LR. In contrast, central intrahepatic non-critical location ($p = .006$) was a protective factor.

In the significant model ($\chi^2 (14) = 64.881; p < .001$) of the multivariable analysis, tumor location near major vessels ($p = .008$, OR $= 1.653$), and in segment IVb ($p < .001$, OR $= 2.656$) proved to be independent prognostic factors with significantly higher rates of LR.

An overview of the uni- and multi-variable logistic regression analyses of factors affecting LR is shown in Table 3. ORs of the multivariable analysis are displayed as a forest plot in Figure 5.

### Technical improvements/learning curve
As a result of several technical improvements, an increase in experience and the aforementioned procedural modifications, PTE and LR rates significantly improved from 90.2% (322/357) to 97.2% (2230/2296) ($p < .001$) and 16.2% (58/357) to 7.1% (162/2296) with ($p < .001$), respectively, for procedures performed before and after January 2008.

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**Table 1.** Patient characteristics of 865 patients undergoing 1341 SRFA sessions for 2653 tumors.

| Patient characteristics | Value |
|-------------------------|-------|
| Age, years (range)      | 64.0 (3.0–88.0) |
| Sex (female/male), n (%)| 259/606 (29.9/70.1) |
| Tumor type, n (%)       | HCC, 422 (48.7); ICC, 35 (4.0); Metastasis, 408 (47.3); Colorectal, 221 (61.1); Other, 140 (39.9) |
| Cirrhosis, n (%)        | 373 (43.8) |
| Child A, n (%)          | 290 (76.5) |
| Child B, n (%)          | 82 (21.6) |
| Child C, n (%)          | 7 (1.8) |
| BCLC stage              | Stage 0, 50 (11.8); Stage A, 192 (45.5); Stage B, 165 (39.1); Stage C, 8 (1.9); Stage D, 7 (1.7) |
| Alpha-fetoprotein (ng/ml), median (range) | 7.9 (0.7–34,311) |
| Number of tumors at initial SRFA | n = 1, n (%) 475 (55.0); n = 2, n (%) 205 (23.7); n = 3, n (%) 89 (10.3); n > 3, n (%) 95 (11.0) |
| Tumor size at initial SRFA | < 3 cm, n (%) 421 (48.7); 3–5 cm, n (%) 294 (34.0); > 5 cm, n (%) 149 (17.2) |
| At initial SRFA         | Tumors, median (range) 1 (1–9); Tumor size, median (range) 3.0 cm (0.5–18.0) |
| Overall treated        | Tumors, median (range) 2 (1–29); Tumor size, median (range) 1.9 cm (0.5–19.0) |
| Number of ablations per patient | Median 1 (1–10) |
| Patients receiving LTX, n (%) | 120 (13.9) |

SRFA: stereotactic radiofrequency ablation; HCC: hepatocellular carcinoma; cRFA: conventional RFA; TACE: transarterial chemoembolization; TAME: transarterial mechanical embolization; HR: hepatic resection; PBC: primary biliary cirrhosis; BCLC: Barcelona Clinic Liver Cancer; HBV: hepatitis B virus; HCV: hepatitis C virus; LTX: liver transplantation

### Complications
Of 30-d mortality was 0.7% (9/1341 ablations) and major perioperative complication rate was 7.9% (106/1341 ablations). Four deaths occurred from major hemorrhage, two from acute liver failure on a background of advanced cirrhosis, two due to sepsis and one as a consequence of acute-on-chronic renal failure. The most common major complications were peri-/intra-hepatic hemorrhage in 34 (2.5%), major pleural effusion in 15 (1.1%), and pneumothorax in 17 (1.2%) patients – managed with angiographic coiling, thoracocentesis and chest tube insertion, respectively.
**Discussion**

This analysis of 2653 primary or metastatic liver tumors underlines the high level of local tumor control achievable using stereotactic RFA, with an overall PTE rate of 96.2% and overall secondary technical efficacy rate of 99.2%. These findings are further strengthened by the fact that more than

| Variables                              | Tumors | PTE (%) | Univariable analysis | Multivariable analysis |
|----------------------------------------|--------|---------|----------------------|------------------------|
| Age (>70/<70)                          | 1256/1397 | 95.3/97.1 | .018<sup>*</sup> | .043<sup>*</sup> | 1.559 | 1.015–2.396 |
| Sex (female/male)                      | 745/1908 | 97.2/95.9 | .110                 |            |            |            |
| Tumor type (HCC/ ICC/metastatic)       | 1139/147/ 1367 | 96.4/94.6/ | .865/ .311/Ref |            |            |            |
| Liver cirrhosis (+/-)                  | 961/1692 | 96.4/96.2 | .799                 |            |            |            |
| Tumor size (>5/<5 cm)                  | 262/2374 | 88.5/97.1 | <.001<sup>*</sup> | <.001<sup>*</sup> | 3.153 | 1.675–5.935 |
| No. RF probes                          |        |         |          |            |            |            |
| Location close to Diaphragm            | 321/2332 | 95.6/96.3 | .554               |            |            |            |
| Liver capsule                          | 847/1806 | 95.0/96.8 | .029<sup>*</sup> | .220       | 1.432 | 0.806–2.543 |
| Organ                                  | 254/2399 | 92.5/96.6 | .001<sup>*</sup> | .220       | 1.432 | 0.806–2.543 |
| Major vessel                           | 415/2238 | 96.1/96.2 | .921               |            |            |            |
| Central bile duct                      | 41/2612 | 97.6/96.2 | .655               |            |            |            |
| Gall bladder                           | 54/2599 | 94.4/96.3 | .490               |            |            |            |
| No-critical location                   | 850/1803 | 97.9/95.5 | .003<sup>*</sup> | .109       | 0.605 | 0.327–1.119 |
| Liver segments                         |        |         |          |            |            |            |
| Segment I                              | 88/2565 | 95.5/96.3 | .698               |            |            |            |
| Segment II                             | 302/2351 | 93.4/96.6 | .007<sup>*</sup> | .042<sup>*</sup> | 1.772 | 1.020–3.079 |
| Segment III                            | 255/2398 | 95.7/96.3 | .623               |            |            |            |
| Segment Iva                            | 214/2439 | 96.7/96.2 | .689               |            |            |            |
| Segment IVb                            | 126/2527 | 96.8/96.2 | .719               |            |            |            |
| Segment V                              | 330/2323 | 96.4/96.2 | .891               |            |            |            |
| Segment VI                             | 485/2168 | 96.1/96.3 | .851               |            |            |            |
| Segment VII                            | 624/2029 | 95.4/96.5 | .190               |            |            |            |
| Segment VIII                           | 636/2017 | 96.4/96.2 | .815               |            |            |            |

PTE: primary technical efficacy; CI: confidence interval; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; No: number; Ref: reference

Bold values marked with an asterisk are statistically significant.

![Forest plot of odds ratio of primary technical efficacy.](image-url)
50% of the tumors treated were larger than 3 cm in size, ranging up to 19 cm.

Whereas early RFA literature reported PTE rates exceeding 90% for small (i.e., <3 cm) HCCs and colorectal liver metastases (CRLMs) \[20–22\], these rates decreases dramatically for larger lesions, with 40–70% for medium HCCs (3–5 cm) \[23,24\] and 23–45% for large HCCs (>5 cm) \[24,25\]. Over the past decades, two main strategies have been developed to overcome the size limitations of single-probe ablations, namely to increase energy transfer to the tissue (i.e., heating).

### Table 3. Uni- and multi-variable logistic regression analyses of predictors for local recurrence (LR) after SRFA.

| Variables                              | Tumors | LR (%)     | Univariable analysis | Multivariable analysis |
|----------------------------------------|--------|------------|----------------------|------------------------|
| Age (>70/<70)                          |        | 9.8/6.9    | .008 *               | .077                   |
| Sex (female/male)                      |        | 8.3/8.3    | .972                 | –                      |
| Tumor type (HCC/ICC/metastatic)        |        | 7.0/14.3/  | .122/0.28/Ref*      | 0.836/1.413/Ref       |
|                                        |        | 8.7        |                      | 0.830–2.406/Ref       |
| Liver Cirrhosis (+/−)                  |        | 7.0/9.0    | .064                 | .786                   |
| Tumor size (>5/<5 cm)                  |        | 15.3/7.5   | <.001 *              | .114                   |
| No. RF probes                          |        | –          | <.001 *              | .329                   |
| Location close to                       |        | –          | –                    | –                      |
| Diaphragm                              |        | 10.6/8.0   | .112                 | –                      |
| Liver capsule                          |        | 9.0/8.0    | .384                 | –                      |
| Organ                                  |        | 11.0/8.0   | .099                 | .242                   |
| Major vessel                           |        | 14.5/7.1   | <.001 *              | .008 *                 |
| Central bile duct                      |        | 22.0/8.1   | .002 *               | .215                   |
| Gall bladder                           |        | 11.1/8.2   | .450                 | –                      |
| Non-critical location                  |        | 6.1/9.3    | .006 *               | .436                   |
| Liver segments                         |        | 22.2/8.2   | .042                 | .145                   |
| Segment I                              |        | 18.2/8.0   | .001 *               | .193                   |
| Segment II                             |        | 7.0/8.5    | .371                 | –                      |
| Segment III                            |        | 7.5/8.4    | .680                 | –                      |
| Segment Iva                            |        | 12.1/8.0   | .034 *               | .744                   |
| Segment IVb                            |        | 19.0/7.8   | <.001 *              | 2.656                  |
| Segment V                              |        | 7.9/8.4    | .771                 | –                      |
| Segment VI                             |        | 7.8/8.4    | .686                 | –                      |
| Segment VII                            |        | 9.8/7.8    | .125                 | –                      |
| Segment VIII                           |        | 9.4/7.9    | .232                 | –                      |

PTE: primary technical efficacy; CI: confidence interval; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; No: number; Ref: reference

Bold values marked with an asterisk are statistically significant.

![Figure 5. Forest plot of odds ratio of LR.](image-url)
using microwave energy or by using multiple RF probes. Microwave ablation (MWA) creates larger ablation zones in a shorter time and is less susceptible to heat sink effects [26]. However, its higher thermal efficiency may lead to more severe damage of vulnerable structures and/or create undesirably large ablation zones with consecutive destruction of an unnecessary amount of healthy liver tissue [27]. Due to the lower energy transfer associated with RFA, multi-probe RFA is more predictable. Nevertheless, the higher number of applicators considerably increases the complexity and difficulty of the procedure and demands a high level of operator experience. Supporting these developments, more recent studies have shown higher PTE rates up to 86–97% for medium and large HCCs (< 10 cm) adopting a multi-probe approach [10,28,29].

In this study, tumor size was an independent predictor of PTE with significantly lower rates in lesions > 5 cm (88.5 vs. 97.1%). We mainly attribute this observation to the fact, that in our institution ablations of very large lesions are often a-priori planned in more than one ablation session, resulting in an artificially lower PTE rate in this subgroup. Nonetheless, the PTE results in this study are still considerably higher than in previously published literature for ‘freehand’ guided multiple-probe RFA or MWA [10,28,29]. Other independent predictors for PTE were location in segment II and patients older 70 years. Since segment II tumors tend to abut stomach, diaphragm or heart, they are often undertreated because of fear of thermal damage at site. On the other hand, we did not find a significant impact of segment II on LR, meaning retreatment usually resulted in sufficient local tumor control. The reason for poorer success rates in older patients could reflect a tendency for a more conservative approach taken by the internationalist, although we did not find any technical explanations for this result.

The technique of SRFA offers three-dimensional ablation planning for optimal alignment of RF probes to achieve overlapping coagulation volumes and the combination with an aiming device facilitates precise path alignment and targeting [30]. In a histopathological validation study in explanted livers of patients treated with SRFA for bridging therapy [31], the authors did not find any residual viable tumor tissue in 98.9% of all HCCs (186/188), and 96.2% (50/52) for lesions > 3 cm. This observation is in line with this study. In fact, LR occurred in 8.3% of the lesions, which compares favorably to previous results of conventional RFA, reporting LR rates ranging from 15.7 to 20.9% for small/medium HCC and 40% for CRLMs [32–35]. Encouragingly, the results of this study approach the recurrence rates reported for HR of 4.6% [36] and 4% [37] for HCC and CRLM, respectively. Tumor size was a predictor of LR in the univariable analysis, but could not be confirmed as an independent predictor in the multivariable model ($p = .103$). However, even though LR rates for tumors > 5 cm were significantly higher at 15.3% (vs. 7.5% for tumors < 5 cm), the results in this study are still considerably better compared to those of conventional US- and CT-guided single probe RFA for large liver malignancies with rates ranging from 58.1 to 68% [35,38]. The importance of technological advances, such as MWA or multi-probe RFA, has also been underlined by other, more recent studies with LR rates of 15.9–19.7% in larger liver malignancies [28,29,39].

Tumor type, or more precisely biology, can affect local control and consequently survival where reported local control rates of RFA for lesions larger than 3 cm are poor [40]. In addition to tumor biology, the visibility of the tumor borders also differs with tumor type. This often leads to undertreatment, emphasizing the importance of an adequate treatment margin. As such, CRLMs tend to require a larger safety margin of 10 mm [41], whereas a safety margin of 5 mm seems sufficient for HCCs [6]. However, in this analysis tumor type did not independently impact on PTE nor on LR. The reason for this could be the precision targeting and predictable ablation area (including an adequate safety margin) achievable using SRFA. Nonetheless, LR was shown to differ significantly between HCC, ICC and metastases in the univariable analysis, which might be explained by tumor biology.

Early investigations [42,43] reported higher LR rates for subcapsularly located tumors, which was attributed to undertreatment for fear of risking thermal damage to adjacent structures or causing liver capsule pain. However, in this analysis subcapsular location had no impact on LR ($p = .384$). On the other hand, location close to major vessels, central bile ducts, conglomerates or location in segment I, IVa and IVb were significant predictors at univariable analysis. However, at multivariable analysis only location close to major vessels and location in segment IVb maintained statistical significance. The increase of LR rates for tumors near major vessels is likely to be due to the ‘heat sink’ effect, being a well-known drawback of RFA due to passive heat conduction [44,45]. Location in segment IVb may be the result of undertreatment of tumors close to the central biliary or vascular structures. For this reason, RFA close to the central bile ducts is considered a relative contraindication by most authors [46,47], although prophylactic cooling of the central bile duct during ablation using chilled saline could reduce thermal injury [47].

In this analysis, we observed a significant improvement regarding PTE and LR rates for lesions treated before/after January 2008. This improvement is attributed to better patient/case selection, increasing operator experience, and important procedural refinements. More specifically, we began to exclude tumors near central biliary structures and distributed coaxial needles around the target tumor with a ‘no touch’ or ‘partial touch’ technique, instead of central placement. This change in electrode configuration leads to disruption of the blood supply surrounding tumors, whilst avoiding collateral damage to vulnerable structures.

In the early years of our SRFA program, an ablation was considered successful if the tumor was completely covered by the ablation zone (i.e., technical success). However, we substantially changed approach and modified the planning accordingly to include a safety margin of at least 5 mm [48], a standard practice for surgical resection, in order to predict technique efficacy. A further decisive improvement was the introduction of an immediate, post-interventional image fusion of pre- and post-interventional CT-scans, enabling a more accurate and faster assessment of the safety margin.
and consecutively the ablation results. In fact, the assessment of the safety margin in side-by-side juxtaposition and ‘cognitive’ image fusion is error-prone and very time-consuming [49]. Furthermore, where target tumors are poorly visualized on CT, the navigation systems’ software can fuse MR images with planning CT data to enable precise trajectory planning and ablation zone coverage [50].

Major limitations of our study lie in its retrospective design, a heterogeneous patient cohort, and a single-center bias. However, the comparison of our results with similar studies is hampered and the results are unlikely to be highly generalizable since stereotactic approaches for thermal ablation of liver malignancies is adopted only by few centers. Thus, we hope this study changes that, helping to aid further interest in this technique.

In conclusion, SRFA is an effective treatment option for primary and metastatic liver malignancies with good local tumor control, even in large and unfavorably located tumors. The presented prognostic factors for adverse local oncological outcome might help to stratify tumors that are less suitable for ablation. Adaptations over time with increasing experience have led to significantly improved local oncological outcome.

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