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Comparative study evaluating pain after hepatectomy versus percutaneous microwave ablation in hepatocellular carcinoma patients: retrospective analysis of a single center's experience

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Abstract

Purpose: To compare post-therapeutic pain and analgesia following surgical hepatectomy versus image-guided percutaneous microwave ablation (MWA) for the treatment of hepatocellular carcinoma (HCC).
Material and Methods: This is a retrospective, single-cener, study of 64 consecutive patients with HCC, who underwent either partial hepatectomy (Group A: 32 patients) or image-guided MWA (Group B: 32 patients) between January 2015 and January 2017. In Group B, MWA was performed under local anaesthesia and conscious sedation. The study's primary outcome measure was the comparison of daily pain score between the two groups, using a self-reported Numeric Visual Scale (NVS) questionnaire. Secondary outcome measure included the comparison of required analgesics (type and dose) administrated. Pain score comparison between the two groups was performed with independent samples Mann-Whitney U test.
Results: Mean pain score was significantly lower each day for Group B compared to Group A (NVS units: 1.82 ± 1.88 vs. 7.67 ± 0.88 in day 1; 0.64 ± 0.84 vs. 7.43 ± 0.93 in day 2, 0 vs. 6.97 ± 1.12 in day 3 and 0 vs. 6.35 ± 1.08 in day 4; $p<0.001$, respectively). In Group A, 13/32 patients (40.6%) required patient controlled analgesia (PCA) using intravenous infusion pump and 19/32 patients (59.4%) underwent epidural catheter placement. In Group B, 4/32 patients (12.5%) required minor analgesia (single intravenous dose of paracetamol)

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only during the first day.
Conclusions: According to the self reported pain scores, image-guided percutaneous MWA resulted in significantly less pain during the follow-up period compared to partial hepatectomy, without the need of epidural or intravenous pump analgesia.

KEY WORDS
pain; hepatectomy; microwave ablation; hepatocellular carcinoma

Introduction

According to the Barcelona Clinic Liver Cancer (BCLC) Staging System, percutaneous thermal ablation techniques are widely accepted treatment options for very early and early stages of HCC [1, 2]. Nowadays, the most commonly used percutaneous thermal modalities for liver tumours include radiofrequency ablation (RFA), microwave ablation (MWA) and cryoablation [3-6]. The extensive use of newer, modern devices for imaging and thermal ablation significantly increased the accuracy, efficacy and safety of percutaneous treatments and decreased complication rates [7]. Post-ablation pain has been reported as a frequent post-procedural adverse event. In most of the cases pain is not severe and auto-resolves in a few days, while it mainly occurs at the treatment site or right shoulder [8]. The frequency and the intensity of post-ablation pain have been related to the total ablative zone and the proximity of the lesion to the liver capsule [9, 10].

The more recent MWA technology creates higher thermal effect to the neoplastic tissue in less time, with most predictable ablation zone when compared to RFA [11]. This is the main reason why it has become the preferable ablative technique in cases requiring larger ablation zones [12-16]. The frequency of complications, such as post-ablation syndrome and pain, between these two thermal ablation techniques seems to be similar [17]. Nevertheless, data comparing post-operative pain between percutaneous ablation techniques and open surgical treatment in malignant liver disease are scarce. Currently, there are no published quantified data comparing pain following hepatectomy versus MWA for HCC.

Open surgical resection of primary lesions of the liver is the main therapeutic option in many cases. The surgical techniques (open and laparoscopic) are based largely on the anatomic description of functional segments, which in turn is based on the organ's blood supply via the hepatic artery and portal vein, its venous drainage via the hepatic veins and, finally, its biliary drainage. Division of the liver into eight functional segments is the most widely-accepted anatomic definition used in the context of hepatic resections [18, 19]. The type of hepatectomy depends on the size, the localisation and the number of the hepatic lesions. Central lesions that infiltrate the great vessels of the liver are excluded from open surgical repair. Partial hepatectomy (wedge resection-atypical segmentectomy) can be performed safely when the lesion is located in the periphery. Postsurgical haemorrhage and liver insufficiency are the most frequent major complications after hepatectomy [20].

We sought to compare post-procedural pain and analgesia following percutaneous, image-guided MWA versus open surgical hepatectomy in patients with HCC.

Material and Methods

This is a retrospective, single-center study, investigating 64 consecutive patients who underwent either hepatectomy or image-guided percutaneous MWA due to HCC between January 2015 and January 2017. The study's inclusion criteria were in accordance to the BCLC criteria for HCC treatment (EASL-EORTC clinical practice guidelines). Patients included in our study were at the age of 18 years or older, with HCC of 1-4 cm maximum diameter and no more than five lesions. All patients with extrahepatic disease, coagulation disorders, platelets <50x109 /L, Child-Pugh class C disease, biliary dilatation or ascites were excluded from the study.

Patients were divided in two groups. A complete blood count and biochemistry profile were performed in both groups, before and after the percutaneous ablation and partial hepatectomy, with particular attention to indices of hepatic function, haemoglobin, bilirubin, AST, ALT and white blood cell counts. All patients had a pre-procedural abdominal computed tomography (CT) scan (range 1 to 50 days before the procedure). Post-proce-

Table 1. Patient demographics and procedural baseline variables

	Group A	*Group B*
AGE	**61 years - range 18-80**	**65 years, range: 35-85**
MALE-FEMALE RATIO	20-12	17-15
CHILD-PUGH STAGE	STAGE A: 32/32	STAGE A: 26/32 STAGE B: 6/32
CIRRHOSIS AETIOLOGY	HCV: 16/32 HBV: 4/32 ALCOHOL CONSUMPTION 12/32	HCV: 18/32 HBV: 3/32 ALCOHOL CONSUMPTION 11/32
HEPATECTOMY TYPE	22 RIGHT HEPATECTOMY 6 PARTIAL HEPATECTOMY 4 LEFT HEPATECTOMY	
ABLATION PROTOCOL	40W x 5 min (12/32) 40W x 10 min (14/32) 60W x 10 min (6/32)	

dural contrast-enhanced abdominal CT scan was performed the following day, for initial assessment of the extent of the ablation zone and to detect any subclinical complications.

Patients who underwent hepatectomy were included in Group A (32 patients; 20 male, 12 female, mean age 61 years, range 18-80 years). Surgical partial hepatectomy was performed under general anaesthesia by three general surgeons with over ten years of experience in hepatobiliary surgery. Most of the patients included in Group A (submitted to hepatectomy), underwent right hepatectomy (22 patients), whereas significantly fewer had partial hepatectomy (6 patients) and left hepatectomy (4 patients). Postoperative opioid analgesics, epidural anaesthesia and PCA were available. All patients of the hepatectomy group required hospitalisation after surgery, ranging from 5 to 20 days.

Patients in Group B, (32 patients; 17 males, 15 female, mean age 65 years, range: 35 – 85 years) underwent image-guided MWA using the 16 G AMICA Microwave probe (Amica, Hospital Service SPA Rome, Italy). All 32 patients of Group B (submitted to percutaneous MWA) underwent ablation of a solitary liver lesion. The technical success rate was 100%. Percutaneous thermal ablation was performed under local anaesthesia and conscious sedation. The ablation protocol was performed according to the manufacturer's guidelines for the desired ablation zone, aiming to achieve total tumour necrosis plus a minimum of 5 mm safety margin; in all cases continuous microwave energy was utilised. All percutaneous ablative techniques were performed by two interventional radiologists with at least 10 years experience in liver ablations. During the procedure, fentanyl 100μg in combination with midazolam up to 15 mg were administered for conscious sedation. Under CT-guidance and aseptic conditions the microwave needle was inserted in the center of the lesion. Ablation session (on terms of energy deliv-

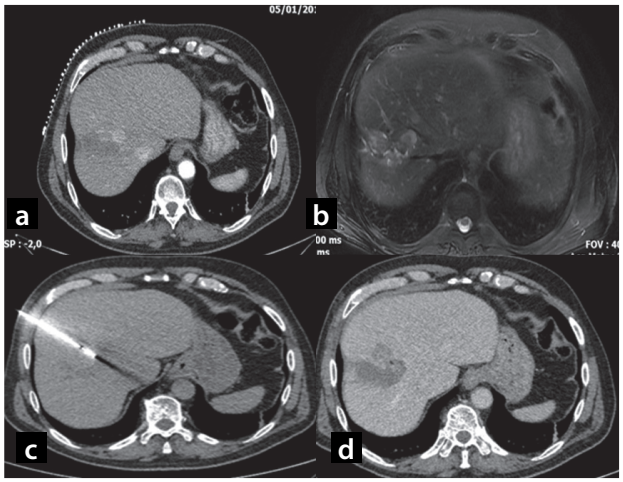

Fig. 1. a. *Axial CT image of a 65 year-old patient with a new HCC lesion in liver section VIII, close to the primary lesion that was ablated with RF a year before,* ***b.*** *MR image of the same lesion,* ***c.*** *Positioning of the electrode within the hepatic lesion,* ***d.*** *Post-ablation contrast-enhanced CT scan demonstrating the ablation zone and the final therapeutic result.*

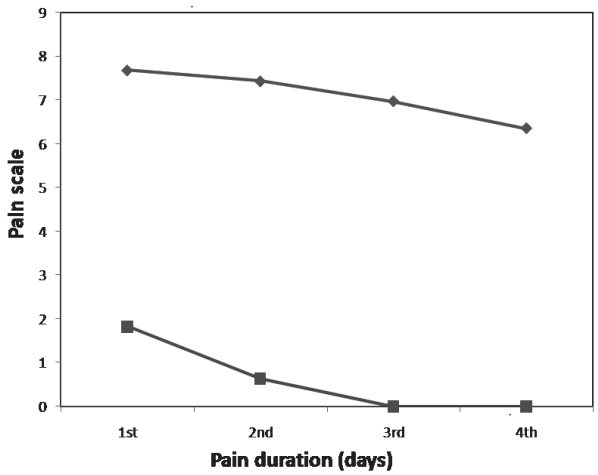

Fig. 2. Pain intensity curves following hepatectomy (rhombus) and MW ablation (squares).

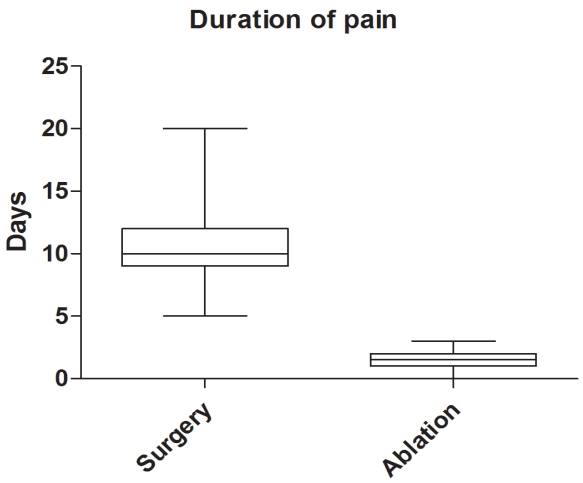

Fig. 3. Box-plot representation of pain duration in the two study groups.

ered and necessary time) was performed according the manufacturer's guidelines depending mainly upon tumour size and desired ablation zone volume. The goal of ablation was a necrotic zone which would include the lesion and a safety margin between 0.5-1 cm. All patients were hospitalised overnight for surveillance (**Table 1**).

Abdominal CT scans were performed on a 64 Philips multislice scanner and EVORAD workstation software (version 3.0) was used for viewing, comparing and creating 3D reconstructions. The ablation zone was defined as the central avascular zone. Abdominal CT scans were performed and evaluated in the arterial, venous and late phase post contrast injection to avoid misinterpretation from peripheral hyperaemia in the arterial phase [21] (**Fig. 1**) .

A dedicated questionnaire with numeric scale was used for recording the characteristics of postoperative pain, daily during the monitoring period. Following ablation or hepatectomy, each patient completed a standard questionnaire for the evaluation of post-procedural pain for the first four days after the procedure. In each case hospitalisation time was also recorded. A Numeric Visual Scale (NVS) questionnaire was used to record post-operative pain and each patient was asked to record the intensity of pain, in a horizontal line with numbers from 0 to 10, where 0 corresponded to complete absence of pain and 10 corresponded to the maximum intensity of pain perceived.

The study's primary outcome measure was to compare the daily self-reported pain score evaluation between the two study groups throughout the follow-up period. Secondary outcome measure was the duration of pain and the comparison of required analgesics (type and dose) administrated between the two study groups. Comparison of the pain scores between the two groups was performed with independent samples Mann-Whitney U test. The threshold of statistical significance was set at $p<0.05$.

Table 2. Average duration of pain for patients undergoing hepatectomy and MWA

Study groups	*Pain duration (days)*
Group A (mean ± SD) (Hepatectomy)	10.75 ± 2.80
Group B (mean ± SD) (MWA)	1.22 ± 0.65

Results

Patients in group A reported pain for a significant longer period of time compared to those included in group B (10.75 ± 2.80 days vs. 1.22 ± 0.65 days, respectively; $p<0.001$), (**Table 2, Fig. 3**). On the first day, the mean post-operative pain in group A (hepatectomy Group) was 7.67 ± 0.88 NVS units, 7.43 ± 0.93 NVS units the second day, 6.97 ± 1.12 NVS units on the third day and 6.35 ± 1.085 NVS units on the fourth day. Corresponding levels post procedural pain in Group B (percutaneous MWA Group) was 1.82 ± 1.88 NVS units on the first day, 0.64 ± 0.84 NVS units on the second day and 0 NVS units on the third and fourth days (**Table 3**). Comparing the post procedural pain levels between the two study Groups, statistically significant differences were observed for each day

Table 3. Average pain scores on the basis of numerical pain scale in patients undergoing hepatectomy and ablation with microwave

Study groups	*1st Day*	*2nd Day*	*3rd Day*	*4th Day*
Group A (mean ± SD) (Hepatectomy)	**7.67 ± 0.88**	**7.43 ± 0.93**	**6.97 ± 1.12**	**6.35 ± 1.08**
Group B (mean ± SD) (MWA)	**1.82 ± 1.88**	**0.64 ± 0.84**	**0**	**0**

(p<0.001). Group A clearly exhibited higher levels, in both pain intensity and duration (**Fig. 2**).

Significantly more patients required analgesia in Group A (100% vs. 12.5%; p=<0.0001). The majority of patients in Group A were given classical opioid analgesics intravenously (IV) and per os. Specifically, 13 patients (40.6%) required the use of continuous PCA (PCA pump connected to a venous line) and in 4 cases (12.5%) an epidural catheter was placed. The majority of patients of Group B required no analgesia (28 cases; 91.5%) and only mild analgesia (an IV dose of paracetamol) was administered in 4 patients (12.5%) during the first days. No clinically significant complications requiring further treatment were observed. Two cases of clinically insignificant pneumothorax occurred in patients of Group B, with hepatic lesions in the sub-diaphragmatic surface of the liver.

Discussion

According to the findings of this study, postoperative pain following MWA ablation is significantly inferior to that after surgical hepatectomy and requires only short-term, mild analgesia with paracetamol. On the other hand, in accordance with the literature, patients in the hepatectomy group required adequate and prompt opioid analgesia using PCA or epidural catheter analgesia to achieve rapid mobilisation [22- 25]. According to current guidelines, the preoperative plan for pain management should be individualised based on various parameters, such as liver and lung functionality, coagulation, co morbidities and the extent of hepatectomy. Opioids are the first choice of analgesics used to control postoperative pain and the most commonly used are morphine, hydromorphone and fentanyl [23-25]. However, several adverse events can be caused by opioids, such as respiratory depression, nausea, vomiting, constipation, hypotension, addiction and exacerbation of hepatic encephalopathy. Specifically, abnormal liver function or cirrhosis, commonly noted in HCC patients, is a cause of reduced metabolism of opioids and benzodiazepines, and therefore the use of opioids could lead to a potentially harmful accumulation of the drug within the liver parenchyma. In patients with reduced renal function, hydromorphone and fentanyl are preferred, due to excessive excretion from the liver [26]. Epidural analgesia is also effective in the treatment of postoperative pain in combination with intravenous administration of opioids, following large open abdominal surgery. It substantially reduces the common respiratory complications, as well as the duration of constipation and provides better pain control than opioids alone. Nonetheless, complications of epidural anaesthesia include epidural haematoma, abscess formation and spinal cord injury, which are exacerbated due to coagulopathy during the initial two to five days after hepatectomy [27].

Nevertheless, the need for satisfactory anaesthesia led to the use of various effective techniques of PCA and epidural analgesia [28]. Non-steroidal anti-inflammatory drugs (NSAIDs) are not generally recommended after hepatectomy, in cirrhotic patients or patients with renal impairment, as they increase the risk of bleeding and can incite hepatorenal syndrome [25].

Pain has been described in the literature as a common consequence after MWA, while its intensity and duration varies [9, 17]. Inter-individual variations are owed to various factors, including the subjective perception of pain, the use of different analgesic schemes in each case and the method of pain recording. In the majority of cases, pain after thermoablation is mild (scale 1-2), and resolves within one to two days, whereas analgesic drugs used are limited to paracetamol. In this series, mean post-procedural

self-reported pain score was below 2 and paracetamol use was minimal.

Post-ablation pain of subcapsular hepatic lesions has been reported to be more intense and prolonged and correlated with the total ablated volume of liver parenchyma [29]. One possible mechanism explaining minimal pain following MWA could be the fact that thermoablation damages the nerve endings of the liver capsule and the abdominal wall is likely to be necrotic, resulting in the absence of post-operative pain [30].

This study has several limitations. First of all, this was a retrospective analysis and, as a result, some cases or data might have been overlooked. Moreover, the number of patients included does not permit a robust statistical subgroup analysis as to indentify factors influencing pain. Nonetheless, the net difference in pain intensity and duration indicates that adding more cases would probably not have significantly changed outcomes. Finally, a reproducibility bias is also present due to the single-center design, as local techniques and expertise could have also influenced results.

In conclusion, in this retrospective study, image-guided MWA resulted in significantly less post-operative pain by means of both intensity and duration compared to surgical hepatectomy for the treatment of HCC. Moreover, analgesics following MWA were limited to NSAIDs and paracetamol. **R**

Conflict of interest

The authors declared no conflicts of interest.

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