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Research article

Interventional oncological treatment of hepatocellular carcinoma (HCC) - A single-center long-term evaluation of thermoablation techniques like LITT, MWA, and TACE in a multimodal application over 26 years

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Purpose

The purpose of the study is to retrospectively evaluate the development and technological progress in local oncological treatments of hepatocellular carcinoma (HCC) by means of ablation techniques like laser interstitial thermal therapy (LITT), microwave ablation (MWA) and transarterial chemoembolization (TACE) in a multimodal application.

Method

This retrospective single-center study uses data generated between 1993 and 2020 (1,045 patients). Therapy results are evaluated using survival rates of Kaplan-Meier estimator, Cox proportional hazard regression and log-rank test.

Results

Median survival times in group LITT (25 patients) are 1.6 years, and, 2.6 years for LITT + TACE (67 patients). For LITT only treatments 1-/3-/5-year survival rates scored 64%, 24% and 20%. Results for combined LITT + TACE treatments were 84%, 37% and 14%. Median survival time in group MWA (227 patients) is 4.5 years. Estimated median survival time for MWA + TACE (108 patients) leads to a median survival time of 2.7 years. In group MWA the 1-/3-/5-year survival rates are 85%, 54%, 45%. Group MWA + TACE shows values of 79%, 41% and 25%. A separate group of 618 patients has been analyzed with TACE as monotherapy. Median survival time of 1 year was estimated in this group. 1-/3-/5-year survival rates are 48%, 15% and 8%. - Cox

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regression analysis showed that the different treatment methods are statistically significant predictors for survival of patients.

Conclusions

Treatments with MWA resulted in best median survival rates, followed by MWA + TACE in combination. Survival rates of MWA only are significantly higher vs. LITT, vs. LITT + TACE and vs. TACE monotherapy.

Abbreviations

*HCC:*hepatocellular carcinoma;

*LITT:*laser interstitial thermal therapy;

*MWA:*microwave ablation;

*TACE:*transarterial chemoembolization

1. Introduction

Liver cancer is estimated to be ranked sixth among the most currently diagnosed cancer. It is the third leading cause of cancer-related death, with 905,677 new cases and 830,180 deaths reported in 2020 worldwide [1]. Hepatocellular carcinoma (HCC) is the most prevalent form of tumor originating from the liver. Potential curative therapy for patients qualified for a surgical intervention could be surgical resection or liver transplant. The benefits of hepatectomy for noncirrhotic HCC would be low perioperative morbidity and mortality and improved long-term outcomes [2]. Furthermore, a selected number of patients with decompensated cirrhosis could benefit from a liver transplant. Finkenstedt et al. reported excellent post-transplant survival for patients with intermediate-stage hepatocellular carcinoma responding to neoadjuvant therapy [3]. However, potential recipients outnumber donors by far, and only less than 20–25% of all patients, i. e. the minority of patients, can be considered for surgical resection due to the presence of multifocal tumors or limited hepatic reserve at the time of diagnosis. For patients with unresectable tumors, palliative treatment aims to manage symptoms, improve life quality and prolong survival [4].

In cases of unresectable liver metastases, modern interventional radiology offers minimally invasive techniques to target tumors locally. Additionally, ablation techniques show curative potential besides resection and liver transplantation [3,5]. Ablative therapies aim to destroy the tumor or eventually reduce its growth. Successful thermal ablation treatment methods are radiofrequency ablation (RFA), laser interstitial thermal therapy (LITT), and microwave ablation (MWA). LITT utilizes high-energy laser light, which induces an increased regional temperature after local absorption by the tissue. The main advantage of LITT over other ablative methods is the ability to monitor the ablation process using thermosensitive T1 sequences. The need to place the sheath for the laser fiber under CT guidance and patient transfer to MRI after that make it a time consuming procedure. The main indication for LITT are patients with five or less liver metastases with a maximum size of 5 cm each.

MWA functions based on the emission of microwaves through a tip of an antenna. These microwaves induce atomic and dipole rotation resulting in friction among high content of water molecules in the tissue. As a result, temperature increases, which finally causes tumor cell death via coagulative necrosis [6]. The consequent thermal ablation would be confined to the particular volume of the necrosis in the ablation zone [7,8]. The technological elaboration of microwave ablation systems gradually gained its popularity in HCC management, especially since the whole ablation procedure can be performed in a relatively short time (less than RFA and LITT), and without the need to transfer the patient between two machines (CT and MRI as in LITT).

Transarterial techniques such as chemoembolization (TACE) and radioembolization (TARE) are shown to be effective therapies that could significantly increase the patient's survival rate. These methods could be utilized as monotherapy for neoadjuvant, symptomatic, or palliative therapy; or be combined with thermal ablation treatments. Thus, thermal ablation, surgical resection, TACE, and TARE could be considered bridging treatments. Smolock et al. report synergetic results for treating HCC up to 3–5 cm using a combined therapy of TACE and MWA compared to TACE as monotherapy. The optimal interval between chemoembolization and thermal ablation is one and two weeks. This period contributes to patient recovery from possible post-embolization symptoms and improved visual contrast for targeting the tumor [9]. Patients with Barcelona Clinic Liver Cancer (BCLC) stage B with multiple and/or large tumors could also benefit from TACE. The objective is the complete devascularisation of all focal tumors by protecting non-affected parts of the liver. TACE, therefore, is performed in several treatment sessions to achieve complete devascularisation of all tumors [7].

The objective of this long-term study is to retrospectively evaluate the development and technological progress in local oncological treatments of HCC over 26 years. The aim is to assess ablation techniques like LITT, MWA, and TACE based on survival time analysis. The findings could guide further research and enhance clinical application. Between 1993 and 2020, the therapies employed in our department evolved. LITT was mainly used for the treatment of HCC between the years 1993 and 2011. However, MWA has slowly replaced LITT with an increasing trend since 2008. TACE treatments were initially applied in 1996. Although RFA is a successful treatment method for specific therapies, they were not included in this study due to the small size of patient groups. Similarly, a small number of patients that received a combination of LITT + MWA treatments were excluded from our study.

2. Materials and methods

This retrospective single-center study analyses the patients treated between 1993 and 2020 in our institute. The ethical committee of the university hospital approved the study. Patient data were extracted from our institute's internal data system after receiving Institutional review board approval. The final data set of 1,045 patients was created based on the following inclusion and exclusion criteria.

3. Patients' selection criteria

As an initial step, the database had to be filtered regarding consistency and completeness of key selection criteria. Main data elements were the availability of the dates of the first and last treatment, and the date of last contact or death. Data regarding tumor stage or other information about cancer relevant health status of patients were not available or were not consistently reported in the database and therefore could not be considered in this study.

The analysis of our dataset concentrates on patients with HCC as the only known primary tumor and as the only ablation treatment region. Narrowing this field of analysis allows focus; however, it limits the number of cases in our database. Within this entity of datasets, five groups were selected in order to analyze different types of relevant treatments or combinations of treatments. We differentiated patients who were treated with LITT, LITT + TACE, MWA, MWA + TACE or TACE as monotherapy.

A very small number of patients received both LITT and MWA during the transfer phase of the ablation from LITT to MWA in our department. This small number of patients was excluded to avoid overlap and inconsistency in the analysis.

3.1. *Treatment selection criteria*

Regarding this long observation period, it has to be considered that treatment methods did evolve over time i.e. chronologically. LITT was applied in earlier phases followed by MWA in later phases. Hence, the decision to treat using LITT or MWA ablation was not based on specific selection criteria related to the patient stage or size of the tumor, but the decision to ablate regardless of the method used was based on the size and number of metastases. For the metastases that did not meet the ablation criteria, TACE was used as a neoadjuvant/down staging procedure to reduce the size, and less likely, the number of metastases to achieve the indication criteria for ablation. It was also used to reduce tumor vascularity and maximize the ablation effect in large lesions. Cases with failed adequate down staging under TACE, remained as TACE monotherapy. TACE as monotherapy has been selected for comparison reasons. This group needs to be interpreted carefully, since TACE treatments as monotherapy were clearly performed in patients with resistant and advanced stages of liver metastases as in patients with TACE and ablation or ablation only.

Overall, the patients' status may certainly differ regarding several health criteria and cancer relevant factors. More solid models would require an extended set of several factors. If available, the addition of factors like tumor size and stage data and the extent of liver involvement may offer further insight. However, it would still leave the discussion open regarding possible effects of other highly relevant parameters. Concerning the amount of cases, further grouping by more factors would lead to further reduction in group size with limited possibilities of statistical analysis.

As a first long-time analysis based on our dataset, this study therefore excludes further multivariate analysis of patients' status. However, it does consider the impact of age, and statistically analyses the initial key question of whether different treatment methods affect survival. The following steps may evaluate possible model extensions including other data sources and further in-depth analysis.

In summary, inclusion criteria are:

- hepatocellular cancer as a single primary tumor (ICD-10 C22.0)
- liver as the only treatment region
- only LITT or LITT + TACE
- only MWA or MWA + TACE
- only TACE as monotherapy
- documented first and last date of treatment at our Hospital
- documented date of birth, and, in case of death, the date of death
- a maximum tumor size of 3 cm diameter for LITT and MWA
- a maximum tumor size of 5 cm diameter for TACE
- maximum number of 3 lesions for LITT and MWA

Exclusion criteria are:

- tumor other than HCC
- missing or inconsistent data
- combinations of MWA and LITT
- combinations of different ablation regions
- patients treated with RFA

3.2. Statistical methods

Raw data was extracted using Microsoft Excel. Excel tables were used as input files for statistical analysis using SPSS, Version 22, as well as R package 4.1, especially software packages „survival“ and “ggplot2” [10,11]. As our primary outcome, overall survival rates were illustrated by the Kaplan-Meier survival estimator [12]. Survival rates and 95%-confidence intervals were calculated by Cox proportional hazard regression. The starting point for calculating the estimator was the date of the first ablation session at the institute. The end date for the calculation was the date of death or the last contact with the patient, either the last ablation session at the institute or the last follow-up date.

Differences between groups of patients based on treatment modalities were analyzed using the Cox-Mantel log-rank test and Kaplan-Meier survival estimates. A p value ≤ 0.05 was considered statistically significant. The sample size was based on available, consistent datasets in the database of our department. Cox regression was used as a prediction method to analyze relations between several predictors of survival [13]. The risk of death was estimated via hazard ratios, including 95%-confidence levels. For all tests, p-values <0.05 was considered significant.

4. Results

Over 26 years, an increasing number of patients were treated for HCC in our institution, and the modalities used changed tremendously. LITT was first documented in 1993 and was mainly performed between 1993 and 2011, with a declining trend after 2008. MWA was first documented in 2008, and the number of procedures increased afterward. Therapies with TACE were performed between 1996 and April 2020, which was the last treatment available within the chosen time frame for this study.

Patients’ characteristics, including age and sex, number of treatments received, and complications, are presented for five treatment modalities or combinations in Table 1.

A total of 25 patients were treated with LITT in 35 treatment sessions, including 19 males and 6 females. The group consisted of patients between 36 and 82 years, with a median age of 68 (Table 1). Considering the group treated with a combination of LITT + TACE, ablation with LITT was applied 94 times among 67 patients, including 50 males and 17 females. A total of 367 treatment cycles with TACE were documented for this group, with 5.5 cycles per patient on average. Patients’ age was between 42 and 85 years with a median age of 68.

227 patients were treated with MWA, averaging 1.7 treatments per patient and 384 treatment cycles combined. 108 patients received a combination of MWA + TACE, with an average of 2.1 MWA per patient in combination with 7.1 TACE cycles per patient. Patients in group MWA were slightly younger than the MWA + TACE group, with an average age of 65 and 68,5 years, respectively.

In our study, we analyzed 618 patients solely treated with TACE. On average, patients were treated 4,1 times with TACE with a median survival time of 1 year. This method reached the highest amount of 2.544 treatments in total.

The complication rate after LITT, LITT + TACE, MWA, and MWA + TACE were 8.6%, 6.4%, 1%, and 0.4%. The lowest complication rate was reported after treatment with MWA + TACE at only 0.4%, followed by MWA with only 1.0%. Post-interventional complications included pleural effusion, subcapsular hematoma, cutaneous wound infection, abscess, and injury of the gallbladder and bile ducts. Pleural effusion was the most common complication after LITT procedures. Common side effects of chemoembolization were postembolization symptoms, which could persist for one week and were treated with antiemetics and analgetics when needed [14]. No post-interventional mortality was reported among the five categories.

Table 2 provides information concerning the survival time for each group. The number of patients is presented in the first row. The number of events indicates cumulative incidence rates, i.e. cases of death. Survival time is presented as the mean and median time values in years (median with upper and lower confidence intervals). 1-, 3- and 5-year survival rates (%) with 95%-confidence intervals by treatment method were calculated based on Cox proportional hazard regression.

The median survival time for the patients treated with LITT was 1.6 years, with a mean survival time of 2.7 years. 1-, 3- and 5-year survival rates were 64% (95%CI: 45%–83%), 24% (95%CI: 7%–41%) and 20% (95%CI: 4%–36%) respectively. During the study period, 24 events of death were documented among a total of 25 patients.

Table 1
Characteristics of patients and results.

Characteristics	LITT	LITT +	TACE	MWA	MWA +	TACE	TACE	TOTALS
Number of patients	25	67		227	108		618	1045
… Male	19	50		178	90		486	823
… Female	6	17		49	18		132	222
Number of treatments	35	94		384	227			740
… Average number of treatments per patient	1,4	1,4		1,7	2,1			
Number of TACE cycles			367			769	2544	3680
… Average number of TACE cycles per patient			5,5			7,1	4,1	
Complication rate per treatment (total) (%)	8,6%	6,4%		1,0%	0,4%		N/A	
Age of patients at first treatment (years)								
… Median age of patients (years)	68	68		65	68,5		67	
… Minimum (years)	36	42		32	20		15	
… Maximum (years)	82	85		85	88		91	

Table 2
Mean values, median and 1-/3-/5-year survival rates (%) with 95%-confidence intervals by treatment method (calculated values based upon Cox proportional hazard regression).

Characteristics	LITT	LITT + TACE	MWA	MWA + TACE	TACE	TOTALS
Number of patients	25	67	227	108	618	1045
Events	24	65	51	55	440	635
Mean survival time (years)	2,7	2,9	6,7	3,8	1,8	2,5
Median survival time (years)	1,6	2,6	4,5	2,7	1,0	1,4
Median lower CI	0,6	1,8	2,7	2,0	0,9	1,3
Median upper CI	2,5	3,0	NA	3,2	1,1	1,6
1-year survival time	64	84	85	79	48	61
1-year 95% lower CI	45	75	79	71	44	58
1-year 95% upper CI	83	92	91	88	53	65
3-year survival time	24	37	54	41	15	26
3-year 95% lower CI	7	25	44	30	12	23
3-year 95% upper CI	41	49	65	53	19	29
5-year survival time	20	14	45	25	8	14
5-year 95% lower CI	4	5	29	13	5	11
5-year 95% upper CI	36	22	60	38	11	18

Patients treated with the LITT + TACE combination (67 patients; 65 events of death) had a median survival time of 2.6 years with a mean time of 2.9 years. 1-, 3- and 5-year survival rates were 84% (95%CI: 75%–92%), 37% (95%CI: 25%–49%) and 14% (95%CI: 5%–22%).

The median survival time for the patients treated with MWA was 4.5 years, with a mean time of 6.7 years (227 patients; 51 death events, others: censored observations). The 1-, 3-, and 5-year survival rates were 85% (95%CI: 79%–91%), 54% (95%CI: 44%–65%), and 45% (95%CI: 29%–60%).

The median survival time for MWA + TACE was 2.7 years, with a mean value of 3.8 years and 55 and 55 reported deaths among 108 patients. The patients' 1-, 3-, and 5-year survival rates were 79% (95%CI: 71%–88%), 41% (95%CI: 30%–53%), and 25% (95%CI: 13%–38%).

Among 618 patients who underwent TACE monotherapy, the median survival time was 1 year, with a mean value of 1.8 years. 1-, 3-, and 5-year survival rates were 48% (95%CI: 44%–53%), 15% (95%CI: 12%–19%), and 8% (95%CI: 5%–11%).

Fig. 1 summarizes the timelines for the cumulative incidence rates, i. e. events, by treatment method. Kaplan-Meier graphs for all five groups are shown: MWA, LITT, MWA + TACE, LITT + TACE, and TACE monotherapy. The table underneath provides further details concerning the number of patients, including patients "at risk," events including patient's death, and the date by which an observation ended, which would be either date of death or the last date of contact with a patient. Dots along the curves represent

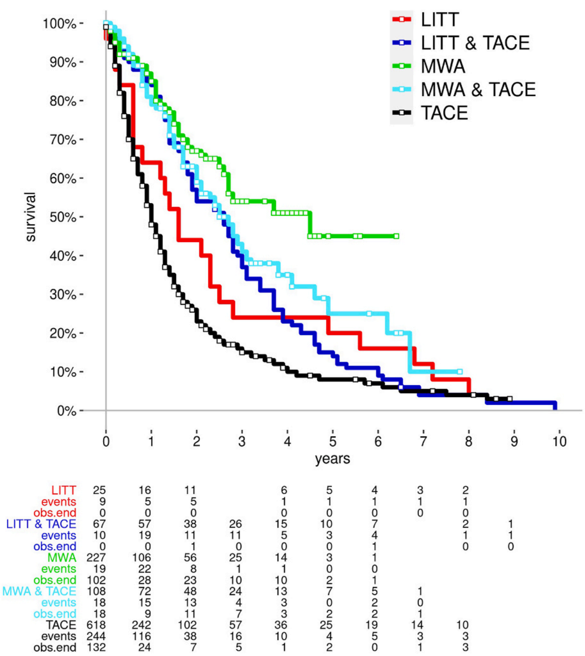


Fig. 1. Kaplan-Meier estimator for different treatment methods MWA, LITT, MWA + TACE, LITT + TACE, TACE and list of events along the time line. Data for number of patients at risk, number of events (death of patient) and number of patients where the observation ended (obs.end).

censored observation, i. e. patients who have left the observation/the study. Several dots may overlay at one point in time.

An example of a combined TACE and MWA treatment is shown in Fig. 2. The MRT scans in Fig. 2a) and b) highlight the liver metastasis before partial remission. Fig. 2c) depicts the TACE treatment as an angiography of the liver, and Fig. 2d) illustrates the CT scan post-embolization. Effects of the chemoembolization can be seen in Fig. 2e) and f) during the follow-up MRT 2 months after the TACE treatment. Fig. 2g) contains the CT scan of MWA 8 months after TACE treatment. MRTs scan 24 h after MWA treatment are displayed in Fig. 2h and i).

Table 3 provides a descriptive comparison between pairs of Kaplan-Meier curves for all possible therapy combinations using a log-rank test. For example, LITT vs. MWA (row b) shows relatively superior survival times ($p = 0.0002$). LITT + TACE vs. MWA scores a p-value of 0.005. Comparing MWA with TACE leads to a p-value <0.001; this is also the case for MWA + TACE vs. TACE.

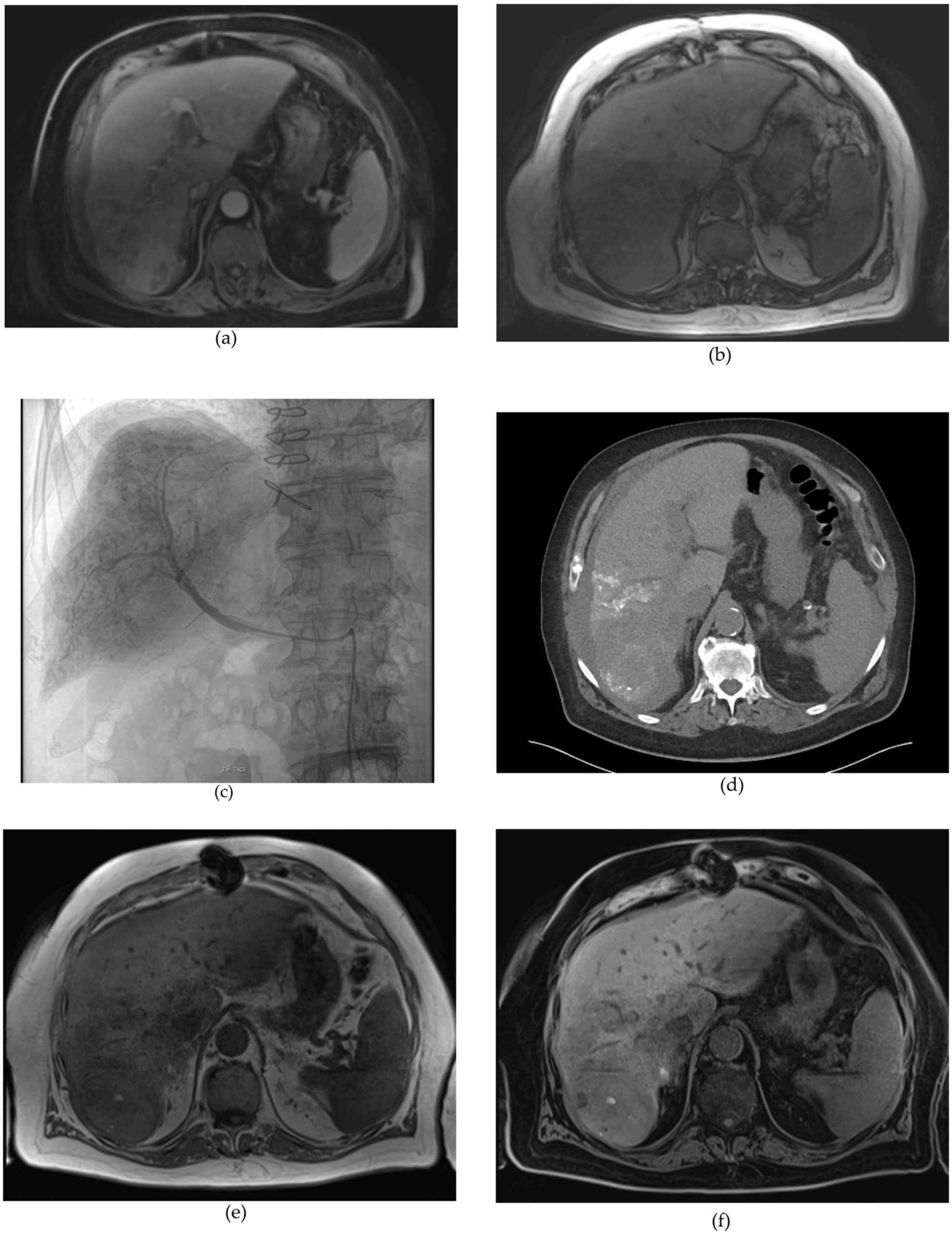
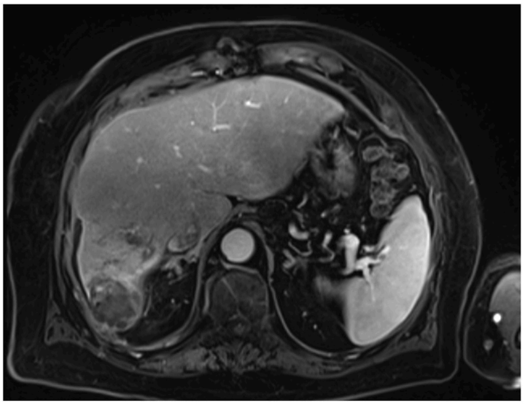
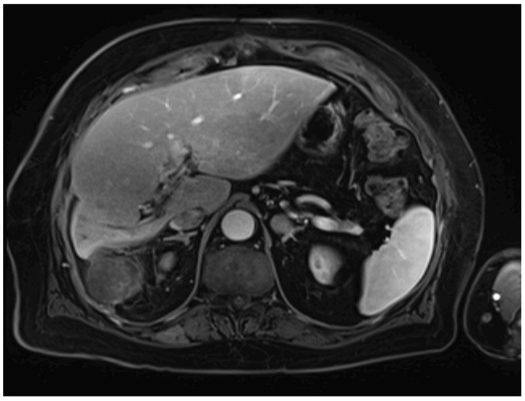


Fig. 2. Treatment of patient with HCC with combined TACE and MWA (a) Initial MRT of metastasis before partial remission (b) Initial MRT of metastasis before partial remission (c) TACE treatment. Angiography of liver. (d) CT scan post embolization. (e) MRT check. 2 month after TACE treatment (f) MRT check. 2 month after TACE treatment (g) CT MWA. 8 months after TACE treatment (h) MRT. 24 hrs. After MWA treatment (i) MRT. 24 hrs. After MWA treatment.

(g)



(h)



(i)

Fig. 2. (*continued*).

Table 3
Descriptive comparison between pairs of Kaplan-Meier curves using log rank-test.

#	Method 1		Method 2	p-value	n (total)	n1	n2
A	LITT	vs.	LITT & TACE	p = 0.850	n = 92	25	67
B	LITT	vs.	MWA	p = 0.002	n = 252	25	227
C	LITT	vs.	MWA & TACE	p = 0.133	n = 133	25	108
D	LITT	vs.	TACE	p = 0.092	n = 643	25	618
E	LITT & TACE	vs.	MWA	p = 0.005	n = 294	67	227
F	LITT & TACE	vs.	MWA & TACE	p = 0.210	n = 175	67	108
G	LITT & TACE	vs.	TACE	p < 0.001	n = 685	67	618
H	MWA	vs.	MWA & TACE	p = 0.088	n = 335	227	108
I	MWA	vs.	TACE	p < 0.001	n = 845	227	618
J	MWA & TACE	vs.	TACE	p < 0.001	n = 726	108	618

A descriptive comparison between pairs of Kaplan-Meier estimates for all possible therapy combinations using a log-rank test is shown in Table 3. There was a significant difference in survival rates between the treatment methods when comparing LITT vs. MWA ($p = 0.0002$), LITT + TACE vs. MWA ($p = 0.005$), MWA vs. TACE ($p < 0.001$), and also comparing MWA + TACE with TACE ($p < 0.001$).

Table 4
Cox regression test adjusted by age of patients and sex (female) (n = 1045, model: $p < 0.001$, $R^2 = 0.0627$).

Predictors	p-value	Hazard ratio	Lower 95%-CI	Upper 95%-CI
Method	0,000	1,327	1,232	1,430
age of patient at first treatment	0,005	1,011	1,003	1,019
Female	0,536	0,943	0,783	1,136

The Cox regression test results as a general test are shown in Table 4, which includes all treatment methods adjusted by the age of patients and sex (share of patients coded as a female in the database). The predictive values of the different treatment methods, not adjusted by the age of patients and sex, are shown in Table 5 by multiple univariate models, i. e. one statistical model per method. Each chosen method is compared to the other methods excluding the chosen method concerning survival prediction. For example, LITT therapy alone was compared to non-LITT therapies. The age of patients and sex as potential predictors are not included in this statistical test, and p-value ≤0.05 indicates a statistically significant predictor for survival, which includes therapies with MWA, MWA + TACE and TACE (p = 0.000). Therapies with LITT and LITT + TACE were not statistically significant predictors, with a p-value of 0,683 and 0,127, respectively. The hazard ratios in the adjacent column indicate the risk of non-survival compared with all other treatment methods applied to the total population of patients.

The results of the multivariate statistical analysis after adjustment by the age of patients and sex are shown in Table 6. The adjustments allow for the calculation of statistical effects of additional potential survival factors such as age and/or sex. Due to restrictions of the algorithm, four ablation methods of LITT, LITT + TACE, MWA, and MWA + TACE were included simultaneously as potenti5al predictors for survival, as well as the age of patients and sex (female). The TACE, as a result, was excluded from the analysis. The test shows the statistical significance of the chosen treatment methods while considering the age and sex of the patients. Hazard ratios associated with the risk of death after each therapy method are shown in the adjacent column as an estimation for the non-survival of patients (Table 6). The estimated Hazard ratio for MWA, MWA + TACE, LITT + TACE, and LITT were 0.29, 0.41, 0.56, and 0.64, respectively. The hazard ratio for the age of patients was 1.01 (95%CI: 0.3–1.9).

5. Discussion

To our knowledge, this is the first retrospective single-center study over a relatively long time period of more than 26 years. The study analyses various patients and treatments performed between 1993 and 2020 (pre Covid-19). Over this period, treatment concepts towards HCC evolved tremendously. This paper aims to point out achievements made in interdisciplinary therapy management over the past 26 years, considering the survival rates of patients with HCC. A total of 740 ablation treatments with LITT or MWA, and 3,680 TACE-cycles, partially applied as combination therapies, were recorded in a sample size of 1,045 patients, including 823 males and 222 females. In total, 635 events of death were recorded during the studied period, others are considered as censored observations.

Earlier in the study period, ablative therapy with LITT was performed. Later on, MWA replaced LITT considering the number of treatments of HCC. Currently, percutaneous ablation of HCC is mainly performed by either RFA or MWA [7]. However, due the limited number of cases, therapies done by RFA were excluded in this study.

The 5-year survival rates after MWA was higher compared to LITT with 45% (95%CI: 29%–60%) and 20% (95%CI: 4%–36%) respectively. More TACE-cycles per patient were performed in MWA + TACE group than LITT + TACE. The 3- and 5-years survival probability rates in group MWA + TACE were 41% and 25% which was higher than the 37% and 14% rate in group LITT + TACE. Furthermore, the lowest post-interventional complication rates among all groups were observed after MWA + TACE and MWA with 0.4% and 1%, respectively. The difference between MWA and MWA + TACE results may be explained by patients' characteristics regarding cancer classification leading to additional TACE applications.

We compared the survival rates using the Kaplan-Meier estimator to evaluate the difference between various therapeutic effects. Our results show a statistically significant difference in survival rates comparing LITT vs. MWA ($p = 0.0002$) and LITT + TACE vs. MWA ($p = 0.005$). Higher survival rates were also confirmed between MWA with TACE ($p < 0.001$) and similarly between MWA + TACE and TACE ($p < 0.001$).

Evaluation of all treatment methods adjusted by the age of patients and sex using the Cox regression test (Table 4) confirms that the chosen treatment method remains a statistically significant predictor for survival rate, and is relevant for the survival of patients. Although the sex of patients ($p = 0.536$) seems not to be a influential predictor, the age of patients appears to be statistically significant predictor. The hazard ratio in the next column of Table 4 indicates, e.g. HR = 1.011 for the age of patients, that an increase in the age of patients by a +1 year the risk for the respective population increases by +1.1%. Different levels of hazard ratios (HR) are driven by the scale of the indicator: the chosen treatment method (methods 1…5) therefore has a span from 1… 5, age of patients spans according to the age within the population e. g. between 50… 90 years.

Our results indicate MWA, MWA + TACE, and TACE were statistically significant survival predictors when not adjusted by the age of patients and sex using univariate analysis (Table 5). However, therapies including LITT and LITT + TACE were not significant survival predictors in this population.

The multivariate statistical analysis after adjustment by the age of patients and sex in four ablation methods of LITT, LITT + TACE, MWA, and MWA + TACE confirmed the statistical significance of the chosen treatment methods while considering the age and sex of

Table 5
Cox regression test not adjusted by age of patients and sex (f/m) as multiple univariate models.

Predictors	p-value	hazard ratio	lower 95%-CI	upper 95%-CI
LITT	0,683	0,918	0,609	1,385
LITT & TACE	0,127	0,818	0,632	1,059
MWA	0,000	0,359	0,269	0,478
MWA & TACE	0,000	0,557	0,422	0,734
TACE	0,000	2,330	1,964	2,763

Table 6
Cox Regression, adjusted by age of patients and sex (f/m) as a multivariate model (n = 1045, model: $p < 0.001$, $R^2 = 0.1156$).

Predictors	p-value	Hazard ratio	Lower 95%-CI	Upper 95%-CI
LITT	0,037	0,644	0,425	0,974
LITT & TACE	0,000	0,564	0,433	0,735
MWA	0,000	0,290	0,217	0,388
MWA & TACE	0,000	0,410	0,309	0,544
Age of patient at first treatment	0,009	1,011	1,003	1,019
Female	0,450	0,930	0,772	1,122

the patients. The analysis confirms the patient's age to be a relevant factor. However, the sex of patients is not statistically relevant. Accordingly, the included four treatment methods are relevant for predicting survival in the selected population. Hazard ratios associated with the risk of death after each therapy method estimate the risk of non-survival of patients (Table 6). The Hazard ratio of 0.64 (95%CI: 0.425–0.974) for LITT indicates a risk-of-death factor of 1–0.64, i. e. a risk factor of −35.6%. Hence, after therapy with LITT, the risk of death is 35.6% improved compared to all other factors included in the model. Accordingly, a lower HR of 0.29 for MWA suggests a 71% improved risk of death compared to all other factors. The lowest Hazard ratio was estimated for MWA (0.29), followed by MWA + TACE (0.41), LITT + TACE (0.56), and LITT (0.64).

In our study, we analogized ablation methods and their combination with TACE as well as TACE monotherapy as a comparison. However, TACE monotherapy is applied to a broader range of tumor stages, like intermediate stages (B), with the purpose of downstaging and early stages (A) in cases of further treatment after initial ablation sessions. Hence, the results of this category should be interpreted more cautiously. It has been included to offer results within the array of relevant applied methods and the statistical significance of each method on survival.

The evolution of technology used for the interventions, including the instruments, the imaging technology, and the later development of chemoembolization during the study period, might impact the results—additional research focusing on each singular modality and the impacts on therapeutic efficacies is therefore recommended.

The treatment success through resection or ablation depends on multiple other factors. Tumor size, the number of lesions, and the degree of liver dysfunction are among those factors which are not considered in our study [15]. For most patients with HCC up to a size of 3 cm, resection and ablation are considered equivalent treatments. Thermal ablation should be offered in the case of HCC with a size of less than 3 cm, unfavorable localization, or limited liver function [7]. Perilesional micrometastasis is common in larger tumors, as shown by Fukutomi et al. in cases of HCC > 3 cm and < 5 cm compared to tumors ≤3 cm [16]. Prior TACE therapy can therefore increase the effectiveness of thermal ablation treatments and enable larger ablation regions that could cover the safety distance. The synergetic effects of such combination therapies are already confirmed by more than 200 studies [7].

Additional studies evaluating more comprehensive data, including patients' characteristics, liver function, tumor size, cancer stage, the extent of liver involvement, and risk factors for HCC, might help clarify further factors impacting the survival rates. The differences in patients' health status and cancer-relevant factors might also affect the therapeutic efficacy, which requires the development of solid models to analyze an extended set of parameters.

As our dataset's first long-term analysis, the current study's primary objective was to clarify the impact of different treatment methods on survival rate. Due to the limited number of patients, designing smaller but more well-defined groups of patients by considering additional factors would limit the strength of the statistical analysis. Therefore we initially considered two patients' characteristics of age and sex and refrained from further multivariate analysis of other characteristics.

One of the main limitations of the current study is the lack of data regarding the size, number and location of the treated lesions in the liver. The main reason is the lack of imaging studies for patients performed before full digitalization of our department, those studies were either given to the patients as hard copies, stored as hard copies in archives or destroyed after exceeding the legal obligatory storage duration. Still due to the consistent protocol of ablation in our department over the years regardless of the ablation method used it can be assumed that patients who were treated with LITT had similar tumor criteria as those treated with MWA since both methods were used chronologically and not at the same time (except for a very short overlap time). The second limitation is that we included a group of patients with more advanced and/or resistant lesions namely the TACE only group since this represented patients who were outside the ablation criteria or with failed downsizing. However, this group was included to complete the spectrum of our study, which aimed at addressing the long-term survival following interventional management of breast cancer liver metastases. Further studies comparing these interventional procedures in randomised studies, while taking into consideration detailed tumor criteria, are required to overcome limitations of the current study.

However, we acknowledge that future in-depth analysis of more comprehensive data would be a crucial next step.

Our analysis confirms the results of previous studies concerning the positive therapeutic effect and clinical relevance of MWA. Additionally, our study demonstrates that survival rates of patients treated with different ablation methods are not solely affected by increasing patients' age but also the chosen treatment method could significantly influence the survival of patients. This initial long-term analysis could therefore be considered the foundation for further comprehensive research regarding the evaluation of techniques and selection of specific groups of patients.

6. Conclusion

During the relatively long observation period, the therapeutic approach toward the HCC, the decision factors, and the eligibility criteria for patients have changed, and the duration of procedures decreased. For example, in the earlier years, LITT was the method more frequently used, which was then replaced by MWA in later phases.

For patients with HCC, percutaneous thermal ablation in combination with TACE treatments show significantly higher survival rates when compared to TACE monotherapy. Similarly, survival rates also show significantly higher values for MWA compared to LITT. However, TACE monotherapy did not show significantly higher survival rates when compared to both groups of LITT and LITT + TACE.

Treatments with MWA resulted in the best median survival time estimations, followed by MWA + TACE in combination. Survival rates of MWA and MWA + TACE treatments were significantly higher than TACE monotherapy, LITT, and LITT + TACE, indicating that these treatment methods might be promising modalities for treating unresectable HCCs.

However, further analysis over a more extended period comparing the effectiveness of methods regarding survival rates is still needed. Our analysis contributes to achieving more reliable indications and long-term effects of the chosen ablative methods. However, further evaluations should clarify the efficacy and priority of these therapies for patients with HCC. The current study provides the foundation for further research regarding the in-depth evaluation of techniques and selection of specific groups of patients. Prospective data remain necessary to evaluate the superiority of either modality further.

Author contribution statement

Thomas J. Vogl, Jason Freichel, Tatjana Gruber-Rouh, Nour Eldin Mohammed, Wolf-Otto Bechstein, Stefan Zeuzem, Nagy N.N. Naguib: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Ulrich Stefenelli: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data included in article/supplementary material/referenced in article.

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