ORIGINAL CONTRIBUTION

EXPERIMENTAL ONCOLOGY

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RADIOFREQUENCY ABLATION AS PART OF INTRAHEPATIC TREATMENT STRATEGIES

Background. Liver resection remains a gold standard for the treatment of colorectal liver metastases; however, radiofrequency ablation (RFA) may serve as an alternative for patients with contraindications to resection or within parenchyma-sparing strategies. The **aim** of this study was to analyze treatment outcomes, prognostic factors, and survival after RFA of intraparenchymal colorectal liver metastases. **Materials and Methods.** A retrospective analysis was performed on 33 patients with colorectal liver metastases who underwent RFA between 2013 and 2023. The ablation was carried out using the Cool-tip RF Ablation System E Series (Covidien) with a maximum output power of 200 W and internally cooled monopolar needles with a 3 cm active tip, under intraoperative ultrasound guidance. **Results.** Patients were stratified according to survival status. Group 1 (n = 23) included patients who underwent RFA and were alive at the time of analysis; Group 2 (n = 10) included those who died of disease progression. The survival was significantly influenced by the presence of synchronous metastases (21.7% vs 100.0%, $p < 0.001$), metachronous metastases (78.3% vs 0, $p < 0.001$), and median time to progression (18 (78.3%) vs 1 (10.0%), $p = 0.0004$). No significant effect was found for sex, age, primary tumor localization or morphology, number of chemotherapy lines before ablation, maximal size and number of metastases, type of surgery for the primary tumor, or the presence of comorbidities. **Conclusion.** RFA in the treatment of colorectal liver metastases is a safe alternative for the unresectable lesions or within parenchyma-sparing strategies. However, liver resection should be considered a priority option when technically feasible. Combining resection and RFA expands the range of patients eligible for radical intervention, potentially improving disease-free and overall survival rates. These findings are limited by baseline group disparities. Randomized or propensity-matched studies are needed to confirm RFA efficacy and define the target population most likely to benefit.

Keywords: colorectal cancer, liver resection, colorectal liver metastases, electrosurgery, radiofrequency ablation.

Colorectal cancer (CRC) is the second most common oncological disease among women and the third among men worldwide [1]. Global statistics report that approximately 20% of CRC patients have synchronous liver metastases, and about one-third develop metachronous hepatic metastases [2, 3]. Surgical removal of metastases remains a primary treatment, significantly improving survival rates [4]. Five-year overall survival after R0 resection reaches 58% with a median survival of 28—46 months [5—7]. Unfortunately, only about 20% of patients with liver metastases are candidates for resection [8, 9].

Over the past decade, treatment strategies for metastatic CRC have become more personalized and multimodal, incorporating liver-directed therapies combining systemic chemotherapy, ablative

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techniques, locoregional therapies, or their combinations. Recent studies have demonstrated that combining liver resection with ablation improves overall and disease-free survival [10]. Radiofrequency ablation (RFA) has been the most studied and widely applied ablative technique since its introduction in the late 1990s [11].

A limiting factor of RFA is the heat-sink effect, which restricts effective ablation due to thermal heterogeneity [12]. Large vessels (>3 mm diameter) «cool» adjacent tumor areas, risking incomplete treatment and potential vascular wall damage with subsequent perfusion disorders and bleeding [13]. Additionally, RFA carries a risk of thermal injury to the biliary tract or adjacent anatomical structures, especially with subcapsular lesions. Therefore, the treatment of the lesions near major vessels, bile ducts, or other organs should be performed by experienced surgeons at expert centers with appropriate technical capabilities; in some cases, RFA is contraindicated [14]. Among the available palliative treatment options, RFA is a reliable choice with low mortality and morbidity rates.

The study aimed to analyze prognostic survival indicators after RFA for intrahepatic colorectal metastases at the National Cancer Institute, Kyiv, Ukraine.

Materials and Methods

Inclusion and exclusion criteria. Inclusion criteria were (i) patients with comorbidities contraindicating surgery; (ii) absence of extrahepatic disease; (iii) metastases ≤30 mm; (iv) ≤20 multifocal hepatic metastases in segments 1—8 treated via using minimally invasive ultrasound- guided techniques. Given evidence on RFA inefficacy for lesions >3—6 cm, patients with >1 lesion ≥6 cm did not undergo RFA [15]. However, patients with a largest lesion of 3 cm received RFA for all lesions during one session. The proximity to the hepatic hilum or main bile duct and the uncorrectable coagulopathy were exclusion criteria.

Data collection. A retrospective analysis was conducted on 33 patients treated with minimally invasive (RFA) approaches at the National Cancer Institute from January 2013 to December 2023. The study followed the Declaration of Helsinki. Standard demographic and clinicopathological data were analyzed, including patient characteristics (gender, age), tumor characteristics (primary site: ascending colon, splenic flexure, hepatic flexure, rectum, rectosigmoid junction, sigmoid colon, cecum, multiple locations), tumor morphology (differentiation: G1, G2, G3, G2/G3), metastasis characteristics (synchronous, metachronous), chemotherapy lines before ablation (none, 1, 2), maximal metastasis size (<10 mm, 10—20 mm, 20—30 mm, ≥30 mm), liver involvement (unilobar, bilobar), number of metastases (1, 2—5, 5—10+), surgery characteristics (anterior resection, low anterior resection, Hartmann's procedure, left/right hemicolectomy, sigmoid resection, intersphincteric rectal resection, Keny — Miles procedure), comorbidities (none, cardiovascular, digestive, 2+ systems), and disease-free interval post-RFA (no recurrence, <6 months, <12 months, >12 months).

Procedure. Ablation was performed using a Cool-tip RF Ablation System E Series (Covidien, USA), maximum output 200 W, monopolar internally cooled electrodes with 3 cm tips under intraoperative ultrasound navigation. Ultrasound systems bk3000 & bk5000 (BK Medical, Denmark) guided interventions. RF-generated alternating current heated tissue to 50—100 °C for 4—6 min, causing coagulation and tumor necrosis. The procedures lasted 10—30 min due to slow tissue heat conduction. The electrodes were centered within each tumor. Complete necrosis required ablation within ≥10 mm margins of healthy tissue. Multiple overlapping ablations were performed as needed. Modern navigation allows safe destruction near Glisson's units previously deemed contraindicated (Fig. 1). Electrode removal involved active coagulation to minimize post-ablation bleeding and tumor dissemination.

The RFA was performed for the management of colorectal liver metastases in elderly patients with the limited hepatic disease. The presented radiological images illustrate the dynamics and outcomes of this approach. The sequential imaging demonstrates the progression of a metastasis located in segment 7 of the liver over a 9-month period without local or systemic disease control (Fig. 2). We represent follow-up scans after the outpatient RFA showing the complete ablation of the lesion, with the replacement of segment 7 by a cystic component within the anatomical boundaries of the treated segment (Fig. 3). Finally, the RFA procedure for a metastasis in segment 8 resulted in a complete cystic transformation and demarcation of the dorsal subsegment (8d) (Fig. 4). These cases demonstrate the efficacy of RFA

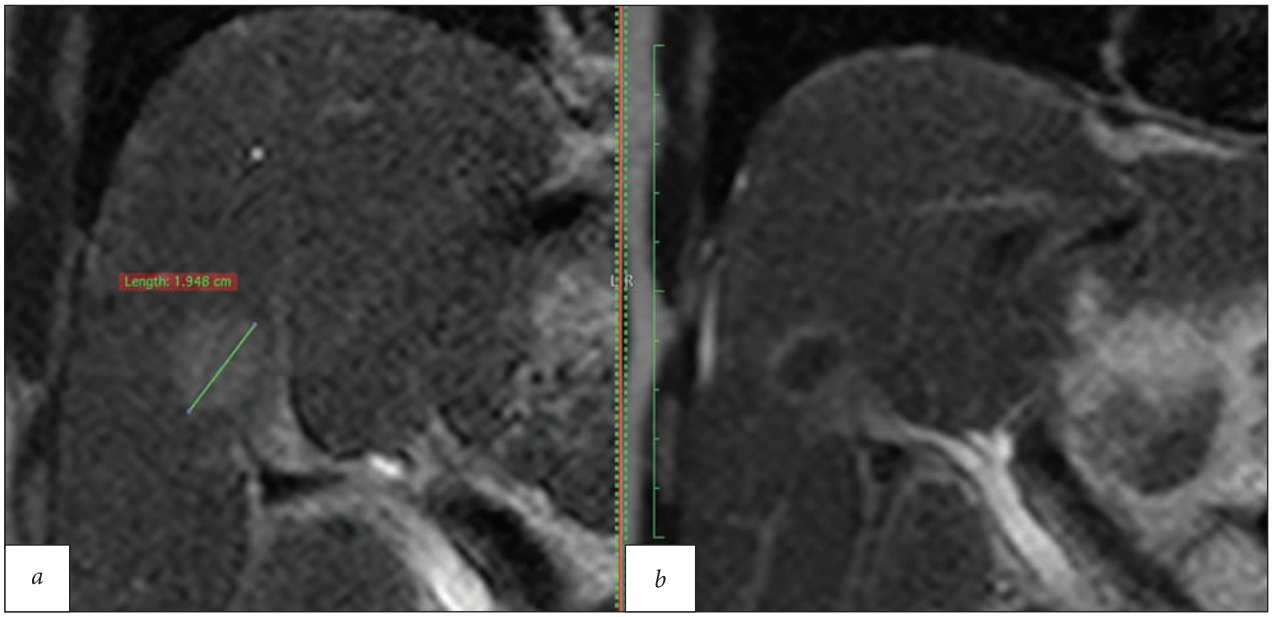

Fig. 1. MRI of the hepatobiliary system before treatment (*a*) and 4 months after the RFA procedure (*b*) in segment 5 of the liver

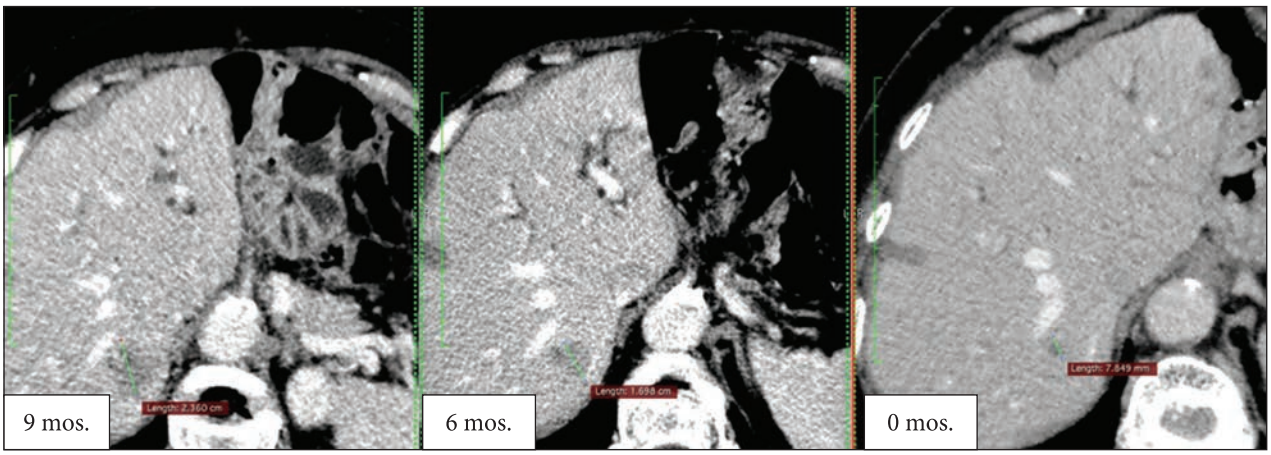

Fig. 2. Dynamics of colorectal liver metastasis growth in segment 7 of the liver in an 81-year-old female patient. On the right — the time of initial detection of the hepatic metastasis (0 months) and subsequent disease progression without local or systemic control at 6 and 9 months, respectively

in achieving local tumor control and post-procedural structural remodeling of the hepatic parenchyma.

Statistical analysis. Statistical analysis of the results was carried out using parametric and non-parametric methods. The compliance of the empirical distribution of quantitative variables with the normal distribution law was assessed using the Shapiro — Wilk test ($n < 50$). For the description of quantitative parameters, mean values were determined with evaluation of their variability and statistical significance; the central tendency was assessed using the mathematical expectation and 95% confidence interval. To compare the median values of normally distributed data, Student's *t*-test was used,

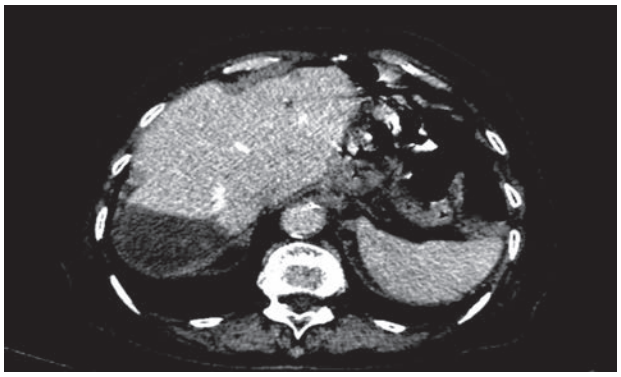

Fig. 3. Subsequent RFA of the above-mentioned lesion performed on an outpatient basis, with complete replacement of segment 7 by a cystic component within anatomical boundaries

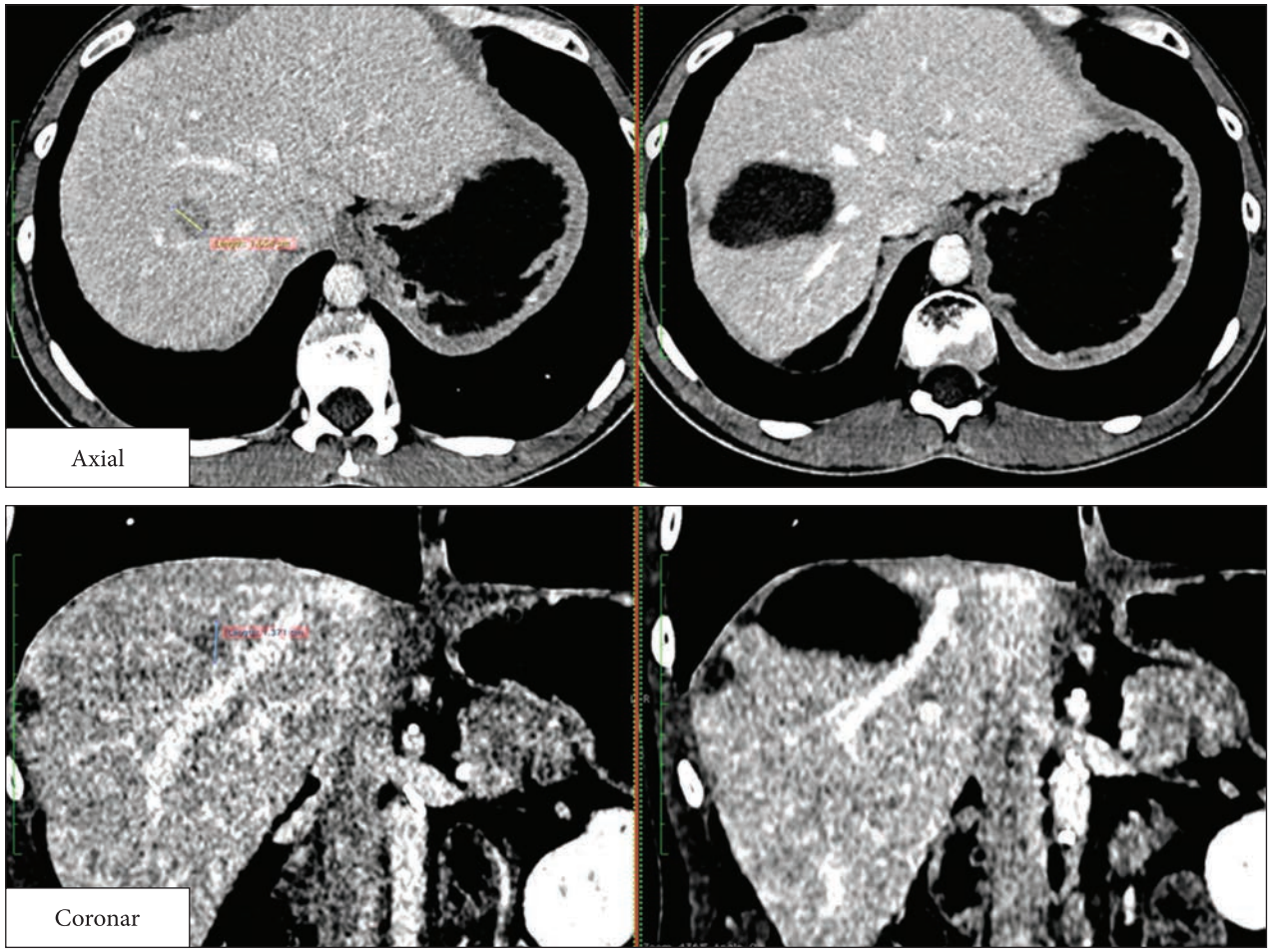

Fig. 4. RFA procedure for a colorectal liver metastasis in segment 8 of the liver, with complete cystic replacement of the anatomical borders of the dorsal part of subsegment 8d

with comparisons performed at a significance level of 0.05. For the qualitative characteristics, analysis of their frequency indicators was carried out with determination of the absolute number of observations and their distribution in percentages. A comparison of the qualitative variables between groups was performed using Pearson's χ^2 test with Yates' correction for continuity. In certain cases, for parameters with a few observations (less than 5), Fisher's exact two-sided test was used to assess the significance of intergroup differences in frequency characteristics.

Results and Discussion

Patients were stratified according to the survival status. Group 1 (n = 23) included patients who underwent RFA and were alive at the time of analysis; group 2 (n = 10) included those who died of disease progression.

For the evaluation and analysis of patient characteristics in groups 1 and 2, the following indicators were selected: patient characteristics (gender, age), tumor characteristics (primary tumor location), primary tumor morphology (differentiation grade), metastatic process characteristics, number of chemotherapy lines before ablation, maximum size of the largest metastasis, liver involvement characteristics, number of metastases, surgery characteristics (type of primary tumor surgery: anterior resection, low anterior resection, Hartmann's procedure, left hemicolectomy, right hemicolectomy, sigmoid resection, intersphincteric resection), Keny — Miles procedure), presence of comorbidities (absence of comorbidities, cardiovascular diseases, digestive diseases, diseases of 2 systems, 3 or more systems), mean time to detection of disease signs after RFA (no recurrence, up to 6 months, up to 12 months, more than 12 months). The median follow-up times were 85 months in group 1 and 42 months in group 2.

The groups did not differ significantly by such indexes as the overall mean age, gender distribution, and primary tumor localization (such as ascending colon, splenic flexure, hepatic flexure, rec-

Impact of factors on the overall survival after RFA of intraparenchymal liver metastases

Factors	Group 1 n = 23	%	Group 2 n = 10	%	*P*-value
Patient Characteristics					
Age	57.56 ± 4.24		59.9 ± 9.14		0.06
Gender:					
Male	11	47.8	5	50.0	0.72
Female	12	52.2	5	50.0	
Tumor characteristics					
Primary tumor localization:					
Ascending colon	2	8.7	2	20.0	0.57
Splenic flexure	3	13.0	0	0	0.54
Hepatic flexure	0	0	1	10.0	0.30
Rectum	7	30.4	2	20.0	0.69
Rectosigmoid junction	1	4.3	1	10.0	0.52
Sigmoid colon	9	39.1	3	30.0	0.71
Cecum	0	0	1	10.0	0.30
2 or more colon or rectal sites	1	4.3	0	0	0.98
Primary tumor morphology					
Differentiation grade:					
G1	0	0	2	20.0	0.85
G2	19	82.6	6	60.0	0.21
G3	3	13.0	2	20.0	0.63
G3/ G4	1	4.3	0	0	0.23
Metastatic process characteristics:					
Synchronous	5	21.7	10	100.0	<0.001
Metachronous	18	78.3	0	0	
Number of chemotherapy lines before ablation					
0	3	13.0	2	20.0	0.63
1	17	73.9	7	70.0	0.99
2	3	13.0	1	10.0	0.90
3 and >					
Maximum size of the largest metastasis					
<10 mm	6	26.1	0	0	0.14
10—20 mm	14	60.9	7	70.0	0.71
20—30 mm	2	8.7	1	10.0	0.90
30 and >	1	4.3	2	20.0	0.21
Liver involvement					
Unilobar	15	65.2	8	80.0	0.68
Bilobar	8	34.8	2	20.0	
Number of metastases					
1	12	52.2	7	70.0	0.46
2—5	7	30.4	1	10.0	0.38
5—10	4	17.4	2	20.0	0.90

End of Table

Factors	Group 1 n = 23	%	Group 2 n = 10	%	***P***-value
Surgery					
Primary tumor surgery:					
Anterior resection	2	8.7	1	10.0	0.90
Low anterior resection	3	13.0	1	10.0	0.90
Hartmann's procedure	2	8.7	0	0	0.90
Left hemicolectomy	5	21.7	0	0	0.29
Right hemicolectomy	2	8.7	4	40.0	0.05
Sigmoid resection	6	26.1	3	30.0	>0.05
Intersphincteric resection of the rectum	1	4.3	0	0	>0.05
Keny — Miles procedure	2	8.7	1	10.0	>0.05
Presence of comorbidities					
None	4	17.4	3	30.0	0.65
Cardiovascular diseases (IHD, hypertension)	4	17.4	1	10.0	>0.05
Digestive system diseases	4	17.4	4	40.0	0.21
2 systems	7	30.4	1	10.0	0.38
3 or more	4	17.4	1	10.0	>0.05
Mean time to detection of disease signs after RFA					
No recurrence	18	78.3	1	10.0	0.0004
Up to 6 months	2	8.7	1	10.0	>0.05
Up to 12 months	1	4.3	4	40.0	0.02
More than 12 months	2	8.7	4	40.0	0.05

tum, rectosigmoid junction, sigmoid colon, cecum, or other colon or rectum sites) (Table).

No significant impact on the overall survival was found for the following factors: primary tumor morphology - differentiation grades G1, G2, G3, G2/G3; number of chemotherapy lines before ablation; maximum size of the largest metastases; liver involvement; number of metastases; surgery characteristics (primary tumor surgery: anterior resection, low anterior resection, Hartmann's procedure, left hemicolectomy, right hemicolectomy, sigmoid resection, intersphincteric resection, Keny — Miles procedure); presence of comorbidities; and the mean time to detection of disease signs post-RFA (Table).

In evaluating metastasis parameters, a significant difference was found in the presence of synchronous metastases (21.7% in group 1 vs. 100.0% in group 2, $p < 0.001$), or metachronous metastases (78.3% in group 1 and none in group 2, $p < 0.001$). Assessment of the mean time to detection of disease signs post-RFA revealed significant differences between the groups: there was no recurrence in group 1 in 78.3% cases vs 10.0% in group 2, $p = 0.0004$.

Our study demonstrated that the use of RFA in patients with metastatic liver involvement from CRC is an effective and safe method that provides acceptable oncological outcomes. RFA reduces intraoperative risks, procedure duration, and postoperative rehabilitation time without compromising long-term overall survival [16, 17]. At the same time, RFA remains an alternative option for patients with limited potential for surgical resection or within parenchyma-sparing treatment strategies [18, 19].

Particular attention in our study was paid to the characteristics of the metastatic process. It was found that the presence of synchronous or metachronous metastases significantly affects overall patient survival [20]. In assessing metastatic process parameters, a statistically significant difference was found between the presence of synchronous and metachronous metastases. It can be assumed that the presence of synchronous colorectal metastases may worsen patients' prognosis. Patients with metachronous metastases demonstrated a longer disease-free period and better oncological prospects. This result indicates the need to stratify pa-

tients according to the nature of metastasis when planning treatment tactics.

A key clinical marker in our cohort was also the duration of the disease-free period after RFA. The longer the remission period, the higher the overall survival rates, confirming the prognostic value of this parameter in assessing the effectiveness of the local intervention [21]. The mean time to detection of disease signs post-RFA without recurrence significantly differed between the groups. This may indicate the undeniable impact of disease progression on the overall survival. This fact emphasizes the importance of dynamic clinical monitoring in the long-term period after ablation.

The obtained results provide the grounds to consider that RFA can be a reasonable component of multimodal treatment for colorectal cancer patients with liver metastases, provided careful selection of candidates, particularly considering metastasis synchrony, and oncological history [22, 23].

To sum up, the use of RFA in the treatment of colorectal liver metastasis is a safe alternative for patients with unresectable lesions or within parenchyma-sparing strategies. However, liver resection should be considered a priority option when technically feasible. The treatment choice should be based on the characteristics of the metastatic process, particularly the synchrony or metachrony of involvement, size and number of metastases, patient age, etc. Additionally, the combined use of surgical resection and RFA expands the range of patients eligible for radical intervention, potentially improving disease-free and overall survival rates. However, these results are limited to the baseline inequality of the comparative groups. To confirm the efficacy of RFA and identify the target population that will benefit most from RFA in the future, randomized studies or propensity score-matched studies should be conducted.

Limitations

The limitations of this study include its retrospective nature, small sample size, and differences in chemotherapy between groups. At the same time, the advantage is the use of a propensity score matching analysis, which allowed for an objective assessment of RFA and resection outcomes in colorectal liver metastases.

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РАДІОЧАСТОТНА АБЛЯЦІЯ ЯК ОДНА ІЗ СТРАТЕГІЙ ПЕЧІНКОВО-СПРЯМОВАНОЇ ТЕРАПІЇ

Стан питання. Резекція печінки залишається золотим стандартом лікування хворих із метастазами колоректального раку, однак радіочастотна абляція (РЧА) може бути альтернативою для пацієнтів із протипоказаннями до резекції або в рамках паренхімозберігаючих стратегій. **Мета** дослідження – проаналізувати результати лікування, прогностичні фактори та виживаність після РЧА інтрапаренхіматозних метастазів у печінці в ДНП «Національний інститут раку». **Матеріали та методи**. Проведено ретроспективний аналіз лікування 33 пацієнтів з метастазами колоректального раку в печінці, які отримували РЧА в 2013—2023 рр. Абляція виконувалася за допомогою апарата Cool-tip RF Ablation System E Series (Covidien) з максимальною потужністю 200 Вт та охолоджуваними однополюсними голками під інтраопераційною УЗД-навігацією. **Результати.** Пацієнтів було стратифіковано за статусом виживання. Група 1 (n = 23) включала пацієнтів, яким було проведено радіочастотну абляцію (РЧА) та які були живими на момент аналізу; група 2 (n = 10) включала тих, хто помер від прогресування захворювання. Виявлено достовірний вплив на виживаність наявності синхронних метастазів (21,7% проти 100,0%, $p < 0,001$), метахронних метастазів (78,3% проти 0, $p < 0,001$) та середнього часу до прогресування (18 (78,3%) проти 1 (10,0%), $p = 0,0004$). Не мали значущого впливу стать, вік, локалізація і морфологія первинної пухлини, кількість ліній поліхіміотерапії, розмір і кількість метастазів, тип первинної операції та наявність супутніх захворювань. **Висновки**. Використання РЧА в лікуванні метастазів колоректального раку в печінку є безпечною альтернативою для пацієнтів із неоперабельними ураженнями або в межах паренхімозберігаючих стратегій, проте резекція печінки повинна розглядатися як пріоритетна опція у випадках, коли її виконання є технічно можливим. Вибір лікування повинен ґрунтуватися на характеристиках метастатичного процесу, зокрема синхронності чи метахронності ураження, розмірах і кількості метастазів, віці пацієнта тощо. Крім того, комбіноване використання хірургічної резекції та РЧА дозволяє розширити коло пацієнтів, яким може бути виконане радикальне втручання, що потенційно покращує показники безрецидивної та загальної виживаності. Однак ці результати обмежуються нерівністю початкового стану порівняльних груп. Для підтвердження ефективності РЧА та визначення цільової групи населення, яка отримає найбільшу користь від РЧА в майбутньому, слід провести рандомізовані дослідження або дослідження співставлення за показником схильності.

Ключові слова: колоректальний рак, резекція печінки, метастази колоректального раку в печінку, електрохірургія, радіочастотна абляція.