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Systematic review

Software-based assessment of tumor margins after percutaneous thermal ablation of liver tumors: A systematic review

Chloé Minier[a,1], Margaux Hermida[a,1], Carole Allimant[a], Laure Escal[a], Marie-Ange Pierredon-Foulongne[a], Ali Belgour[a], Lauranne Piron[a], Patrice Taourel[b], Christophe Cassinotto[a], Boris Guiu[a,*]

[a] Department of Radiology, St-Eloi University Hospital, 34090, Montpellier, France
[b] Department of Radiology, Lapeyronie University Hospital, 34090, Montpellier, France

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ABSTRACT

Purpose: The purpose of this study was to make a systematic review of clinical studies evaluating software-based tumor margin assessment after percutaneous thermoablation (PTA) of liver tumors.
Materials and methods: A systematic literature search was performed through Pubmed/MEDLINE, Embase and the Cochrane Library. Original studies published in English that reported on software-based assessment of ablation margins (AM) following PTA of liver tumors were selected. Studies were analyzed with respect to design, number of patients and tumors, tumor type, PTA technique, tumor size, target registration error, study outcome(s) (subtypes: feasibility, comparative, clinical impact, predictive or survival), and follow-up period.
Results: Twenty-nine articles (one multi-center and two prospective studies) were included. The majority were feasibility (26/29, 89.7%) or predictive (23/29, 79.3%) studies. AM was a risk factor of local tumor progression (LTP) in 25 studies (25/29, 86.2%). In nine studies (9/29, 31%) visual assessment overestimated AM compared with software-aided assessment. LTP occurred at the location of the thinnest margin in nine studies (9/29, 31%). Time for registration and analysis was heterogeneously reported, ranging between 5–30 min. Mean target registration error was reported in seven studies (7/29, 24.1%) at 1.62 mm (range: 1.20–2.23 mm). Inter-operator reproducibility was high (kappa range: 0.686–1). Ascites, liver deformation and inconspicuous tumor were major factors of co-registration error.
Conclusion: Available studies present a low level of evidence overall, since most of them are feasibility, retrospective and single-center studies.

1. Introduction

Indications of image-guided percutaneous thermal ablation (PTA) for the treatment of liver tumors (either primary or secondary) have widely expanded over the past ten years [1–3]. PTA using radiofrequency (RFA) or microwave (MWA) has become a validated local curative option in colorectal liver metastases (CRLMs), especially in patients not eligible for surgery [1,2]. In addition, PTA is a validated first-line treatment as is surgical resection in patients with early-stage hepatocellular carcinoma (HCC), according to European Association for the Study of Liver Disease/ American Association for the Study of Liver Diseases recommendations [1,3]. In a recent French nationwide study, PTA was even presented as the most widely-used curative treatment in HCC both in cirrhotic and non-cirrhotic patients [4].

As a local treatment, patient treated by PTA may show local tumor progression (LTP), which occurs in 1–27% of HCC [1, 5–7] and in 3–41% of CRLMs [1,8,9]. LTP is largely due to insufficient ablative margin (AM) [1,8,10–13]. In this context, the precise evaluation of the ablation margins has attracted a growing interest. Laimer et al. showed that for each millimeter increase of the minimal AM post-RFA treatment of HCC, the relative risk for LTP decreased by 30% [13]. As in surgery, the ideal minimal margin is subjected to debate, but it is commonly accepted that a minimal ablative margin of 5 mm provides satisfactory local tumor control of HCC or CRLMs [1,8,13,14].

Abbreviations: AR, Augmented reality; AM, Ablative margin; CRLMs, Colorectal liver metastases; CT, Computed tomography; HCC, Hepatocellular carcinoma; LTP, Local tumor progression; MAM, Minimal ablative margin; MWA, Microwave ablation; NA, Not applicable; NOS, Newcastle-Ottawa scale; NR, Not reported; PTA, Percutaneous thermal ablation; RFA, Radiofrequency ablation; TRE, Target registration error

* Corresponding author.
E-mail address: B-guiu@chu-montpellier.fr (B. Guiu).
[1] These authors share first co-authorship.

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The ablation zone can be easily visualized at the end of procedure as a hypoattenuating area on computed tomography (CT) images obtained during the portal venous phase of enhancement. Visual comparison of pre- and post-ablation CT images is commonly used to check that AMs are satisfactory. However, such visual evaluation of treatment success proved to be frequently misjudged, regardless of the experience of the radiologist [15]. These poor results as well as the subjectivity of visual assessment support the need to evolve our practice. Importantly, local recurrence observed during follow-up may result from either residual unablated tumor (*i.e.*, presence of residual viable tumor at the ablative margin) or local tumor progression (reappearing viable tumor) [16].

Visual (*i.e.*, subjective) evaluation of imaging follow-up is the most common way to evaluate treatment success after PTA, whereas pathologists analyze resection margins after surgery using an objective approach, which defines R0/R1/R2 status. Therefore, it has become essential for interventional oncologists to objectively evaluate the success of a complete ablation.

A growing interest has been observed in software allowing segmentation, rigid or/and non-rigid registration, and assessment of AM. However, the liver is subject to mobility and deformation with respiratory movements, which makes coregistration technically-challenging between pre- and post-evaluations acquired at different times. Accurate assessment of AM immediately after PTA would permit to complete the ablation during the same procedure if the AM is deemed insufficient or in case of residual tumor. Over the past decade, several software-based methods for assessing AM were published in different clinical contexts (tumor types, imaging modalities or timing of pre- and post-PTA evaluation) but to our knowledge, no systematic review has been published so far.

It has now become particularly important to analyze capabilities, accuracy, and limitations of available ablation-confirmation software before conducting clinical trials incorporating these tools, in order to guarantee the completeness of PTA with adequate margins.

The purpose of this study was therefore to conduct a systematic review of clinical studies evaluating software-based tumor margin assessment after PTA of liver tumors.

2. Materials and methods

This systematic review was initially registered in PROSPERO (number CRD42021243449; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=243449). This review was performed in compliance with the guidelines specified by the Cochrane database of systematic reviews [17].

2.1. Study selection

The research was conducted on three databases: Pubmed/MEDLINE, Embase and The Cochrane library. The keywords used were “software”, “ablation techniques”, “liver neoplasms”, image processing”, “imaging, three-dimensional”, “volumetric assessment”, “ablation”, “ablative margin”, “local tumor progression”, “radiofrequency ablation”. MeSH Terms (“software”, “ablation techniques”, “liver neoplasms”, “image processing, computer-assisted”) and free-text research were both used (Appendix 1). There was no limitation date. The research was completed on December 11, 2021.

Selection criteria included original studies published in English that reported on software-based assessment of margins or treatment success following PTA of liver tumors. Case-reports and studies reporting on less than 10 patients were not considered. Exclusion criteria were the following: non-hepatic tumors, non-English papers, ongoing study, non-human study, no coregistration of pre- and post-treatment images, ultrasound-only imaging, or no description of the method used for coregistration.

2.2. Definitions

AM were defined as the region ablated beyond the borders of the tumor to achieve complete tumor destruction, according to the Cardiovascular and Interventional Radiological Society of Europe Standards of Practice on Thermal Ablation of Liver Tumors [1]. Primary treatment success (also considered as complete ablation) addresses whether the tumor was completely covered [18]. Local tumor progression (LTP) was defined as “the appearance of tumor foci at the edge of the ablation zone, after at least one contrast-enhanced follow-up study had documented adequate ablation and an absence of viable tissue in the target tumor and surrounding ablation margin by using imaging criteria” [19].

2.3. Coregistration

2.3.1. Principles

Coregistration allows two pre- and post-PTA images to be matched. For this purpose, linear or non-linear transformation models can be used. Rigid transformations belong to the group of linear transformations combining translation and rotation axes and are classically used for organs in closed environments, with limited mobility (*e.g.*, the brain) [20]. Rigid transformation processing is fast, but when applied to the liver, it often requires adjustments by a system of manually-determined anatomical landmarks, such as vessel bifurcations, cysts or calcifications [21].

For mobile organs such as the liver, non-linear (or elastic or non-rigid) transformations have been developed to better compensate for the organ’s movements (more often based on B-splines) [22]. As in rigid coregistration, additional landmark can be added to improve even more the quality of registration.

Prior to rigid or non-rigid registration, DICOM files need to be transferred into the software. Generally, the whole liver (on pre- and post-PTA images), liver tumor(s) (on pre-PTA images) and the ablation (ie. necrosis) zone (on post-PTA images) are segmented. Segmentation can be either manual, semi-automatic (most frequently), or fully automatic. Then, the ablation margin(s) are assessed by using manual or automatic method of measurement (depending on the software).

2.3.2. Coregistration quality

Coregistration quality was extracted from studies, whenever available. Quality could be either subjectively assessed using a rating scale or objectively evaluated using target registration error (TRE), corresponding to the difference in distance between coregistered pre- and post-PTA images, regarding predefined anatomical landmarks [23]. When technical settings affecting coregistration quality were reported, these data were also extracted.

2.4. Quality assessment of studies

Quality assessment was evaluated by the Newcastle-Ottawa scale (NOS), an instrument developed to assess the quality of non-randomized studies [24]. This scale included selection, comparability and outcome. Selection integrates the representativeness of the exposed cohort, the selection of the non-exposed cohort, the ascertainment of exposure, the demonstration that outcome of interest was not present at the onset of study. Comparability integrates the comparability of cohorts based on the design or analysis. Outcome integrates the assessment of outcome (blind assessment, auto-evaluation) if the follow-up was long enough for outcomes to occur, and the assessment of adequacy of the follow up of cohorts (Appendix 2). Thresholds for converting the NOS to the Agency for Healthcare Research and Quality’s (AHRQ) standards are reported in Appendix 3.

2.5. Data extraction

Studies were initially screened according to inclusion/exclusion criteria by two radiologists (C.G. and M.H., with respectively 2- and 6 years of experience in PTA) through titles and abstracts. In case of disagreement, a consensus was found between the two reviewers. A third radiologist (B.G., with 17 years of experience in PTA) adjudicated in case of persistent disagreement. A full-text review was then conducted to confirm eligibility. A summary of the study selection process is presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement) flow diagram (Figure 1).

From each study, several items were extracted including reference, study design, period of inclusion, outcomes, number of included patients, exclusion criteria, number of lesions and their type, follow-up period, software used, interval between PTA and post-treatment evaluation (CT or MR images), NOS and conversion to AHRQ standards [24], key steps for the segmentation and registration, feasibility of a manual correction, time for use, margins endpoint (quantitative, semi-quantitative or binary), tumor size, rate of LTP, results, inter- or intra-operator reproducibility, authors' views on limitations and benefits of the software.

In order to classify the outcomes of each study, we distinguished 5 main axes (which could be combined): studies reporting on feasibility of quantitative margin assessment (feasibility); studies reporting on comparison between software-based and visual margin assessment (comparative); studies evaluating the possibility of an additional treatment (clinical impact); studies evaluating the predicting ability of software-based evaluation for the occurrence and/or the location of further LTP (predictive); and studies examining the impact of software-based evaluations on oncological outcomes such as progression free-survival or overall survival (Survival). All data were extracted by the two principal radiologists (C.G. and M.H.) with disagreement resolved by the third radiologist (B.G.).

3. Results

3.1. Literature research

After duplicates were removed, a total of 679 articles were screened by their titles and abstracts. Based on exclusion criteria, 610 articles were discarded. The remaining 69 articles were assessed for eligibility. Full-text analysis resulted in a final selection of 29 references in this systematic review (Fig. 1)

3.2. Studies characteristics

Studies characteristics, (*i.e.*, study design), number of patients and tumors, tumor type, PTA technique (RFA, MWA or cryoablation), tumor size, study outcome(s) (subtypes: feasibility, comparative, clinical impact, predictive or survival), follow-up period and NOS are reported in Table 1.

Most studies were single-center (28/29, 97%), one was a multicenter study [25] and two were prospective studies [5,26]. A large majority of lesions were HCCs (24/29, 83%) (with a total of 2248 HCCs), followed by CRLMs (with a minimum of 317 CRMLs since data from one study were missing). The number of included patients ranged between 10 and 444 (median: 59.5 patients)

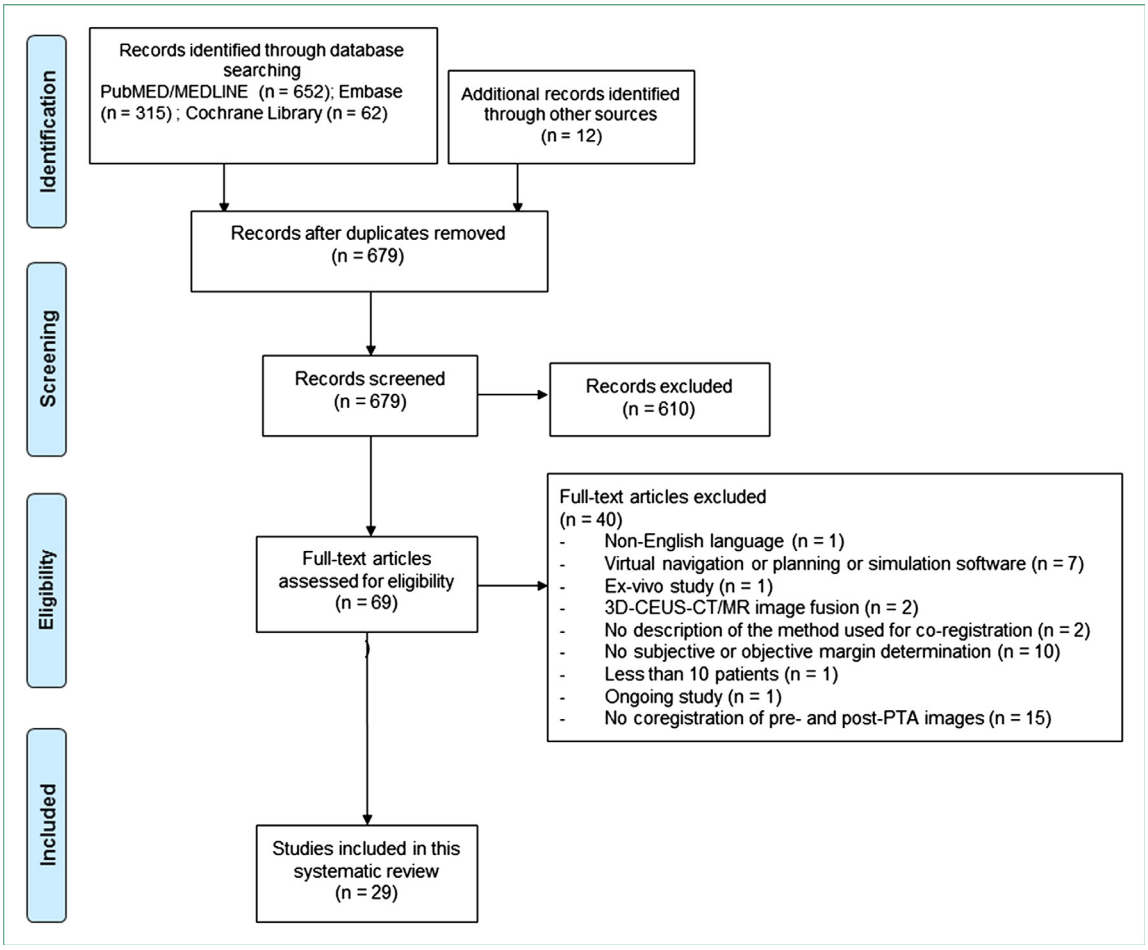

Fig. 1. Flow-chart summarizing the different steps of the literature review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.

Table 1
Published studies.

References	Study design	Number patients/ lesions	HCC/CRMLs/Others	Ablation	Tumor size (mm, range)	Follow-up (month, median or mean	Outcome	NOS	AHRQ
Li et al. [25]	RS	444/444	HCC	RFA/ MWA	19 [15–23]	19.9	F/P	8	Good
Sandu et al. [53]	RS	NR/65	CRLMs	MWA	NR	NA	F	NA	NA
An et al. [36]	RS	141/141	HCC	MWA	23 ± 9 [NR]	28.9	F/P/C	7	Good
Laimer et al. [13]	RS	110/176	HCC	RFA*	25.2 ± 14.9 [NR]	26.0 ± 10.3	F/P	8	Good
Laimer et al., [43]	RS	45/76	CRLMs	RFA*	24.3 [3–75]	36.1 ± 18.5	F/P	8	Good
An et al. [28]	RS	68/68	HCC	MWA	27.8±7.2 [8–47]	21 [3 - 44]	F/P/OS	8	Good
Chen et al. [55]	RS	35/47	H/CRLM/O (n = 5/19/23)	Cryo	27.0 ± 15.1 [NR]	≥ 6	F/P	6	Poor
Hendriks et al. [37]	RS	18/18	HCC	RFA	20 [12–45]	9.5	F/P/C	7	Good
Kaye et al. [38]	RS	72/93	CRLMs	RFA	NR****[6 - 55]	NR	F/C/P	7	Good
Sibinga Mulder et al. [39]	RS	29/29	CRLMs	RFA	22 [8–42]	44.7 ± 20.5	F/P	7	Fair
Solbiati et al. [42]	RS	50/90	HCC	MWA	27 ± 20 [NR]	≥ 12	F/P	5	Poor
Jiang et al. [34]	RS	134/159	HCC	RFA	20 ± 9 [10–49]	26 [2–69]	F/P	8	Good
Solbiati et al. [32]	RS	38/38	H/C (n= 28/10)	MWA	NR [7–33]	NA	F	NA	NA
Takeyama et al. [35]	RS	31/61	HCC	RFA	11.2 ± 4.4 [5 - 24]	37.9 ± 12.4 [12–67]	F/P/C	9	Good
Vandenbroucke et al. [31]	RS	20/45	C/O***	RFA	18.6 [6-41]	110 weeks [26 - 232]	P	7	Good
Yoon et al. [26]	PS	68/88	HCC	RFA	16 ± 6 [6–32]	48 [0.9–72.6]	C/I/P	8	Good
Hocquelet et al. [30]	RS	16/16	HCC	RFA	NR [18 -27]	2.2 year [1.76–2.63]	F/P/OS	7	Good
Park et al. [33]	RS	178/178	HCC	RFA	17.3 ± 6.1 [5–40]	≥ 12	F/P	8	Good
Tani et al. [27]	RS	19/21	H/C/O (n = 3/9/9)	MWA/RFA/Cryo	20 [9 - 41]	NR	F/P	6	Poor
Makino et al. [40]	RS	67/92	HCC	RFA	12.9 [4.8–41.4]	NR	F	8	Good
Tang et al. [29]	RS	75/75	HCC	RFA	24.0 ± 7 [8 - 41]	NR	F/OS	7	Poor
Wang et al. [41]	RS	52/62	HCC	RFA	20 ± 10 [10–31]	14.2 ± 5.4 [1–23]	F/P/C	7	Good
Sakakibara et al. [44]	RS	84/134	HCC	RFA	13.8 ± 4.6 [NR]	NR	F/P/C	8	Good
Shin et al. [5]	PS	150**/150	HCC	RFA	19.5 ± 7.9** [NR]	29.21 ± 10.84 [0–42]	F/P/C/I	6	Good
Makino et al. [7]	RS	85/94	HCC	RFA	14.0 ± 5.2 [NR]	21.0 [2–75]	P/C	8	Good
Passera et al. [52]	RS	10/10	H/NR (n = 5/5)	RFA	NR [10 - 40]	NA	F	NA	NA
Tomonari et al. [45]	RS	12/13	HCC	RFA	14.5 ± 4.8 [8–23]	15.2 [3–27]	F/C/P	5	Poor
Kim et al. [23]	RS	31/38	HCC	RFA	19 [10–35]	NR	F/C	8	Good
Kim et al. [6]	RS	103/110	HCC	RFA	27 ± 6 [21–48]	28.1 [12.9–46.6]	F/P/C	8	Good

Brackets indicate range. PS = Prospective study; RS = Retrospective study; CRLM = Colorectal liver metastases, O = Other lesions, NR = Not reported, NA = Not applicable, Cryo = Cryoablation; RFA = Radiofrequency ablation, NOS = Newcastle-Ottawa scale, AHRQ = Agency for healthcare research and quality.
F: Feasibility, C = Comparative, I = Clinical Impact, P = Predictive, OS = Overall survival.
* Stereotactic.
** Values for study group. For control group: n = 90 and mean tumor size: 21 ± 6.6 mm.
*** 16 patients with colorectal liver metastases (CRLMs) and 4 for patients with other lesions.
**** Median: 18 mm.

The large majority of studies used RFA (23/29; 79%); of these, seven (7 /29; 24%) used MWA and two (2//29; 7%) used cryoablation. Only one study reported on all three types of PTA [27]. The diameter of ablated tumors ranged between 3 and 75 mm.

Twenty-six out of 29 references were feasibility studies (26/29; 90%), and 23 (23/29; 79%) were predictive ones. Only three studies investigated survival [28–30].

NOS evaluation revealed only one study with the highest score (*i.e.*, 9), whereas 10 studies (10/26; 39%) reached a score of 8. This scale was not applicable forthree studies (3/29; 10%) because they were not cohort studies. The AHRQ classified 20 studies (20/26; 77%) as good, one (1/26; 4%) as fair and five (5/26; 19%) as poor.

3.3. Technical features

Studies mainly investigated dedicated software (23/29; 79%), whereas only five (5/29; 17%) reported on non-dedicated software. A total of 13 different dedicated and four non-dedicated software were evaluated.

Technical features were reported in Table 2. Among software, margin endpoints were obtained through quantitative (n = 1), semi-quantitative (n = 3) or binary (n = 6) evaluations, whereas this information was not reported for seven software programs or methods. The AMs were automatically obtained in four software programs, (Ablation-fit®, HepaCare® Siemens Healthineers, MIM MAESTRO®, MyLab Twice® [all company names are reported in Tables]). Otherwise, the authors themselves had to visually locate and manually measure the smallest ablation margin.

Most studies investigated margins by fusion of CT (16/29; 55%) or MR images (8/29; 28%), or both (5/29; 17%). One study used contrast-enhanced PET-CT [31] and only one studied pre-operative CT with post-operative cone beam CT registration [32].

Time for use was reported in 23 studies (23/29; 79%), but very inhomogeneously. The total usage times ranged between 5 to 30 min or more when it was indicated (23/29; 79%). Only the segmentation time or the coregistration time was available in six studies.

Inter-operator reproducibility was reported in only five studies (5/29; 17%) and again, very heterogeneously. Indeed, it referred either to the registration (3/6) or to the minimal AM (5/6). When it was reported, inter-reader reproducibility was quite high (kappa range: 0.686 – 1).

3.4. Co-registration

The success rate in coregistration was available in only 12 studies (Table 3). In 10 of them, this rate was greater than 80%. Exclusion criteria were identified and collected in Table 3. The most common exclusion criteria which could have influenced the success rate of coregistration and/or, which could be a limiting factor of the software are also gathered in Table 3. They were purely technical in nine studies (9/14; 31%). Ascites (artificial or not) was reported as an exclusion criterion in three studies and as a factor coregistration error in four others. Other limiting factors included liver deformation or different patient's positions, and undetectable tumor on pre-ablation imaging. Mean TRE was reported in 7/29 studies (24%) at 1.62 mm (range: 1.20–2.23 mm).

Table 2
Studies characteristics.

References	Software	Rigid/ Non rigid	Margin end point	Margin assessment	Pre-/Post-ablation modality	Interval between ablation and control	Time for use	Inter-operator Reproductibility	TRE (mm)
Laimer et al. [43]	Ablation-fit®; R.A.W. Srl	Non-R	S-Q	A	CT / CT	Day 0	5–20 min	NR	NR
Solbiati et al. [42]	Ablation-fit®; R.A.W. Srl	Non-R	S-Q	A	CT / CT	Day 0	Registration: <3 min	NR	NR
Sakakibara et al. [44]	AquariusNET Viewer®, TeraRecon	R	B	NR	CT or MRI / CT or MRI	≤ Day 3	To create 3D registration ≈ 10 min	NR	NR
Yoon et al. [26]	HepaCare®, Siemens Healthineers	Non-R	B	A	MRI / CT	Day 0	NR	NR	NR
Park et al. [33]	HepaCare®, Siemens Healthineers	Non-R	B	A	MRI / CT	Day 0	Registration: 35.32 ± 15.39 s Interpretation: 150.00 ± 16.91 s	NR	NR
Shin et al. [5]	HepaCare®, Siemens Healthineers	Non-R	B	A	CT / CT	Day 0	Registration: 5 min	NR	NR
Kim et al. [23]	HepaCare®, Siemens Healthineers	Non-R	B	A	CT / CT	Day 0	Processing time: 123.3 ± 16.8 s Interpretation: 66.1 ± 34.9 s to 149.3 ± 40.7 s*	Regarding safety margin assessment κ: 0.807 −0.869	1.3 ± 1.1 [0–8.4]
Chen et al. [55]	Integrated Registration, GE Healthcare	R	NA	M	MRI / CT	Day 0	14.57 ± 1.64 min [10.08 −16.52]	NR	NR
Vandenbroucke et al. [31]	Integrated Registration, GE Healthcare	R	NA	M	PET-CT / PET-CT**	Day 0	Variable >30 min in some cases	NR	NR
Makino Y et al. 2015 [40]	Integrated Registration, GE Healthcare	R	NA	M	CT / CT or MRI/ MRI	≤ 7 days ≤ 1 month	CT fusion imaging: ≤ 15 min / MRI fusion imaging: ≤ 20 min	NR	1.5 [0.27–2.92]1.2 [0.26–3.0]
Makino et al. [7]	Integrated Registration, GE Healthcare	R	NA	M	CT / CT	≤ 7 days	< 15 min	NR	1.5 ± 0.68
Tomonari et al. [45]	Integrated Registration, GE Healthcare	R	NA	M	CT / CT	1 week after	NR	NR	NR
Kaye et al. [38]	MIM MAESTRO® (MIM software, Inc.)	R	B	A	CT / CT	1 - 2 months	4.26 ± 1.5 min	NR	NR
Hendriks et al. [37]	Mirada RTx® software (Mirada Medical Ltd.)	Non-R	NA	M	CT / CT	Day 0	NR	Coregistration: κ = 0.88 (SE: 0.12; P < 0.01) Quantitative assessment of MAM: κ = 0.88 (SE: 0.12; P < 0.01) Qualitative categorical assessment of MAM***: κ = 0.24 (SE of 0.28; P = 0.16)	NR
Sibinga Mulder et al. [39]	Mirada RTx® software (Mirada Medical Ltd.)	Non-R	NA	M	CT / CT	Day 0	NR	Completeness of the ablation: κ = 1.0 (P < 0.001) Measurement of the MAM: κ = 0.723 (P < 0.001)	NR
An et al. [28]	MITK® (Hokai Company)	Non-R	S-Q	NR	MRI / MRI	≤ 1 week	Segmentation ≈ 2 min Registration: Median: 121.3 sec	NR	1.7 ± 0.3

(*continued on next page*)

Table 2 (*Continued*)

References	Software	Rigid/ Non rigid	Margin end point	Margin assess ment	Pre-/Post-ablation modality	Interval between ablation and control	Time for use	Inter-operator Reproductibility	TRE (mm)
Li et al. [25]	MyLab Twice®,	Non-R	B	A	MRI / MRI	≤ 1 month	NR	NR	NR
An et al. [36]	Esaote	Non-R	B	A	MRI / MRI	≤ 3 months	Median registration time: 183.5 s	NR	1.6 ± 0.8
Wang et al. [41]	Esaote	Non-R	B	A	MRI / MRI	1 month	Creation of image fusion: 15.5 ± 5.5 min [8–22 min] AM evaluation: 9.6 ± 3.2 min [6–14 min]	NR	NR
Jiang et al. [34]	Myrian®, Intrasense	Non-R	NA	M	CT / CT	1 month	≈ 30 min	NR	NR
Tang et al. [29]	Myrian®, Intrasense	Non-R	NA	M	CT / CT	1 month	≈ 30 min	NR	NR
Laimer et al. [13]	Syngo.via® VB20A, Siemens Healthineers	R	NA	M	CT / CT	Day 0	> 15 min	NR	NR
Kim et al. [6]	CT workstation: Virtual Place Advance Plus version 2.03, Aze Corporation	R	NA	M	CT / CT	Day 0	NR	NR	NR
Takeyama et al. [35]	Volume Analyzer Synapse® VINCENT version 5.1, Fujifilm, Medical Systems	R	NA	M	MRI / MRI	≤ Day 3	To create registration image: 10–15 min	Agreement level for registration error: κ = 0.686 Agreement level for the AM grading on fusion imaging: κ = 0.693	NR
Tani et al. [27]	Registration, fusion and volumetric approach: 3D Slicer® 3D distance map: ITK	Non-R	Q	NR	MRI / MRI	≤ Day 3	Manual tasks: 10–15 min Computation: 15 min	NR	2.23 ± 0.95
Hocquelet et al. [30]	Segmentation: ITK-SNAP	NR	B	NR	MRI / MRI	1 month	Registration < 7 min Segmentation < 1 min	Mean DSC values on pre- and post-ablation scans between 2 repeated segmentations: 0.98 ± 0.03 and 0.96 ± 0.03	2 ± 0.9
Solbiati et al. [32]	Registration: ITK libraries and Elastix toolbox	Non-R	NA	NR	CT / CE-CBCT	Day 0	Landmark selection and coregistration: 30 to 120s	"Identical grades of 43.3, 37.4, 78.9, and 60.5% assigned for registration quality, position clinical, indication, and confidence improvement"	NR
Sandu et al. [53]	*Introduced a method*[****]	Non-R	S-Q	NR	CT / CT	Day 0	Segmentation: 5-30 min Computation AM: 30 sec	NR	NR
Passera et al. [52]	Segmentation: MevisLab *Described a method for AM*	Non-R	B	NR	CT / CT	Day 15 - 20	Segmentation: 10 min Registration: 40 min	NR	NR

A = Automatic; M = Manually; MAM = Minimal ablative margin; R = Rigid registration; Non-R = Non-rigid registration; CE-CBCT = Contrast-enhanced cone beam CT; DSC = DICE similarity coefficient between the region-of-interest encompassing the liver in the registered volume and its counterpart in the reference frame; Q = Quantitative; S-Q = Semi-quantitative; B = Binary; NR = Not reported, NA = Not applicable

* Depends on the reader.

** ^{18}FDG PET/CT.

*** Categorical margin assessment: negative, 0 to 5 mm or ≥ 5 mm.

**** Article found in AblaSure® software publications website.

Table 3
Registration quality.

References	Software	Success rate (%)	Exclusion criteria affecting registration quality	Other results
Laimer et al. [43]	Ablation-fit®; R.A.W. Srl	NR	Tumor not visible in CT-scan; need of preinterventional image fusion with MRI (n = 55)	NR
Solbiati et al. [42]	Ablation-fit®; R.A.W. Srl	NR	NR	NR
Sakakibara et al. [44]	AquariusNET Viewer®, version 4.4.6.50, TeraRecon	95.7	NR	**Unsuccessful**: 2 in left lobe (high deformity); 1 pre-post-MRI: blurry hypointensity in the HBP; 3 pre-post-CT: very slight enhancement in arterial phase of pre-CT
Yoon et al. [26]	HepaCare®, Siemens Healthineers	100	NR	NR
Park et al. [33]	HepaCare®, Siemens Healthineers	NR	Use of artificial ascites (n = 215) Technical failure (n = 13)	This registration technique is limited in patients with a large amount of ascites
Shin et al. [5]	HepaCare®, Siemens Healthineers	NR	Use of artificial ascites during RFA (n = NR)	NR
Kim et al. [23]	HepaCare®, Siemens Healthineers	100%	Use of artificial ascites (n = 56)	According to 2 different radiologists: 87.3% - 90.3%: good image quality; 9.7% - 12.9%: medium quality; 22.6%: landmark-based constraints were added
Chen et al. [55]	Integrated Registration, GE Healthcare	97.9	NR	NR
Vandenbroucke et al. [31]	Integrated Registration, GE Healthcare	89	Did not achieve adequate fusion (n = 1)	Easily for spherical tumors Manual correction of polymorph shaped tumors 5/45 cases: local manual adjustment was repeated several times in the 3 planes, very time-consuming (up to 30min)
Makino et al. [40]	Integrated Registration, GE Healthcare	CT: 67.4 MRI: 93.5	NR	**CT fusion**: 32.6% evaluation impossible: tumor undetectable (n = 19), or detectable but too inconspicuous for treatment evaluation on CT fusion images (n = 11); Incidence of hypovascularity significantly greater: impossible 15/30 (50.0%) **MRI fusion:** cause severe deformation of the liver
Makino et al. [7]	Integrated Registration, GE Healthcare	NR	No apparent tumor images on pre-RFA CT (n = 66)	NR
Tomonari et al. [45]	Integrated Registration, GE Healthcare	NR	NR	NR
Kaye et al. [38]	MIM MAESTRO®	NR	Incompatible image format (n = 4) Sub-optimal rigid registration results (n = 15)	NR
Hendriks et al. [37]	Mirada RTx software®, Mirada Medical Ltd.	NR	Lateral patient positioning on the postablation scan (n = 11) Coregistration quality of pre- and post-ablation scans ≤3 (n = 7)	Difference in position and shape of the liver may hamper reliable image coregistration
Sibinga Mulder et al. [39]	Mirada RTx software®, Mirada Medical Ltd.	62	Technical failure (n = 3)	Cause for suboptimal coregistration: difference in liver position during pre- and post-ablation scans
An et al. [28]	MITK®, Hokai Company	100	NR	NR
Li et al. [25]	MyLab Twice®, Esaote	NR	Data image format is incompatible with registration (n = 169) Images alignement deviation was too large to meet the actual situation (n=187)	NR
An et al. [36]	MyLab Twice®, Esaote	100	Data image format is incompatible with registration (n = 9) Images alignment deviation was too large to meet the actual situation (n = 8)	NR
Wang et al. [41]	MyLab Twice®, Esaote	98.4	NR	Cause of error of fusion for 1/62: significant deformation of the liver and massive ascites after RFA
Jiang et al. [34]	Myrian®, Intrasense	NR	NR	NR
Tang et al. [29]	Myrian®, Intrasense	NR	Failed image fusion data (n = 1)	NR
Laimer et al. [13]	Syngo.via® VB20A, Siemens Healthineers	NR	Extensive liver deformation due to stereotactic RFA of large or multiple tumors leading to an inacceptable (n = 20)	NR
Kim et al. [6]	CT workstation: Virtual Place Advance Plus version 2.03, Aze Corporation	NR	Technical failure of RFA (n = 18)	23/123 tumors: unable to assess fusion; Difficult in some cases to synchronize the 2 sets of CT images completely, because the liver is not a rigid organ

(*continued*)

Table 3 (*Continued*)

References	Software	Success rate (%)	Exclusion criteria affecting registration quality	Other results
Takeyama et al. [35]	Volume Analyzer Synapse VINCENT® version 5.1, Fujifilm Medical Systems	NR	NR	Good: 53/61; Fair: 6/61; Poor: 2/612; HCCs excluded due to liver deformation and massive ascite; Artificial pleural effusion was used in 15/59 (25.4%)
Tani et al. [27]	3D Slicer version 4/ITK	NR	NR	NR
Hocquelet et al. [30]	Segmentation: ITK-SNAP freeware	NR	NA	When implemented motion compensation strategy was applied, the average positionning error decreased from 17.3 ± 8 mm to 2 ±0.9 mm Intrarater variation in positioning landmarks was 2 mm (voxel size)
Solbiati et al. [32]	ITK libraries / Elastix toolbox	NR	NR	**Registration quality:** Scored high: Reader 1: 4.3 ±0.6, Reader 2: 4.4 ± 0.5 No 1 and 2 **Perceived increase of confidence for treatment evaluation:** Higher increase of confidence 96.1% as high or very high; 3.9% as discrete
Sandu et al. [53]	*Introduced a method*	100	NR	NR
Passera et al. [52]	MevisLab *Described a method for AM*	80	NR	2 patients: not possible due to contingent image features: 1 serious fluid effusion, 1 RFA and hepatic resection

RFA = Radiofrequency ablation; HBP = Hepatobiliary phase; NR = Not reported; NA = Not applicable; AM = Ablative margin.

3.5. *Visual* vs. *quantitative assessment*

In the 9/29 studies (31%) that compared visual and software-based assessment, visual assessment tended to overestimate the AM (*i.e.*, margins were considered large enough when actually they were not). Two studies investigated the impact of software according to the level of experience of the readers and showed that a reassignment of AM adequacy was more frequent when the readers were less experienced [23,33].

Two prospective studies investigated how software-based evaluation could influence the ablation protocol (additional ablation) [5,26].

3.6. *Local tumor progression*

AM was found as a risk factor of LTP in 25 studies (25/29; 86%). In 9/29 studies (31%), multivariable analysis was performed to check for independency of AM as a predictor for LTP. In four studies (4/9; 44%) [6,7,34,35], AM was the only risk factor of LTP. For five studies (5/9; 56%), AM was associated with another risk factor (pre-neutrophil-lymphocyte ratio [29], maximal tumor diameter [25,28], older age [36], treatment refractory tumors [26]).

Thresholds used for minimal AM were highly variable among studies: ≥ 0 mm (6/29; 21%); ≥ 1 mm (1/29; 3%); ≥ 2 mm (3/29; 10%); ≥ 3 mm (3/29; 10%); ≥ 5 mm (10/29; 34%) or a volume (1/29; 3%).

Anatomical location of LTP was investigated in 9 studies (9/29; 31%). In all studies, LTP occurred at the location where either residual non-ablated tumor or the thinnest AM was identified.

3.7. *Survival*

Only 3 studies (3/29; 10%) investigated the impact of AM on survival endpoints [28–30], all in the context of HCC treatment. Samples size ranged between 16 and 75 patients. Two out of three showed a significant difference in overall Survival [29,30] according to the AM.

4. Discussion

This systematic review identified clinical studies focused on software-based quantitative evaluation of AM. In all studies, feasibility of software-based assessment was claimed by the authors. Nevertheless, only 62–100% of registration success rate were reported in the articles. A considerable number of lesions were excluded from studies due to ascites [5,23,33], technical failure [29,31,33,37–39], incompatible image format [38], liver deformation or different patient's positions [13,35,37,39–41]. These are strong and frequently overlooked limitations of the currently available software. Artificial ascites, for instance, is commonly used during PTA to protect adjacent structures.

In 10/29 studies, the only risk factor for LTP was minimal AM [6,7,13,34,35,37,39,42–44]. Studies comparing visual and quantitative assessment reported an overestimation of AM with side-by-side assessment and reclassified some AM as inadequate, even though they were previously considered satisfactory [6,7,26,33,35–37,41,44]. For Kim et al., using side-by-side comparison, 34.5% (38/110) of tumors were considered with at least 5-mm AM *vs.* only 2.7% (3/110) with quantitative analysis ($P < 0.0001$) [6].

In a prospective study, Shin et al. found a significant difference ($P = 0.0101$) in terms of LTP between study group (10.67% with software-based assessment by HepaCare®) and control group (23.33% with visual assessment only) [5]. They demonstrated that extra registered CT images increased from 8% (12/150) to 23.33% (35/150) the proportion of patients requiring additional RFA. They also compared the 42-month disease free-survival rates, and found a significant difference between study group (52.67 %) and control group (28.89 %) ($P = 0.0027$). Tang H. et al. found a significant difference in 1-, 3- and 5-years OS rates between the group with AM ≥5 mm *vs.* the group with 0< AM <5 mm: 94.3%, 73.8%, 64.6%, *vs.* 86.2%, 60.5%, 47.6%, respectively ($P = 0.046$) [29]. They also found a significant difference in recurrence free-survival rate between these two groups (50.6% *vs.* 35.6% at 5 years; $P = 0.042$). These results suggest that a sufficient AM might be a predictive factor of patient's oncological outcome. Interestingly, many studies showed that LTP preferentially occured at the location of the thinnest AM [7,27,37,38,41,42,44,45].

In this review, 12/29 studies (41%) used post-PTA images performed 3 days – 1 month after PTA. However, the zone shrinks rapidly during the weeks following PTA, depending on the technique [46–48]. With irreversible electroporation, the ablation zone decreases much faster than with RFA or MWA or it even disappears completely [49]. These data underline that post-PTA evaluation should be performed as early as possible in order to precisely evaluate AM. Otherwise, there is a risk of underestimation. The ideal approach is certainly to perform post-PTA evaluation after completion of PTA, to allow re-ablation in case of incomplete treatment or insufficient margin. However, intra-procedural analysis of the AM basically implies performing PTA in CT rooms, even when they are performed under ultrasound guidance. Angio-CT systems incorporating three imaging modalities (ultrasound, CT, angiography) on-board have recently gained increased interest [50] worldwide and might improve even more the work-flow.

This systematic review highlights the considerable heterogeneity in the threshold for adequate AM. The same debate has been observed in surgery for decades [51]. Whatever the optimal threshold for AM, it remains questionable whether we are really able to achieve this threshold in all cases through re-ablation during or after the initial procedure. In the prospective study, for 22 patients with insufficient AM (using HepaCare® or visual inspection), only five of them have benefited from an additional RFA and one from transarterial chemoembolization [26]. The reasons why they could not perform additional RFA in the other cases were: nearby hepatic vessels, concerns regarding damage of anatomical structures at proximity (heart, central bile duct), patients' intolerance to additional RFA or unstable vital signs for additional conscious sedation. Shin et al. and Sakakibara et al. warned against the risk of overzealous treatment, which can be deleterious for patients with a considerable increase in the risk of complications and impairment of liver function [5, 44]. Ideally, assessment of a truly achievable AM based on anatomical criteria should be evaluated pre-operatively using registration software to make the decision to ablate or not and to personalize follow-up.

Other limitations within studies were identified. First, the time for use was one of the main limiting factors [13,43]. Time necessary to obtain AM could be as long as 20 minutes or more [13,27,29,31,34,40,41,43,52,53], which does not seem applicable in clinical practice. Physician-software interactions should be optimized in a sterile environment, through easy and fast process to be as close as possible to daily practice. This point has been overlooked in investigated series and certainly needs greater attention. Second, coregistration of two sets of imaging is a well-known challenge, especially in the liver. Defining anatomical landmarks on different image datasets to improve coregisration can be challenging, even for experienced radiologists, with the risk of many potential sources of error [13]. Despite non-rigid registration, difference in position and shape of the liver remains a limit to the quality or even the possibility of coregistration [27,37,39]. In this review, mean TRE was 1.62 mm (range: 1.20–2.23 mm). Within the same series, range for TRE could be larger, as in Kim et al. (mean TRE: 1.3 ± 1.1 [SD] mm; range: 0–8.4 mm) [23]. According to the Shannon Theorem, a registration error of 1.5 mm becomes significant for an expected margin of 3 mm or lower. Archip et al. reported that error registration was significantly lower in non-rigid than in rigid registration [22]. Nevertheless, in our systematic review, TRE did not really differ between rigid [7,40] and non-rigid [23,27,28,36] registrations. This might be mitigated by the fact that only one software (Integrated Registration, GE Healthcare) with rigid registration was evaluated. Rigid registration might be acceptable to determine whether AM is >3-5 mm, since it is faster and easier than non-rigid registration and it is reliable enough to provide such binary (*i.e.*, adequate *vs.* inadequate) evaluation. Third, the problem of subcapsular tumors is also a limitation of the assessment of AM by coregistration. Sandu et al. assumed that AM might appear erroneously small in quantitative measurements due to the inherent impossibility of obtaining AM in subcapsular tumors [53]. Therefore, they proposed an algorithm for accurate measurement. Finally, imaging-guided marked techniques (such as tumor tagging using ethiodised oil) were not used in series examined in this review [54]. Further studies are thus needed to evaluate the feasibility and performance of ablation-confirmation software in this context, yet particularly useful to address the issue of invisible tumors at ultrasound or CT [54].

Finally several limitations of this systematic review must be acknowledged. First, only one study was multi-center and only two were prospective. Therefore, the level of evidence is low with a lack of external validity. The ideal way to evaluate the benefit of such software-based assessment would have been a multi-center randomized study demonstrating a change in patient management that could translate into improved oncological outcome. Only one trial is ongoing, namely the randomized phase II trial (COVER-ALL, NCT04083378) with the aim to evaluate whether the feedback of non-rigid registration (using Morfeus software) during PTA will increase the minimal AM. Second, data from the different studies were difficult to homogenize due to a lack of standardization: some data were not systematically reported (TRE available in only seven studies, inter-operator reproducibility in five studies and time for use in 23 studies) or reported with various outcomes (cumulative incidence of LTP *vs.* LTP rate, variability of reported time of use, different definitions of ablation margins or complete ablation with different scores).

In conclusion, PTA of liver lesions has a growing importance in oncology and will certainly continue to expand. Software-assisted post-ablation assessment has an emerging role to improve and standardize PTA. In this review, we reported that AM was the only significant risk factor for LTP in most studies, underlining the major therapeutic impact of margin assessment software. However, available clinical studies present a low level of evidence overall since most of them are feasibility, retrospective and single-center studies and since they lack standardization in reported outcomes. Data summarized in this review should help to improve the state of the art in ablation-confirmation software with the ultimate goal to improve patients' outcome.

Human right

Not applicable for systematic review

Informed consent and patient details

Not applicable for systematic review

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CRediT authorship contribution statement

Chloé Minier: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Margaux Hermida:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Carole Allimant:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Laure Escal:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Marie-**

Ange Pierredon-Foulongne: Data curation, Formal analysis, Investigation, Writing – review & editing. **Ali Belgour:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Lauranne Piron:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Patrice Taourel:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Christophe Cassinotto:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Boris Guiu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Supplementary materials

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