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NEW TECHNOLOGY

Laparoscopic image-based navigation for microwave ablation of liver tumors—A multi-center study

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Abstract

Background Stereotactic navigation technology has been proposed to augment accuracy in targeting intrahepatic lesions for local ablation therapy. This retrospective study evaluated accuracy, efficacy, and safety when using laparoscopic image-guided microwave ablation (LIMA) for malignant liver tumors.

Methods All patients treated for malignant liver lesions using LIMA at two European centers between 2013 and 2015 were included for analysis. A landmark-based registration technique was applied for intraoperative tumor localization and positioning of ablation probes. Intraoperative efficiency of the procedure was measured as number of registration attempts and time needed to achieve sufficient registration accuracy. Technical accuracy was assessed as Fiducial Registration Error (FRE). Outcome at 90 days including mortality, postoperative morbidity, rates of incomplete ablations, and early intrahepatic recurrences were reported.

Results In 34 months, 54 interventions were performed comprising a total of 346 lesions (median lesions per patient 3 (1–25)). Eleven patients had concomitant laparoscopic resections of the liver or the colorectal primary tumor. Median time for registration was 4:38 min (0:26–19:34). Average FRE was 8.1 ± 2.8 mm. Follow-up at 90 days showed one death, 24% grade I/II, and 4% grade IIIa complications. Median length of hospital stay was 2 days (1–11). Early local recurrence was 9% per lesion and 32% per patient. Of these, 63% were successfully re-ablated within 6 months.

Conclusions LIMA does not interfere with the intraoperative workflow and results in low complication and early local recurrence rates, even when simultaneously targeting multiple lesions. LIMA may represent a valid therapy option for patients with extensive hepatic disease within a multimodal treatment approach.

Keyword Liver · Ablation · Image-guided surgery · Surgical navigation · Laparoscopy · Minimal invasive surgery

For patients with hepatocellular carcinoma (HCC) and colorectal liver metastases (CRLM), surgical resection remains the standard of care in a curative treatment setting [1, 2]. However, resection of primary and secondary liver malignancies is only feasible in a minority of patients due to advanced liver disease, intrahepatic tumor distribution, or concurrent medical conditions [3]. Local ablation strategies have evolved in the last decades, providing hope of cure for patients with unresectable liver tumors, and are frequently used in combination with or as an alternative to

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The original version of this article was revised: The subtitle “Laparoscopic navigation for hepatic ablation” is an error and must be deleted. The Given Names and Family Names were inverted. The correct order is: Pascale Tinguely, Matteo Fusaglia, Jacob Freedman, Vanessa Banz, Stefan Weber, Daniel Candinas and Henrik Nilsson.

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surgical resection [4, 5]. More recent data supporting the use of ablative strategies as a valid alternative to resection for small HCC are available [6]. For CRLM, local ablation is currently mostly used for non-resectable lesions in liver-only or liver-predominant disease [7, 8]. Furthermore, patients with advanced age and concomitant comorbidities are increasingly put forward for treatments with a curative intent. This patient population may particularly profit from the combination of a locally effective, minimal invasive and tissue-sparing intervention, and repeat therapy sessions are well tolerated in case of hepatic recurrence [9, 10].

In order to ensure adequate tumor targeting and thus local tumor control with ablation, two important aspects remain of relevance during surgery. Firstly, optimal intraoperative localization and visualization of the intrahepatic lesions are required. However, the use of intraoperative ultrasound—the standard of care in most institutions—has its limitations. This is particularly true for livers with altered parenchyma, e.g., after extensive neoadjuvant chemotherapy or in the setting of liver steatosis or cirrhosis [11, 12]. Furthermore, image quality is reduced as a result of post-ablation heat artifacts and renders the treatment of multiple lesions located within the same region difficult. Secondly, precise placement of the ablation probe in the tumor center is essential [13]. Ultrasound-guided probe placement in the intraoperative setting, in which both the ablation probe and the actual lesion must be displayed in one image plane, is challenging and requires considerable experience [14].

In a laparoscopic setting, additional challenges with respect to precise placement of the ablation probes arise. Apart from the lack of haptic feedback when guiding the ablation probe, limited trajectories especially to superior and posterior liver segments render precise probe placement more difficult.

Stereotactic image guidance has been proposed to overcome the present limitations in localization and targeting of intrahepatic tumors. The main goal is to improve the sensitivity of intraoperative tumor localization and to improve precision in tumor targeting [15]. The use of stereotactic navigation in solid organs such as the liver was first proposed in the late 1990s [16]. To date, several advanced navigation systems have been introduced [17, 18] and have successfully been applied and validated in open liver surgery [19, 20]. Technology has further evolved and the first navigation systems specifically developed for the use in a laparoscopic setting have become available [20, 21]. While technical analyses on laparoscopic navigation have been widely presented on phantoms and ex vivo [22–25], only few data reporting clinical outcome are available to date [20, 26, 27].

Based on our preliminary work in an open surgical setting [19], we hypothesize that laparoscopic image-guided microwave ablation (LIMA) is an accurate and efficient approach for patients with malignant liver lesions. In a first step, we report on the technical accuracy, efficacy—measured as the interference with the intraoperative workflow—as well as on overall safety when using LIMA for the treatment of malignant liver tumors.

Materials and methods

Between January 2013 and October 2015, all patients treated with LIMA for malignant liver tumors at two European HPB centers (Department of Visceral Surgery, Inselspital Bern, Switzerland and the Department of Surgery and Urology, Danderyd Hospital Stockholm, Sweden) were included in this retrospective analysis. The study protocol was approved by the Regional Ethical Review Boards in Bern (KEK-Nr. 234/15) and in Stockholm (Dnr 2016/603-31).

Patient population

In both centers, stereotactic image guidance (CAS-ONE, CAScination AG, Bern, Switzerland) and microwave ablation (Acculis MTA System, AngioDynamics, Latham, NY, USA) were used as a standard of care for all patients in whom laparoscopic ablative treatment of liver tumors was agreed upon at the local multidisciplinary tumor board.

Laparoscopic ablation was applied in the cases where a percutaneous CT- or ultrasound-guided procedure was precluded, due to the following reasons:

- The need for additional diagnostic laparoscopy
- Lesions located in the proximity of organs prone to thermal injury during ablation (stomach, gallbladder or colon)
- Multiple lesions (>3–5), where a percutaneous approach would have been too time-consuming
- Simultaneous laparoscopic resection of the primary tumor
- Combined liver resection and ablation strategies

Selection criteria for LIMA are presented in Table 1.

Pre-surgical planning and intraoperative set-up

Prior to surgery, 3D reconstructions of the patient's liver based on preoperative CT or MRT scans were obtained (MeVis Distant Service AG, Bremen, Germany). Generally, the most recent images (no older than 3 months) were used for 3D reconstruction. In patients with vanishing lesions, the virtual model was created by fusion of anatomy

Table 1 Patient selection criteria

CRLM[a]

Patients with both (A) and (B)
- (A) Non-resectable lesions, due to
    - -Patient comorbidity and/or
    - -Insufficient functioning liver remnant due to
        - -Number of lesions and/or
        - -Distribution of lesions and/or
        - -Quality of the underlying liver parenchyma
- (B) Deemed appropriate for curative-intent treatment due to
    - -Adequate response to chemotherapy and/or
    - -Qualification for multimodal treatment approach

Patients with "vanishing" lesions (complete radiological response to neoadjuvant chemotherapy)

Patients with synchronous CRLM undergoing simultaneous laparoscopic resection of the primary tumor

Patients with a planned two-staged hepatectomy

HCC[b]

BCLC Stage 0/A, including patients listed for liver transplantation (bridging/downstaging concept)

BCLC Stage B (lesions 3–5 cm)

NET[c] **metastases**

Debulking procedures for symptomatic disease

[a] Colorectal liver metastases

[b] Hepatocellular Carcinoma

[c] Neuroendocrine Tumor

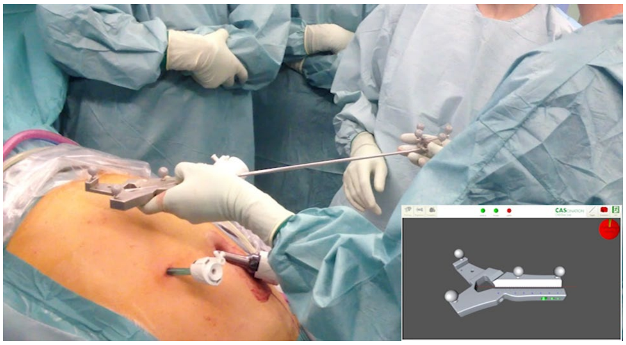

Fig. 1 Calibration of the laparoscopic pointer, using a calibration tool indicated at the *bottom right*

information from earlier images, where the lesions were still visible, with latest available image sets. The 3D image data were then uploaded to the navigation system for use in the intraoperative navigation process.

For surgery, patients were placed in a supine position when targeting lesions located in the left liver and the right anterior segments. For lesions located in segments VI and VII, a partial left lateral position was preferred. The navigation system was placed at the patient's head, allowing for an optimal overview over the surgical field by the infrared camera. Surgical instruments used for navigation were fitted with optically trackable infrared markers and calibrated using a custom-made calibration tool (Fig. 1).

Surgical and navigation technique

Intraperitoneal pressure was kept at 10–12 mmHg during the whole procedure. Mobilization of the liver mainly included transection of the round and falciform ligament up to the hepatic veins, in order to allow access for the laparoscopic pointer for registration. Further liver mobilization was kept to a minimum in order to prevent alterations in liver shape, which might cause impairment of registration accuracy.

A rigid four-landmark-based registration technique was applied, using a previously described algorithm [17]. After selecting four landmarks on the liver surface and/or on major vessel bifurcations on the 3D image model, corresponding points were chosen on the actual liver using an optically tracked and calibrated laparoscopic pointer (Fig. 2).

Typical anatomical landmarks included the groove between the right and middle hepatic vein close to the inferior vena cava, the rim of the round ligament, the main portal vein bifurcation, the groove near the gallbladder tip as well as visible subcapsular tumors, if present.

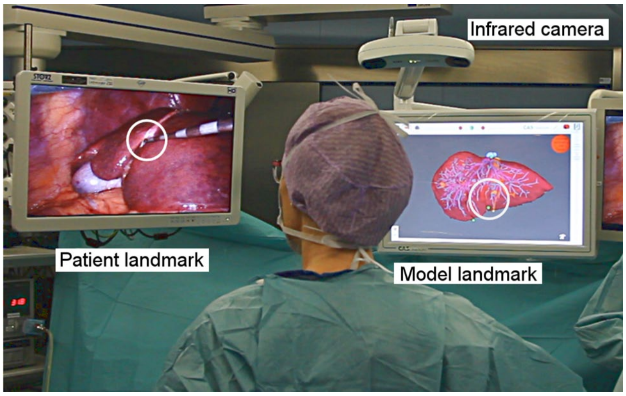

Fig. 2 Registration process showing patient and model landmarks on both screens. The infrared camera overlooks the surgical site, tracking instruments in space

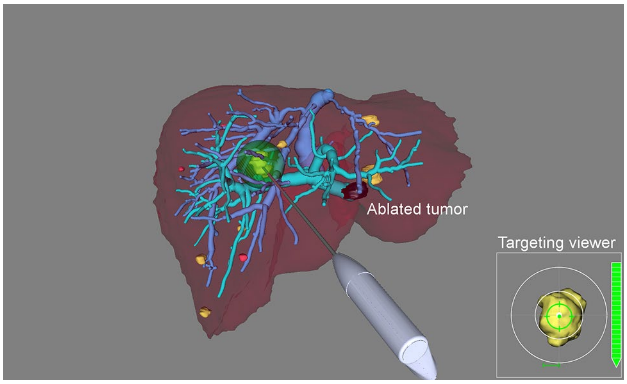

Fig. 3 Navigated placement of the ablation antenna using the targeting viewer on the *bottom right*. A simulation of the ablation zone is shown at the tip of the probe

After registering four anatomical landmarks, accuracy of the registration process was assessed as Fiducial Registration Error (FRE), combined with visual inspection of a correct overlay of tracked instruments on the preoperative liver model. An FRE <10 mm combined with adequate accuracy on visual inspection (indicating acceptable correspondence of the intraoperative liver position with the computed 3D model) was considered acceptable for navigated placement of ablation probes. Otherwise, the registration process was repeated until adequate registration accuracy was reached.

Subsequently, ablation probes were inserted through a separate skin incision and navigated towards the tumor center using a specific targeting viewer (Fig. 3). An additional percutaneous trocar was applied to avoid bending when long ablation probes (>20 cm) were required. Intratumoral placement of the ablation probe was confirmed by intraoperative ultrasound if possible.

Microwave ablation was performed using lesion-specific settings of energy and time. Based on the assessment using intraoperative ultrasound, repeat ablations were performed, if necessary. For tumors >3 cm, multiple parallel needle repositioning procedures were used for creating overlapping ablation zones. For additional hemostasis and to prevent tumor seeding, needle track ablation was systematically performed.

All surgeries were carried out by one of three surgeons (PT, JF, HN).

Data extraction and analysis

As a general measure of the image guidance process, registration accuracy was assessed as FRE. As a measure of intraoperative efficacy, the number of registration attempts and time spent on intraoperative calibration and registration were recorded. Safety of the procedure was assessed as 90-day morbidity and mortality, including all complications arising within this time frame. Complications were graded according to the Dindo-Clavien classification [28]. Follow-up imaging was carried out 90 days post-treatment by CT and/or MR imaging and interpreted by an independent radiologist. Early local recurrence was defined as the presence of tumor (persistent contrast enhancement patterns) within 10 mm from the edge of the ablation zone, representing incomplete ablation or early recurrence at the site of ablation. The appearance of new intrahepatic lesions was documented.

Demographical, procedural and follow-up data were extracted from patient records. Lesion size, measured as largest diameter in 3D, lesion volumes, and segmental location (Couinaud's segments I–VIII) were extracted from available 3D image datasets. All technical data were recorded prospectively and later extracted from the navigation system's log file.

Statistics

Descriptive statistics were used for presentation of patient characteristics and outcome data. Continuous data are shown as mean and standard deviation or median and range, where appropriate. Linear regression analysis was applied to estimate correlations. Fisher's exact test was used to evaluate possible differences between proportions. The threshold for statistical significance was set to $\alpha = 0.05$. STATA 14 (StataCorp, College Station, Texas 77845 USA) and GraphPad Prism V 6.0 (GraphPad Software, Inc., La Jolla, CA, USA) were used for all statistical analyses.

Results

Overall, 51 patients underwent a total of 54 LIMA procedures (one patient required two, one patient three interventions at a later date). During these interventions, a total of 346 tumors were targeted for ablation. Twenty-eight (52%) patients were ablated for CRLM, 22 (41%) patients for HCC lesions, two patients for hepatic metastases of neuroendocrine tumor (NET), one patient for melanoma, and one patient for a carcinoma of the adrenal gland. The median number of ablated tumors per patient was three (range 1–25), and average lesion size and tumor volume were 16.7 ± 9.8 mm and 1.8 ± 3.7 ml, respectively. Hepatic lesions were distributed across all the liver segments.

Relevant patient and tumor characteristics are summarized in Table 2.

Eleven patients had simultaneous laparoscopic resections of either liver lesions (atypical or segmental resections, $n=4$), or of the colorectal primary tumor ($n=7$). In seven patients, clearance of one hepatic lobe or section was performed within a planned two-staged approach. Ablation of vanishing lesions was performed in 7/28 (25%) of patients treated for CRLM.

Table 2 Patient and lesion characteristics

Age, years	63.3 ± 9.3
Gender (*m/f*), *n* (%)	28/23 (55/45)
ASA score, *n* (%)	
1	2 (4)
2	21 (41)
3	21 (41)
4	7 (14)
Lesion origin, *n* (%), [total *n* of lesions]	
HCC	28 (52), [41]
Colorectal	22 (41), [267]
Neuroendocrine	2 (4), [32]
Other	2 (4), [6]
No. of lesions per patient	3 [1–25]
Lesion size (largest diameter in 3D, mm)	16.7 ± 9.8 [4.9–56.5]
Segmental location of lesions, *n* (%)	
Seg I	8 (2)
Seg II/III	95 (28)
Seg IVa/b	60 (17)
Seg V	39 (11)
Seg VI	38 (11)
Seg VII	31 (10)
Seg VIII	75 (22)

Categorical data are shown as number and percentage, continuous data are shown as mean ± standard deviation or median [range]

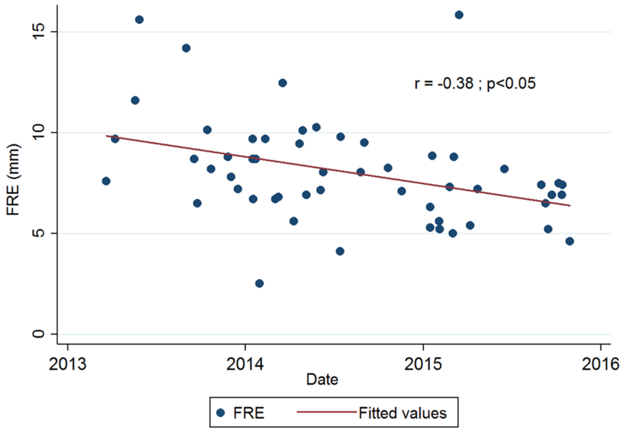

Fig. 4 Evolution of registration accuracy over time, expressed as Fiducial Registration Error (FRE, in millimeters)

Technical accuracy and intraoperative efficacy

Registration was completed successfully in all patients. The average FRE was measured as 8.1 (± SD 2.8) millimeters. Registration accuracy improved significantly over time ($r=-0.38$, $p<0.05$, Fig. 4).

Median time between acquisition of preoperative CT or MR images with generated 3D reconstructions and surgery was 25 (range 7–135) days. No correlation between registration accuracy and the time between 3D reconstruction and surgery was shown ($r=-0.02$, $p=0.90$).

During surgery, a median of 2 (range 1–10) registration attempts were needed in order to acquire an adequate registration, requiring a median time of 04:38 (range 00:26–19:34) min per registration. Median time for intraoperative calibration of surgical instruments was 01:10 (range 00:12–03:38) min. Mean overall operating time was 131 ± 94 min, and median length of hospital stay (LOS) was 2 (range 1–11) days. In the LIMA-only group without concomitant hepatic or colonic resections ($n=40$), mean operating time was 102 ± 64 min, and LOS was 1 (range 1–7) day.

Perioperative morbidity and mortality

At a 90-day follow-up, all patients who had LIMA without concomitant hepatic or colonic resection ($n=40$) were alive. One patient with combined LIMA and colon resection developed a hepatorenal syndrome 2 months post-surgery and consequently died.

The overall 90-day complication rate was 28% (15/54). Six patients (11%) showed a grade I complication. These consisted of two patients with accentuated postoperative pain requiring readmission 4 and 14 days post-surgery, respectively, two patients with ascites leak from the port site and one patient with a combined port site bleeding and cardiac decompensation, requiring diuretics and inhalations. Seven patients (13%) developed a grade II complication. Five patients required antibiotic treatment for either urinary tract infection ($n = 2$), fever of unknown origin ($n = 2$) or wound infection ($n = 1$). One patient developed partial thrombosis of the left portal vein treated with low molecular weight heparin, and one patient required transfusion due to a perihepatic hematoma. Two patients (4%), developed a grade IIIa complication, both requiring drainage of an intrahepatic abscess with additional drainage of a pleural effusion in one patient. Both patients with a grade IIIa complication were ablated for large lesions (39 and 42 mm), located centrally within segment VIII.

Conversion to open surgery was necessary in one patient due to limited laparoscopic access to lesions located in the right posterior segments.

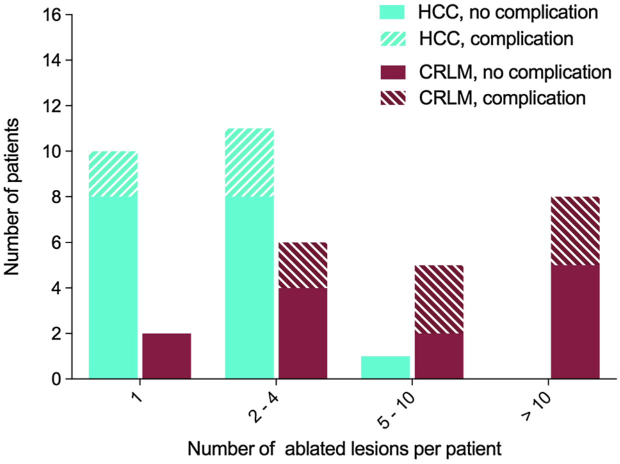

Fig. 5 Clinical complications according to number of ablated lesions per patient and tumor entity

There was no statistically increased risk of complications in the setting of multiple simultaneous ablations, independent of lesion origin (overall $p = 1.00$, subgroup analysis for HCC $p = 1.00$, for CRLM $p = 0.94$). Tumor entity also did not influence complication rates ($p = 0.37$), as shown in Fig. 5. In the group of patients in whom ≥20 CRLM lesions were ablated ($n = 5$), one patient developed a minor complication (perihepatic hematoma).

The main technical and clinical efficay and safety data are summarized in Table 3.

Early local recurrence

The overall rate of early local recurrence per lesion was 9.3% (30/322) at a 90-day follow-up. One patient with 24 ablated lesions was excluded from 90-day analysis due to death 2 months postoperatively. Early local recurrence occurred in 8% (20/243) of ablated CRLM and 20% (8/41) of ablated HCC lesions.

Per patient, early local recurrence rate was 32% (16/50). Out of these patients, ten (63%) underwent successful re-ablation within 6 months, mostly consisting of percutaneous MWA. Four patients went on to a palliative treatment due to diffuse intrahepatic progression (Fig. 6).

Ablated vanishing lesions showed a local recurrence rate of 7.8% (4/51) per lesion and 29% (2/7) per patient. Five patients with ablation of ≥20 lesions per patient showed early local recurrences in 8% (9/110) of ablated tumors, with a median of 1 (range 0–5) early local recurrences per patient.

Six patients with simultaneous LIMA and resection of the colorectal primary tumor showed early local recurrences in 7% (5/68) of ablated lesions.

Out of all included patients, 16 (32%) developed new intrahepatic lesions within 90 days. In the 16 patients with

Table 3 Intraoperative efficacy and overall safety

FRE (mm)	8.1 ± 2.8
No. of registration attempts	2 [1–10]
Time per registration (min)	04:38 [00:26–19:34]
Time for instrument calibration (min)	01:10 (00:12–03:38)
Time between 3D image reconstruction and surgery (days)	25 [7–135]
Duration of surgery (min)	131 ± 94
Length of hospital stay (days)	2 [1–11]
Clinical complications within 90 days, *n* (%)	
Grade I	6 (11)
Grade II	7 (13)
Grade IIIa	2 (4)
Grade IIIb/IV	0
Mortality	1 (2)

Categorical data are shown as number and percentage, continuous data are shown as mean ± standard deviation or median [range]

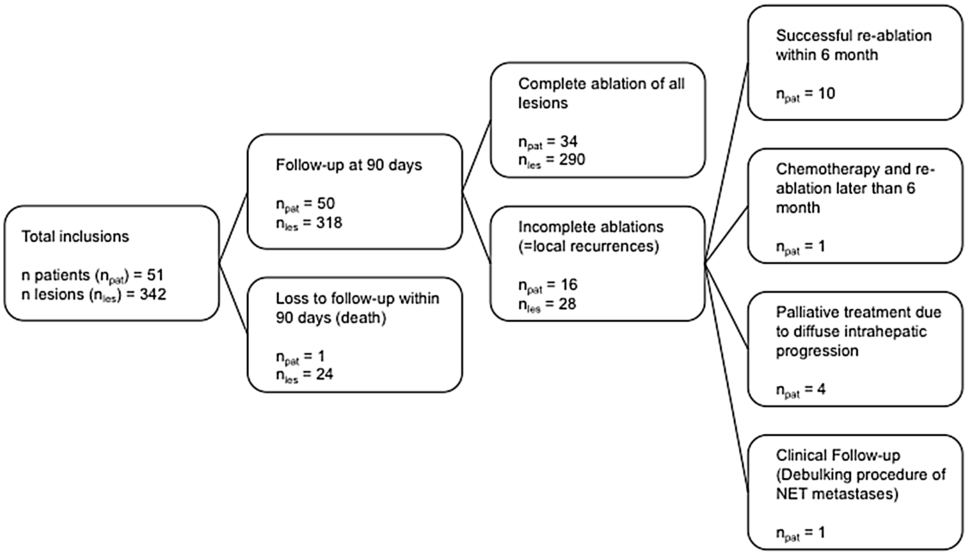

Fig. 6 Treatment of patients with local recurrences detected at a 90-day follow-up

local recurrences, nine (56%) showed concurrent occurrence of new intrahepatic lesions.

Discussion

This work confirms technical accuracy, intraoperative efficacy, and safety of using novel laparoscopic navigation technology for ablation of liver tumors. To our knowledge, this is currently the largest clinical series of patients who underwent laparoscopic ablation of malignant liver disease using image-guided navigation.

Local ablation therapy as an adjunct or an alternative to resection for the treatment of malignant liver lesions has gained importance over the last years, mainly due to its tissue-sparing nature and applicability in a minimal invasive setting. With only 10–20% of patients with malignant liver lesions being amenable to surgical resection, ablation represents a promising alternative and/or adjunct within a multimodal approach to improve survival in these patients [29, 30]. For treatment of CRLM, recent works underline the efficiency and oncological benefits of such a multimodal approach for patients with hepatic lesions initially deemed unresectable [9, 31, 32]. Philips et al. [33] recently validated the use of MWA with or without comcomitant resection in patients with bilobar unresectable CRLM, showing comparable survival in both patient groups, similar to that following two-stage hepatectomy.

Our results validate LIMA as a safe treatment option for patients with malignant liver tumors, with an acceptable morbidity (87% of all complications being minor complications and only two patients developing liver-specific complications) and with very low mortality (zero mortality in ablation-only patients). Complication rates are similar to other series reporting morbidity after laparoscopic microwave ablation, ranging from 11 to 60% [34–36], although few studies define subgroups according to the severity of complications. Interestingly, there was no correlation between the number of lesions ablated and the risk of postoperative complications. We included five patients with extensive bilobar CRLM (≥20 lesions/patient). In all five settings, patients had responded well to chemotherapy and thus remained in a curative-intent treatment strategy, despite the presence of multiple lesions. In these five patients, a maximum of five local recurrences occurred, with one patient presenting no local recurrence at any of the 21 ablation sites.

While our overall early local recurrence rate of 9% after MWA compare to the current literature [36, 37], the majority of patients treated in our study were patients otherwise not amenable to any other form of potentially curative treatment. Several studies report local recurrence rates as low as <1% after laparoscopic MWA [38]. However, definition of local recurrence and the time-point of assessment are often unclear. Furthermore and contrary to others, we did not differ in the definition of incomplete ablation and early local recurrence, as a precise distinction in an early follow-up after ablation is generally difficult. Without doubt, we included patients with very high numbers of lesions, with lesion sizes up to 57 mm and difficult to target intrahepatic locations. However and more importantly, 63% of patients with local tumor recurrence benefitted from a repeat ablation within 6 months of the initial treatment, resulting in a complete tumor control in these patients.

This treatment approach, involving multiple repeat ablations in patients with multiple bilobar CRLM, has previously been shown to be advantageous for these patients with extensive tumor burden, resulting in a long-term survival benefit [9, 33]. According to liver-first strategies [39–41], the aim of these multimodal and consecutive treatment strategies is to remove >80% of tumors with the possibility of addressing the remaining lesions by further liver-directed therapies, resection, or chemotherapy. In this context, LIMA potentially opens up options for the treatment of patients with more extensive tumor burden and allows an efficient treatment of a multitude of tumors. This is particularly the case in patients where a percutaneous approach would be too time-consuming or when the primary colorectal tumor is simultaneously resected. While the combined approach of simultaneous hepatic and colorectal resection in these latter cases has been validated [42–44], patients in whom resection is precluded may particularly benefit from an efficient clearance of hepatic tumor load, while keeping the amount of tissue trauma to a minimum. In this series, acceptable morbidity and early local recurrence rates were shown in this subgroup of patients (mortality 1/6, no major complications, early local recurrence 7% of ablated lesions), further underlining safety of LIMA in these patients.

As optimal intraoperative guidance and precise placement of ablation probes is essential for a successful ablation therapy, the study of usability and efficacy of novel guidance technology in this context becomes mandatory. However, to show true superiority when applying novel navigation technology over the standard intraoperative image guidance techniques (such as ultrasound) is as important as it is challenging. As an initial step, we here describe intraoperative efficacy in terms of usability, as the utilization of image guidance is known to come at the cost of additional intraoperative procedural efforts. This has been a barrier to the application of navigation technology in liver surgery on a broad scale. When using LIMA, the main step potentially disrupting normal intraoperative workflow is the registration process itself. Additional time spent for registration was around 10 min per patient (04:38 min per registration with two attempts per patient), and additional time for instrument calibration was 01:10 min. In the light of an average overall procedural time of 131 min, this additional 8% seems to be acceptable and might be compensated during the targeting phase of the procedure, where multiple tumors can efficiently be treated using few different registrations.

Another frequently mentioned limitation when applying registration-based navigation in soft-tissue surgery is the potential alteration in liver morphology. This might arise due to changes in liver size and/or shape over time or due to intraoperative manipulation of the liver, eventually impairing registration accuracy. Surprisingly, no correlation between the time lapse between acquisition of preoperative reference images and registration accuracy was found in our analysis. This further underlines accuracy and usability of LIMA, without relevant additional preoperative efforts such as additional imaging or specific changes in surgical time schedules.

Average FRE values of 8.1 ± 2.8 mm reached in the present study lie within the range of accuracy levels (5–10 mm) considered acceptable for ablations in the literature [20, 38], and correspond to values from navigated ablations in open liver surgery [17, 19]. Furthermore, a significant improvement in registration accuracy was evident over time, suggesting a relatively steep learning curve when using the navigation system for registration. While FRE is non-conclusive with respect to the effective targeting accuracy [45], it remains the only readily available surrogate and was used as general parameter of the available registration accuracy.

In conclusion, LIMA does not interfere with the intraoperative workflow and results in low complication and early local recurrence rates, even when simultaneously targeting multiple lesions. LIMA may represent an efficient treatment option for patients with extensive hepatic disease or difficult to target lesions. This might be beneficial for patients treated within a multimodal approach and might ultimately increase patient eligibility for curative-intent treatment.

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Compliance with ethical standards

Disclosures Drs. Stefan Weber and Daniel Candinas report grants from CTI and from Eurostars-Eureka during the conduct of the study and are co-founders and shareholders in CAScination AG, manufacturer of the navigation technology under investigation in this study. Drs. Pascale Tinguely, Matteo Fusaglia, Jacob Freedman, Vanessa Banz and Henrik Nilsson have no conflicts of interest or financial ties to disclose.

References

1. Llovet JM, Schwartz M, Mazzaferro V (2005) Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 25:181–200. doi:10.1055/s-2005-871198
2. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M (2006) Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 94:982–999. doi:10.1038/sj.bjc.6603033
3. Adam R, Vinet E (2004) Regional treatment of metastasis: surgery of colorectal liver metastases. Ann Oncol Off J Eur Soc Med Oncol 15(Suppl 4):103–106. doi:10.1093/annonc/mdh912
4. Lencioni R, de Baere T, Martin RC, Nutting CW, Narayanan G (2015) Image-guided ablation of malignant liver tumors: recommendations for clinical validation of novel thermal and non-thermal technologies- a western perspective. Liver Cancer 4:208–214. doi:10.1159/000367747

5. de Jong KP, Wertenbroek MWJLAE (2011) Liver resection combined with local ablation: where are the limits? Dig Surg 28:127–133. doi:10.1159/000323823
6. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, Rossi S (2008) Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology 47:82–89. doi:10.1002/hep.21933
7. Mahnken AH, Pereira PL, de Baère T (2013) Interventional oncologic approaches to liver metastases. Radiology 266:407–430. doi:10.1148/radiol.12112544
8. Pathak S, Jones R, Tang JMF, Parmar C, Fenwick S, Malik H, Poston G (2011) Ablative therapies for colorectal liver metastases: a systematic review. Colorectal Dis 13:e252–e265. doi:10.1111/j.1463-1318.2011.02695.x
9. Engstrand J, Nilsson H, Jansson A, Isaksson B, Freedman J, Lundell L, Jonas E (2014) A multiple microwave ablation strategy in patients with initially unresectable colorectal cancer liver metastases- a safety and feasibility study of a new concept. Eur J Surg Oncol 40:1488–1493. doi:10.1016/j.ejso.2014.05.003
10. Mise Y, Aloia TA, Brudvik KW, Schwarz L, Vauthey J-N, Conrad C (2016) Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. Ann Surg 263:146–152. doi:10.1097/SLA.0000000000001194
11. van Vledder MG, Torbenson MS, Pawlik TM, Boctor EM, Hamper UM, Olino K, Choti M a (2010) The effect of steatosis on echogenicity of colorectal liver metastases on intraoperative ultrasonography. Arch Surg 145:661–667. doi:10.1001/archsurg.2010.124
12. Irshad A, Anis M, Ackerman SJ (2012) Current role of ultrasound in chronic liver disease: surveillance, diagnosis and management of hepatic neoplasms. Curr Probl Diagn Radiol 41:43–51. doi:10.1067/j.cpradiol.2011.07.003
13. van Duijnhoven FH, Jansen MC, Junggeburt JMC, van Hillegersberg R, Rijken AM, van Coevorden F, van der Sijp JR, van Gulik TM, Slooter GD, Klaase JM, Putter H, Tollenaar RAEM (2006) Factors influencing the local failure rate of radiofrequency ablation of colorectal liver metastases. Ann Surg Oncol 13:651–658. doi:10.1245/ASO.2006.08.014
14. Sindram D, McKillop IH, Martinie JB, Iannitti DA (2010) Novel 3-D laparoscopic magnetic ultrasound image guidance for lesion targeting. HPB (Oxford) 12:709–716. doi:10.1111/j.1477-2574.2010.00244.x
15. Peterhans M, Oliveira T, Banz V, Candinas D, Weber S (2012) Computer-assisted liver surgery: clinical applications and technological trends. Crit Rev Biomed Eng 40:199–220 pii]
16. Herline AJ, Stefansic JD, Debelak JP, Hartmann SL, Pinson CW, Galloway RL, Chapman WC (1999) Image-guided surgery: preliminary feasibility studies of frameless stereotactic liver surgery. Arch Surg 134:644-9-50. doi:10.1001/archsurg.134.6.644
17. Peterhans M, vom Berg A, Dagon B, Inderbitzin D, Baur C, Candinas D, Weber S (2011) A navigation system for open liver surgery: design, workflow and first clinical applications. Int J Med Robot 7:7–16. doi:10.1002/rcs.360
18. Kingham TP, Scherer MA, Neese BW, Clements LW, Stefansic JD, Jarnagin WR (2012) Image-guided liver surgery: intraoperative projection of computed tomography images utilizing tracked ultrasound. HPB (Oxford) 14:594–603. doi:10.1111/j.1477-2574.2012.00487.x
19. Banz VM, Müller PC, Tinguely P, Inderbitzin D, Ribes D, Peterhans M, Candinas D, Weber S (2016) Intraoperative image-guided navigation system: development and applicability in 65 patients undergoing liver surgery. Langenbeck's Arch Surg 401:495–502
20. Kingham TP, Jayaraman S, Clements LW, Scherer MA, Stefansic JD, Jarnagin WR (2013) Evolution of image-guided liver surgery: transition from open to laparoscopic procedures. J Gastrointest Surg 17:1274–1282. doi:10.1007/s11605-013-2214-5
21. Langø T, Vijayan S, Rethy A, Våpenstad C, Solberg OV, Mårvik R, Johnsen G, Hernes TN (2012) Navigated laparoscopic ultrasound in abdominal soft tissue surgery: technological overview and perspectives. Int J Comput Assist Radiol Surg 7:585–599. doi:10.1007/s11548-011-0656-3
22. Fusaglia M, Tinguely P, Banz V, Weber S, Lu H (2016) A novel ultrasound-based registration for image-guided laparoscopic liver ablation. Surg. Innov 23 (4) 397–406
23. Harms J, Feussner H, Baumgartner M, Schneider A, Donhauser M, Wessels G (2001) Three-dimensional navigated laparoscopic ultrasonography: first experiences with a new minimally invasive diagnostic device. Surg Endosc 15:1459–1462. doi:10.1007/s004640090071
24. Hildebrand P, Kleemann M, Schlichting S, Martens V, Besirevic A, Roblick U, Bruch HP, Bürk C (2009) Prototype of an online navigation system for laparoscopic radiofrequency ablation. Hepatogastroenterology 56:1710–1713
25. Rauth TP, Bao PQ, Galloway RL, Bieszczad J, Friets EM, Knaus DA, Kynor DB, Herline AJ (2007) Laparoscopic surface scanning and subsurface targeting: implications for image-guided laparoscopic liver surgery. Surgery 142:207–214. doi:10.1016/j.surg.2007.04.016
26. Sindram D, Simo KA, Swan RZ, Razzaque S, Niemeyer DJ, Seshadri RM, Hanna E, McKillop IH, Iannitti DA, Martinie JB (2015) Laparoscopic microwave ablation of human liver tumours using a novel three-dimensional magnetic guidance system. HPB (Oxford) 17:87–93. doi:10.1111/hpb.12315
27. Hammill CW, Clements LW, Stefansic JD, Wolf RF, Hansen PD, Gerber DA (2014) Evaluation of a minimally invasive image-guided surgery system for hepatic ablation procedures. Surg Innov 21:419–426. doi:10.1177/1553350613508019
28. Dindo D, Demartines N, Clavien P-A (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213. doi:10.1097/01.sla.0000133083.54934.ae
29. Mayo SC, Pawlik TM (2010) Thermal ablative therapies for secondary hepatic malignancies. Cancer J 16:111–117. doi:10.1097/PPO.0b013e3181d7ea07
30. Hof J, Wertenbroek MWJLAE, Peeters PMJG, Widder J, Sieders E, de Jong KP (2016) Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases. Br J Surg 103:1055–1062. doi:10.1002/bjs.10162
31. Sindram D, Lau KN, Martinie JB, Iannitti DA (2010) Hepatic tumor ablation. Surg Clin North Am 90:863–876. doi:10.1016/j.suc.2010.04.014
32. Evrard S, Rivoire M, Arnaud J-P, Lermite E, Bellera C, Fonck M, Becouarn Y, Lalet C, Puildo M, Mathoulin-Pelissier S (2012) Unresectable colorectal cancer liver metastases treated by intraoperative radiofrequency ablation with or without resection. Br J Surg 99:558–565. doi:10.1002/bjs.8724
33. Philips P, Groeschl RT, Hanna EM, Swan RZ, Turaga KK, Martinie JB, Iannitti DA, Schmidt C, Gamblin TC, Martin RCG (2016) Single-stage resection and microwave ablation for bilobar colorectal liver metastases. Br J Surg 103:1048–1054. doi:10.1002/bjs.10159
34. Iannitti D a, Martin RCG, Simon CJ, Hope WW, Newcomb WL, McMasters KM, Dupuy D (2007) Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. HPB (Oxford) 9:120–124. doi:10.1080/13651820701222677
35. Kuang M, Lu MD, Xie XY, Xu HX, Mo LQ, Liu GJ, Xu ZF, Zheng YL, Liang JY (2007) Liver cancer: increased microwave delivery to ablation zone with cooled-shaft antenna–experimental and clinical studies. Radiology 242:914–924. doi:10.1148/radiol.2423052028

36. Groeschl RT, Pilgrim CHC, Hanna EM, Simo KA, Swan RZ, Sindram D, Martinie JB, Iannitti DA, Bloomston M, Schmidt C, Khabiri H, Shirley LA, Martin RCG, Tsai S, Turaga KK, Christians KK, Rilling WS, Gamblin TC (2014) Microwave ablation for hepatic malignancies: a multiinstitutional analysis. Ann Surg 259:1195–1200. doi:10.1097/SLA.0000000000000234
37. Leung U, Kuk D, D'Angelica MI, Kingham TP, Allen PJ, DeMatteo RP, Jarnagin WR, Fong Y (2015) Long-term outcomes following microwave ablation for liver malignancies. Br J Surg 102:85–91. doi:10.1002/bjs.9649
38. Zaidi N, Okoh A, Yigitbas H, Yazici P, Ali N, Berber E (2016) Laparoscopic microwave thermosphere ablation of malignant liver tumors: An analysis of 53 cases. J Surg Oncol 113:130–134. doi:10.1002/jso.24127
39. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD (2006) Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. Br J Surg 93:872–878. doi:10.1002/bjs.5346
40. Andres A, Toso C, Adam R, Barroso E, Hubert C, Capussotti L, Gerstel E, Roth A, Majno PE, Mentha G (2012) A survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases: a LiverMetSurvey-based study. Ann Surg 256:772-8-9. doi:10.1097/SLA.0b013e3182734423
41. Lam VWT, Laurence JM, Pang T, Johnston E, Hollands MJ, Pleass HCC, Richardson AJ (2014) A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. HPB (Oxford) 16:101–108. doi:10.1111/hpb.12083
42. Feng Q, Wei Y, Zhu D, Ye L, Lin Q, Li W, Qin X, Lyu M, Xu J (2014) Timing of hepatectomy for resectable synchronous colorectal liver metastases: for whom simultaneous resection is more suitable–a meta-analysis. PLoS ONE 9:e104348. doi:10.1371/journal.pone.0104348
43. Yin Z, Liu C, Chen Y, Bai Y, Shang C, Yin R, Yin D, Wang J (2013) Timing of hepatectomy in resectable synchronous colorectal liver metastases (SCRLM): Simultaneous or delayed? Hepatology 57:2346–2357. doi:10.1002/hep.26283
44. Kelly ME, Spolverato G, Lê GN, Mavros MN, Doyle F, Pawlik TM, Winter DC (2015) Synchronous colorectal liver metastasis: a network meta-analysis review comparing classical, combined, and liver-first surgical strategies. J Surg Oncol 111:341–351. doi:10.1002/jso.23819
45. Fitzpatrick JM (2010) The role of registration in accurate surgical guidance. Proc Inst Mech Eng H 224:607–622. doi:10.1243/09544119JEIM589