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World J Clin Cases 2021 July 6; 9(19): 4881-5351



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The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJCC* as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing, Production Department Director: Yun-Xiaoqian Wu, Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

July 6, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Retrospective Study

Microwave ablation combined with hepatectomy for treatment of neuroendocrine tumor liver metastases

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Author contributions: Zhang JZ designed the study, acquired and analyzed the data, and wrote the paper; Li S acquired and analyzed the data, and revised the paper; Zhu WH acquired and analyzed the data, and revised the paper; Zhang DF designed the study, revised the paper, and supervised the study.

Supported by Peking University People's Hospital Scientific Research Development Funds, No. RDY2017-28.

Institutional review board statement: The study was reviewed and approved by the Peking University People's Hospital Institutional Review Board (No. 2020PHB334-01).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors have no conflict of

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Abstract

BACKGROUND

Hepatectomy is the first choice for treating neuroendocrine tumor liver metastases. However, most patients with neuroendocrine tumor liver metastases are not suitable for hepatectomy. Ablation combined with hepatectomy can be an alternative to liver resection.

AIM

To explore the clinical effect of microwave ablation combined with hepatectomy for the treatment of neuroendocrine tumor liver metastases.

METHODS

In this study, the data of patients who underwent microwave ablation combined with hepatectomy for the treatment of neuroendocrine tumor liver metastases from June 2015 to January 2018 were reviewed. Before the operation, the patients did not receive any treatment for liver neuroendocrine tumors. After a multidisciplinary expert group discussion, all patients were deemed unsuitable for liver resection. All patients were diagnosed with neuroendocrine tumors by pathology. The overall survival time and progression-free survival time were followed by telephone calls and outpatient visits after surgery.

RESULTS

Eleven patients with neuroendocrine tumor liver metastases were treated by microwave ablation combined with hepatectomy between June 2015 and January 2018. The median number of liver metastatic nodules was 4 (range, 2 to 43). The median number of lesions resected was 1 (range, 1 to 18), and the median number of lesions ablated was 3 (range, 1 to 38). The mean operation time was 405.6 (\pm 39.4) min. The median intraoperative blood loss was 600 mL (range, 50 to 3000). Ten patients had a fever after surgery. The median duration of fever was 3 d (range, 0 to 21). Elevated bilirubin levels occurred in all patients after surgery. The

interest related to the manuscript.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 14, 2021

Peer-review started: January 14, 2021

First decision: April 4, 2021

Revised: April 13, 2021

Accepted: May 6, 2021

Article in press: May 6, 2021

Published online: July 6, 2021

P-Reviewer: Kordzaia D

S-Editor: Gao CC

L-Editor: Wang TQ

P-Editor: Wang LL



median bilirubin on the first day after surgery was 28.5 (range, 10.7 to 98.9) $\mu\text{mol/L}$. One patient developed respiratory failure, renal insufficiency, and pneumonia after the operation. No patient died postoperatively during hospitalization. The mean overall survival time after surgery was 34.1 (± 3.7) mo, and the median progression-free survival time was 8 (range, 2 to 51) mo. One year after surgery, ten patients survived and five patients survived without progression. Three year after surgery, eight patients survived and two patients survived without progression.

CONCLUSION

Microwave ablation combined with hepatectomy not only makes the patients obtain a survival rate similar to that of patients undergoing hepatectomy, but also has a low incidence of postoperative complications.

Key Words: Liver; Neoplasm metastasis; Microwave; Hepatectomy; Neoplasm; Endocrine tumor

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Core Tip: Liver resection is the first choice for treating neuroendocrine tumor liver metastases. Due to the strict indications for hepatectomy, most patients with neuroendocrine tumor liver metastases are not suitable for hepatectomy. Ablation combined with hepatectomy is an alternative treatment option. Here, this study analyzed the clinical effect of microwave ablation combined with hepatectomy in the treatment of neuroendocrine tumor liver metastases. The results show that microwave ablation combined with hepatectomy not only makes the patients obtain a survival rate similar to that of patients undergoing hepatectomy, but also has a low incidence of postoperative complications.

Citation: Zhang JZ, Li S, Zhu WH, Zhang DF. Microwave ablation combined with hepatectomy for treatment of neuroendocrine tumor liver metastases. *World J Clin Cases* 2021; 9(19): 5064-5072

URL: <https://www.wjgnet.com/2307-8960/full/v9/i19/5064.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i19.5064>

INTRODUCTION

Neuroendocrine tumors originate from neuroendocrine cells and grow relatively slowly. Neuroendocrine tumors occurs mostly in the gastrointestinal tract and pancreas[1,2]. Patients with neuroendocrine tumors often progress to liver metastases. Liver metastases can be found in more than half of patients with neuroendocrine tumors[1]. A previous study has shown that neuroendocrine tumors with liver metastases often have a worse prognosis[3]. Liver resection is the first choice for treating neuroendocrine tumor liver metastases. Due to the strict indications for hepatectomy, most patients with neuroendocrine tumor liver metastases are not suitable for hepatectomy. Ablation combined with hepatectomy has attracted the attention of clinicians in the treatment of neuroendocrine tumor liver metastases.

Ablation techniques include radiofrequency ablation, microwave ablation, cryoablation, laser ablation, and other means. Radiofrequency ablation combined with hepatectomy for treating neuroendocrine tumor liver metastases has been reported by Taner *et al*[4] and Elias *et al*[5]. Cryoablation combined with hepatectomy for treating neuroendocrine tumor liver metastases has been reported by Saxena *et al*[6]. Due to the frequent postoperative complications, long operation times, and more complicated operations, compared with radiofrequency ablation and microwave ablation, the use of cryoablation is rare[7,8]. Compared with radiofrequency ablation, microwave ablation produces higher local temperature and ablation range. And microwave ablation heat transfer is not affected by tissue carbonization, which makes the heat transfer more rapid and the ablation more complete. The stronger heat generation efficiency of microwave ablation often makes the operation time of microwave

ablation shorter[9]. In addition, microwave ablation has greater advantages in treating nodules larger than 3 cm and nodules close to large vessels[10,11]. Therefore, our institution has attempted to use microwave ablation combined with hepatectomy for the treatment of neuroendocrine tumor liver metastases. This is the first report about microwave ablation combined hepatectomy for treating neuroendocrine tumor liver metastasis.

MATERIALS AND METHODS

This study reviewed patients who underwent microwave ablation combined with hepatectomy for the treatment of neuroendocrine tumor liver metastases.

Inclusion criteria

All patients were treated by microwave ablation (FORSEA MTC-3 Microwave Ablation System, Nanjing, Jiangsu, China) combined with hepatectomy in our institution. All patients were confirmed to have neuroendocrine tumors by pathology. After a multidisciplinary expert group discussion, all patients were deemed unsuitable for liver resection. None of the patients received any treatment for neuroendocrine tumors before surgery, such as liver resection, ablation, radiotherapy, or chemotherapy. All patients were confirmed to have multiple nodules by preoperative imaging and intraoperative ultrasound, which did not meet the indications for hepatectomy.

Surgical procedure

All patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) examination before the operation to clarify the number and location of the tumors. Intraoperative ultrasound exploration further clarified the number and size of the nodules. For nodules larger than 3 cm, a large number of nodules smaller than 3 cm concentrated on a liver segment, or tumors located on the liver surface, surgical resection was usually selected. For nodules less than 3 cm, microwave ablation was usually selected. When tumors are located deep in the liver, hepatectomy will lead to the severe loss of normal liver tissue and liver function. Therefore, microwave ablation was usually selected. For intrahepatic nodules, all hepatectomy margins were greater than 0.5 cm from the tumor. All pathologies after hepatectomy confirmed R0 resection. All nodules found by intraoperative ultrasound were removed by liver resection or microwave ablation. The microwave ablation power was 70 W. For tumors less than 1 cm, the ablation time was 5 min. For tumors with a diameter of 1-2 cm, the ablation time was 10 min. For tumors with a diameter of 2-3 cm, the ablation time was 20 min. For tumors larger than 3 cm, the ablation was repeated multiple times.

Postoperative status and follow-up

All patients returned to the ward or intensive care unit (ICU) for close observation after surgery. All patients underwent CT or MRI examination 1 mo after surgery to determine whether the lesions were ablated completely. After that, all patients underwent CT/MRI examination every 3 mo. All patients were followed by telephone calls and outpatient visits.

Statistical analysis

Continuous variables were tested by the Shapiro-Wilk test to determine whether they followed a normal distribution. Continuous variables that were proved to have a normal distribution are reported as the mean and standard deviation. Otherwise, continuous variables are reported as medians. Categorical variables are reported as frequencies or percentages. *P* values less than 0.05 were considered significant. Data were analyzed with Statistical Package for the Social Sciences version 21.0 (SPSS 21.0).

RESULTS

Tests of normality

Except for operation time and postoperative overall survival time, other continuous variables were not normally distributed (Shapiro-Wilk test for all continuous variables; Table 1).

Table 1 Results of tests of normality

Continuous variable	P value
Age	0.036 ^a
Number of lesions	0.000 ^a
Number of hepatectomy	0.000 ^a
Number of microwave ablation	0.001 ^a
Blood loss	0.042 ^a
Operative time	0.121
Postoperative hospital stay	0.019 ^a
Bilirubin on the first day after surgery	0.000 ^a
Duration of the fever	0.003 ^a
Progression-free survival time	0.003 ^a
Postoperative survival time	0.832

^a*P* < 0.05.

Patients

Eleven patients with neuroendocrine tumor liver metastases underwent microwave ablation combined with hepatectomy from June 2015 to January 2018. There were three males and eight females with a median age of 62 (range, 36 to 69) years. The pathological grades of the 11 patients included G3 in six cases, G2 in four, and G1 in one. The primary site of neuroendocrine tumors included four cases in the pancreas, one in the rectum, one in the colon, and five in unclear sites. All patients had multiple liver tumors. Patients had a median liver nodule of 4 (range, 2 to 43). Seven patients had bilobar tumors, and four patients had tumors in only one lobe. Because the single lobe tumors of the four patients were too deep, a large amount of normal liver tissue would be lost if only hepatectomy was performed. Due to the high recurrence rate of neuroendocrine tumors after liver metastasis, normal liver tissue should be preserved as much as possible for the second operation. Therefore, only hepatectomy was not considered as a surgical option for these four patients with tumors in one lobe. In addition, deep liver tumors are often close to large blood vessels, and patients undergoing hepatectomy will have a higher surgical risk. Carcinoid syndromes such as blushing, diarrhea, heart valve injury, bronchial stenosis, and asthma were not found in any patients. Of the 11 patients, four were associated with metabolic-related diseases such as hypertension, diabetes, and hyperlipidemia, and one was associated with systemic lupus erythematosus and asthma. The details of the information of the patients are summarized in [Table 2](#).

Surgical procedure

Of the six patients with liver metastases with a clear primary site, all of them had their primary tumors removed at the same time. All patients underwent ultrasound examinations to confirm the number and distribution of liver metastases. Intraoperative ultrasound examination of all patients revealed all the nodules found by preoperative MRI, among which three patients had additional nodules found by intraoperative ultrasound. The mean operation time was 405.6 (± 39.4) min. The patient's median intraoperative blood loss was 600 (range, 50 to 3000) mL. The median nodules removed by hepatectomy was 1 (range, 1 to 18). The median nodules removed by microwave ablation was 3 (range, 1 to 38). The total number of liver metastasis nodules was 139, and the total number of microwave ablation nodules was 104. Among 11 patients with microwave ablation combined with hepatectomy, the total number of microwave ablation nodules accounted for 74.8% of the total nodules found in the patients by intraoperative ultrasound. There were 43 liver metastases in No. 5 patient. Fourteen nodules were concentrated in segment V of the liver, and four were located on the liver surface. The other 25 nodules were diffusely distributed in the liver. The surgeon removed the nodules in segment V and on the liver surface through hepatectomy. The remaining diffusely distributed nodules were removed by microwave ablation. The details of the surgical information are summarized in [Table 3](#).

Table 2 Patients' basic information

Patient No.	Sex	Age	Origin	Pathological grade	Bilobar or not	Number of lesions
1	Female	62	Colon	G2	Yes	23
2	Male	62	Unknown	G3	Yes	7
3	Male	53	Pancreatic	G2	Yes	41
4	Male	53	Unknown	G3	No	2
5	Female	69	Unknown	G3	Yes	43
6	Female	36	Unknown	G1	Yes	4
7	Female	63	Rectum	G3	No	2
8	Female	65	Pancreatic	G2	Yes	8
9	Female	37	Pancreatic	G3	No	4
10	Female	57	Pancreatic	G3	No	3
11	Female	63	Unknown	G2	Yes	2

Table 3 Surgical information

Patient No.	Number of hepatectomy	Number of microwave ablations	Blood loss (mL)	Operative time (min)
1	2	21	50	360
2	1	6	1500	427
3	3	38	3000	690
4	1	1	1500	480
5	18	25	2400	510
6	1	3	200	320
7	1	1	300	270
8	4	4	700	310
9	2	2	500	510
10	1	2	600	305
11	1	1	200	280

Postoperative status

Of the 11 patients, four entered the ICU after surgery. The median postoperative hospital stay for all patients was 14 (range, 7 to 37) d. Ten patients had a fever after surgery. The median duration of fever was 3 (range, 0 to 21) d. Elevated bilirubin levels occurred in all patients after surgery. The median bilirubin on the first day after surgery was 28.5 (range, 10.7 to 98.9) $\mu\text{mol/L}$. No patient died during postoperative hospitalization. One patient (No. 3 patient) developed respiratory failure, renal insufficiency, and pneumonia after surgery. The remaining patients had no complications. The details of the postoperative information are summarized in Table 4.

Follow-up

Eleven patients underwent regular re-examination after the operation, and all the patients were re-examined by CT or MRI 1 mo after the operation, which indicated complete ablation. Thereafter, CT or MRI of the abdomen was performed every 3 mo. The preoperative and postoperative imaging examinations of No. 7 patient are shown in Figure 1. All patients were treated with octreotide after the operation. The patient's mean overall survival time after surgery was 34.1 (\pm 3.7) mo, and the median postoperative progression-free survival time was 8 (range, 2 to 51) mo. One year after surgery, ten patients survived and five patients survived without progression. Three years after surgery, eight patients survived and two patients survived without progression. The details of the follow-up information are summarized in Table 5.

Table 4 Postoperative information

Patient No.	Postoperative hospital stay (d)	Bilirubin on first day after surgery ($\mu\text{mol/L}$)	Duration of the fever (d)
1	12	27.2	4
2	22	34.2	2
3	22	98.9	21
4	37	30.5	4
5	15	28.7	2
6	8	15.9	0
7	12	10.7	3
8	12	23.4	2
9	14	28.5	8
10	14	14.3	12
11	7	34.8	1

Table 5 Follow-up information

Patient No.	Progression-free survival time (mo)	Relapse before follow-up	Postoperative survival time (mo)	Died before follow-up
1	26	No	26	No
2	2.5	Yes	48	Yes
3	13	Yes	38	No
4	8	Yes	24	Yes
5	20	Yes	23	Yes
6	51	No	51	No
7	7	Yes	45	Yes
8	2	Yes	34	No
9	2	Yes	11	Yes
10	8	Yes	41	No
11	6	Yes	35	No

DISCUSSION

Hepatectomy is the first choice for the treatment of neuroendocrine tumor liver metastases. Surgical resection can not only improve the patient's ectopic endocrine-related symptoms but also greatly improve the survival time[12]. Due to the widespread nature of tumors, most patients with neuroendocrine tumor liver metastases do not meet the indications for liver resection. Only 10% of patients with neuroendocrine tumor liver metastasis meet the indications for hepatectomy[13]. In addition, patients with neuroendocrine tumor liver metastases after hepatectomy still have a higher recurrence rate. Zhang *et al*[14] reported that the recurrence-free rate in patients with neuroendocrine tumor liver metastasis after liver resection is approximately 60% after 3 years. Most patients cannot stand secondary hepatectomy. The emergence of ablation technology provides new treatment options for patients with neuroendocrine tumor liver metastases who cannot undergo hepatectomy. The application of ablation technology is flexible. It can be used alone to ablate lesions to reduce the burden of patients' tumors, or it can be combined with hepatectomy for patients who do not have indications for hepatectomy. Some retrospective clinical studies have confirmed the clinical efficacy of ablation in the treatment of liver neuroendocrine tumors. However, reports about surgical resection combined with ablation for neuroendocrine tumor liver metastases are still limited.

Patients with unresectable liver neuroendocrine tumors had a 5-year survival rate of only 22%[15]. According to previous studies and data from our center, after

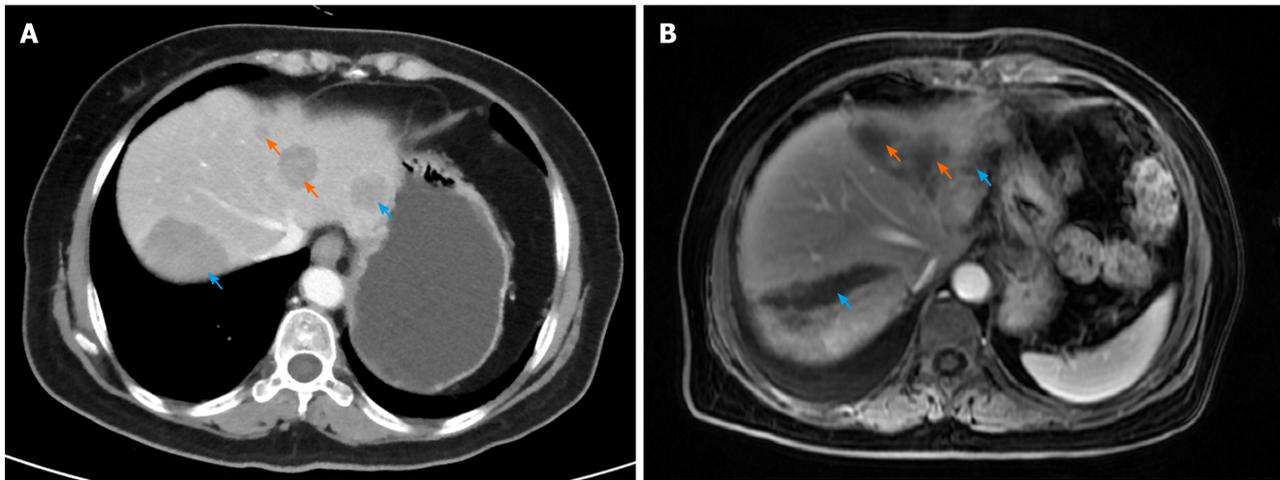


Figure 1 Preoperative computed tomography and postoperative magnetic resonance images of No. 9 patient with neuroendocrine tumor liver metastases. The nodules pointed to by the red and blue arrows underwent microwave ablation and hepatectomy, respectively. A: Preoperative computed tomography; B: Magnetic resonance imaging 1 mo after surgery.

undergoing ablation combined with liver resection, the 1, 3, and 5-year survival rates of these patients were more than 87.5%, 73%, and 61%, respectively[4-6]. This result was similar to the survival rate of patients who only underwent hepatectomy[14]. Therefore, hepatectomy combined with ablation not only expands the surgical indications of patients who do not meet the indications for hepatectomy but also results in an increased survival rate similar to that of hepatectomy. For patients with neuroendocrine tumor liver metastases who are not suitable for hepatectomy, ablation combined with hepatectomy can be used as a new treatment option. However, previous studies have shown that the 1, 3, and 5-year progression-free survival rates of patients undergoing ablation combined with hepatectomy were approximately 60%, 28%, and 17%, respectively, which were much lower than those of patients undergoing hepatectomy[5,14]. Therefore, microwave ablation combined with hepatectomy may lead to a higher recurrence rate than hepatectomy.

Among the 11 patients with microwave ablation combined with hepatectomy, the number of nodules removed by microwave ablation accounted for 74.8% of the total number of nodules found during intraoperative ultrasound. No patient died during postoperative hospitalization. One case had complications including respiratory failure, renal insufficiency, and pneumonia. All patients only had a slight increase in bilirubin level after surgery. Of the 11 patients, ten developed a fever. Among them, eight patients had a fever that lasted less than 10 d, and two patients had a fever that lasted more than 10 d. Because ablation produces a large number of necrotic cells, the absorption of heat is a very common phenomenon in ablation therapy. The previous literature also reported that the ablation of abdominal tumors was accompanied by a large amount of heat absorption. The absorbed heat generated after ablation can be relieved within 10 d after surgery. For fever that lasts longer, it is necessary to consider whether a postoperative infection has occurred[16]. The incidence of complications was low in patients receiving microwave ablation combined with hepatectomy.

CONCLUSION

Microwave ablation combined with hepatectomy expands the indications for patients with neuroendocrine tumor liver metastasis that are not suitable for hepatectomy. The patients not only obtain a survival rate similar to that of patients undergoing hepatectomy, but also have improved quality of life. However, microwave ablation combined with hepatectomy has a higher recurrence rate than hepatectomy.

ARTICLE HIGHLIGHTS

Research background

Hepatectomy is the first choice for treating neuroendocrine tumor liver metastases. However, most patients with neuroendocrine tumor liver metastases are not suitable for hepatectomy. Ablation combined with hepatectomy can be an alternative to liver resection.

Research motivation

This study evaluated the clinical efficacy of microwave ablation combined with hepatectomy for the treatment of neuroendocrine tumors with liver metastases. It provides new treatment options for patients who are not suitable for only hepatectomy.

Research objectives

This study aimed to explore the clinical effect of microwave ablation combined with hepatectomy for the treatment of neuroendocrine tumor liver metastases.

Research methods

In this study, the data of patients who underwent microwave ablation combined with hepatectomy for the treatment of neuroendocrine tumor liver metastases from June 2015 to January 2018 were reviewed.

Research results

Eleven patients with neuroendocrine tumor liver metastases were treated by microwave ablation combined with hepatectomy between June 2015 and January 2018. One patient developed respiratory failure, renal insufficiency, and pneumonia after the operation. No patient died postoperatively during hospitalization. The mean overall survival time after surgery was 34.1 (\pm 3.7) mo, and the median progression-free survival time was 8 (range, 2 to 51) mo.

Research conclusions

Microwave ablation combined with hepatectomy not only makes the patients obtain a survival rate similar to that of patients undergoing hepatectomy, but also has a low incidence of postoperative complications. For patients with neuroendocrine tumor liver metastases who are not suitable for hepatectomy, ablation combined with hepatectomy can be used as a new treatment option.

Research perspectives

Due to the low incidence of neuroendocrine tumors, there are currently no prospective studies on neuroendocrine tumor liver metastases. Limited research suggests that ablation combined with hepatectomy for neuroendocrine tumor liver metastasis can prolong the survival rate of patients and improve the quality of life of patients. Prospective or retrospective studies of large cases will be needed in the future.

ACKNOWLEDGEMENTS

We thank Liu HX of Peking University People's Hospital for reviewing statistical methods.

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