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Predyktory przeżycia u pacjentów poddawanych termoablacji mikrofalowej przerzutów raka jelita grubego do wątroby

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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1. **Franke J**, Rosiak G, Milczarek K, Konecki D, Wnuk E, Cieszanowski A.
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Spis treści

Wykaz stosowanych skrótów (w kolejności alfabetycznej)

AGR	stosunek albumin do globulin *(albumin-to-globulin ratio)*
CEA	antygen karcynoembrionalny *(carcinoembrionic antigen)*
CLM	przerzuty raka jelita grubego do wątroby *(colorectal liver metastases)*
CRC	rak jelita grubego *(colorectal cancer)*
IRE	nieodwracalna elektroporacja (*irreversible electroporation)*
LMR	stosunek limfocytów do monocytów *(lymphocyte-to-monocyte ratio)*
LTPFS	czas przeżycia wolnego od progresji lokalnej *(local tumor progression free survival)*
MWA	ablacja mikrofalowa *(microwave ablation)*
NLR	stosunek neutrofili do limfocytów *(neutrophil-to-lymphocyte ratio)*
OS	całkowity czas przeżycia *(overall survival)*
PLR	stosunek płytek krwi do limfocytów *(platelet-to-lymphocyte ratio)*
RFA	ablacja prądem o częstotliwości radiowej (radiofrequency ablation)

Streszczenie w języku polskim

Rak jelita grubego (CRC) należy do najczęstszych nowotworów złośliwych na świecie i stanowi istotny problem zdrowotny również w Polsce. Pomimo postępu w diagnostyce i leczeniu, znaczna liczba pacjentów rozwija przerzuty odległe, które najczęściej lokalizują się w wątrobie. Leczenie pacjentów z przerzutami raka jelita grubego do wątroby (CLM) wymaga spersonalizowanego podejścia. Chociaż przez długi czas leczenie chirurgiczne pozostawało złotym standardem, obecnie coraz większą rolę odgrywają techniki małoinwazyjne, takie jak przezskórna termoablacja mikrofalowa (MWA), zwłaszcza u pacjentów z chorobą oligometastatyczną.

Od dawna próbowano zidentyfikować kliniczne i laboratoryjne czynniki prognostyczne u pacjentów onkologicznych, które mogłyby przewidywać całkowity czas przeżycia (OS) oraz miejscową kontrolę. Badane biomarkery mogą obejmować bezpośrednie markery związane z nowotworem, na przykład antygen karcynoembrionalny (CEA) w przypadku raka jelita grubego oraz pośrednie, do których zaliczyć można wskaźniki aktywności układu immunologicznego wyliczane z rutynowych badań krwi – takie jak stosunek limfocytów do monocytów (LMR), neutrofili do limfocytów (NLR), płytek krwi do limfocytów (PLR) oraz stosunek albumin do globulin (AGR). Choć ich wartość prognostyczna była oceniana u pacjentów poddanych resekcji chirurgicznej lub ablacji prądem o częstotliwości radiowej (RFA), niewiele badań skupia się na ich roli w przypadku pacjentów leczonych metodą MWA z powodu CLM.

Niniejsza rozprawa stanowiąca cykl publikacji, analizuje potencjał prognostyczny prostych biomarkerów z krwi obwodowej u pacjentów z CLM poddanych termoablacji mikrofalowej. Przedstawia również aktualny stan wiedzy na temat skuteczności, bezpieczeństwa oraz czynników wpływających na przeżycie całkowite i czas przeżycia wolnego od progresji miejscowej.

***Franke J**, Rosiak G, Milczarek K, Konecki D, Wnuk E, Cieszanowski A. Biomarkers of Survival in Patients with Colorectal Liver Metastases Treated with Percutaneous Microwave Ablation. Cancers 2025, 17, 1112.*

W tym badaniu oceniono wartość prognostyczną łatwo dostępnych biomarkerów z krwi obwodowej u 57 pacjentów z CLM leczonych MWA. Analiza obejmowała poziom CEA, gęstość CEA (wartość CEA w odniesieniu do objętości zmian), a także wskaźniki NLR, LMR, PLR i AGR. Wyznaczono istotne wartości progowe dla poszczególnych wskaźników i wykorzystano je w analizie jednoczynnikowej i wieloczynnikowej.

Podwyższone stężenie CEA, wysoka gęstość CEA oraz zwiększony LMR były związane z krótszym całkowitym czasem przeżycia, natomiast wyższe wartości NLR i lewostronna lokalizacja guza pierwotnego korelowały z lepszymi wynikami leczenia. W analizie wieloczynnikowej istotne statystycznie pozostały jedynie poziom CEA, NLR i lokalizacja guza pierwotnego, podczas gdy LMR stracił niezależną wartość prognostyczną. Najsilniejszym negatywnym czynnikiem prognostycznym okazał się poziom CEA > 29,1 ng/mL (HR = 4,10). Z kolei wartość NLR > 2,05 miała działanie ochronne (HR = 0,29), a nowotwory lewostronne wiązały się z lepszym przeżyciem (HR = 0,25). Wyniki te podkreślają znaczenie prostych biomarkerów oraz markerów nowotworowych w prognozowaniu przeżycia.

***Franke J**, Rosiak G, Konecki D, Milczarek K, Cieszanowski A.*
Technical Aspects, Methodological Challenges and Factors Predicting Outcome of Percutaneous Ablation for Colorectal Liver Metastases. Pol J Radiol. 2025;90:279–285.

Artykuł ten stanowi przegląd literatury dotyczącej technicznych, klinicznych i biologicznych czynników wpływających na wyniki przezskórnej ablacji przerzutów raka jelita grubego do wątroby. Zestawiono ze sobą metody RFA, MWA oraz nieodwracalną elektroporację (IRE), wskazując ich zalety i ograniczenia, kładąc nacisk na metody termoablacji, z racji ich powszechniejszego stosowania. Choć MWA wykazuje pewne przewagi techniczne nad RFA, to efekty kliniczne – w zakresie miejscowej progresji i całkowitego przeżycia – są generalnie porównywalne.

Kluczowym czynnikiem skutecznej kontroli miejscowej jest uzyskanie odpowiedniego marginesu ablacyjnego. Badania jednoznacznie wskazują, że margines ≥ 5 mm, a najlepiej > 10 mm, znacząco obniża ryzyko wznowy. Wprowadzenie oprogramowania do trójwymiarowej oceny marginesu ablacji zwiększa precyzję oceny doszczętności zabiegu w porównaniu do tradycyjnej oceny 2D metodą „na oko”, polegającej na porównaniu obrazów przed i po zabiegu. Dodatkowo zaawansowane techniki obrazowania, takie jak tomografia komputerowa z arteriografią wątrobową, poprawiają wizualizację zmian podczas zabiegu oraz ocenę marginesów po ablacji, co dodatkowo zmniejsza ryzyko progresji miejscowej.

Biologia guza również istotnie wpływa na wyniki leczenia. Mutacje genetyczne, zwłaszcza w genach RAS, BRAF oraz obecność niestabilności mikrosatelitarnej, wpływają zarówno na kontrolę miejscową, jak i przeżycie. Przykładowo, pacjenci z mutacjami RAS osiągają gorsze wyniki, nawet przy technicznie udanych zabiegach. Do innych niekorzystnych czynników prognostycznych należą większy rozmiar guza, lokalizacja okołonaczyniowa lub podtorebkowa.

Aktualne badania kliniczne, w tym zakończone niedawno badanie COLLISION, potwierdzają skuteczność ablacji u starannie dobranych pacjentów. Dla małych przerzutów ablacja osiąga porównywalne przeżycie długoterminowe w porównaniu do resekcji chirurgicznej, przy jednocześnie niższym ryzyku powikłań.

Wnioski

Przedstawione publikacje dowodzą, że wybrane markery laboratoryjne mają znaczenie prognostyczne u pacjentów z przerzutami raka jelita grubego do wątroby leczonych metodą MWA. Wysoki poziom CEA wiąże się z krótszym przeżyciem, natomiast podwyższony wskaźnik NLR koreluje z lepszymi wynikami. Inne wskaźniki, takie jak AGR, LMR i PLR, nie wykazują istotnej wartości prognostycznej. Lokalizacja guza pierwotnego również wpływa na przeżycie – pacjenci z lewostronnym guzem pierwotnym rokują korzystniej niż z prawostronnym.

Skuteczność leczenia zależy w dużej mierze od aspektów technicznych, zwłaszcza uzyskania odpowiedniego marginesu ablacyjnego (ablacja A0), który jest kluczowy zarówno dla przeżycia całkowitego, jak i miejscowej kontroli choroby. W tym kontekście zaawansowane oprogramowanie do oceny marginesów ablacyjnych staje się istotnym elementem zabiegu, oferując dokładniejsze i bardziej wiarygodne wyniki niż tradycyjne metody analizy porównawczej obrazów.

Streszczenie w języku angielskim

Colorectal cancer (CRC) ranks among the most prevalent malignancies globally and poses a significant health burden in Poland. Despite progress in diagnostic tools and treatment strategies, a substantial number of patients develop distant metastases, most commonly in the liver. Patients with colorectal liver metastases (CLM) require a personalized treatment approach. While surgical resection remains the gold standard, minimally invasive techniques such as percutaneous microwave ablation (MWA) have emerged as effective alternatives, particularly for patients with oligometastatic disease.

There is increasing interest in identifying clinical and laboratory markers that predict overall survival (OS) and local tumor control. Frequently studied biomarkers include the tumor specific markers, such as carcinoembryonic antigen (CEA), as well as tumor nonspecific parameters, in example systemic immunological indicators derived from routine blood tests—such as the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and albumin-to-globulin ratio (AGR). While their prognostic value has been examined in patients treated with surgery or radiofrequency ablation (RFA), relatively few studies have focused specifically on their role in patients undergoing MWA for CLM.

This dissertation, structured as a series of publications, explores the prognostic potential of simple, blood-derived biomarkers in patients with CLM treated with MWA. It also provides an overview of the current evidence on the efficacy, safety, and prognostic factors influencing overall survival and local tumor progression-free survival.

***Franke J**, Rosiak G, Milczarek K, Konecki D, Wnuk E, Cieszanowski A. Biomarkers of Survival in Patients with Colorectal Liver Metastases Treated with Percutaneous Microwave Ablation. Cancers 2025, 17, 1112.*

This study assessed the prognostic significance of readily available blood-based biomarkers in 57 patients with CLM treated using MWA. The analysis included CEA, CEA density (CEA level relative to lesion volume), and inflammatory markers such as NLR, LMR, PLR, and AGR. Significant biomarkers cut-off values were determined and incorporated into univariate and multivariate analysis.

Elevated CEA levels, high CEA density, and increased LMR were associated with worse overall survival, whereas higher NLR values and left-sided primary tumor location were linked to improved outcomes. However, in multivariable regression analysis, only CEA, NLR, and tumor sidedness remained statistically significant predictors, while LMR lost its independent prognostic value. The most pronounced negative prognostic factor was a CEA level greater than 29.1 ng/mL, with a hazard ratio (HR) of 4.10. Conversely, an NLR above 2.05 was associated with a protective effect (HR = 0.29), as well as left-sided primary tumors were correlated with improved survival (HR = 0.25). These findings highlight the relevance of systemic inflammation markers and tumor burden indicators in survival prediction.

Franke J*, Rosiak G, Konecki D, Milczarek K, Cieszanowski A.*
Technical Aspects, Methodological Challenges and Factors Predicting Outcome of Percutaneous Ablation for Colorectal Liver Metastases. Pol J Radiol. 2025;90:279–285.

This article reviews the current literature on the technical, clinical, and biological factors influencing outcomes following percutaneous ablation of CLM. It compares RFA, MWA, and irreversible electroporation (IRE), outlining their respective advantages and limitations, with major focus on thermoablative modalities as the one most commonly used. Although MWA presents several technical advantages over RFA, clinical outcomes in terms of local tumor progression and overall survival are generally comparable. A critical determinant of successful local control is achieving an adequate ablation margin. Studies consistently show that margins of at least 5 mm, and ideally >10 mm, are associated with significantly reduced recurrence rates. The introduction of 3D margin assessment software has improved accuracy over traditional 2D visual „eye-balling" meaning comparison of pre- and postablation images, enhancing detection of insufficient margins. Moreover, advanced imaging techniques such as CT hepatic arteriography have improved intraprocedural visualization and post-procedural margin evaluation, further reducing local tumor progression rates.

Tumor biology also significantly impacts outcomes. Genetic mutations—especially in RAS, BRAF, and microsatellite instability affect both local tumor control and overall survival. For example, patients with RAS mutations often have worse outcome even when technically successful ablations are performed. Other negative prognostic factors include larger tumor size, perivascular or subcapsular location.

Ongoing clinical trials, including the recently published COLLISION studies, support the use of ablation in selected patients, showing that for small CLMs, ablation can offer non-inferior long-term survival compared to resection, additionaly with lower complication rates.

Conclusions

The publications presented in this dissertation confirm that selected laboratory markers have prognostic value in patients with colorectal liver metastases treated with microwave ablation. A high CEA level is associated with shorter overall survival, while an elevated neutrophil-to-lymphocyte ratio (NLR) correlates with longer survival. Other markers, such as AGR, LMR, and PLR, do not show a significant association with prognosis. The location of the primary tumor also plays a role—patients with left-sided colorectal cancer tend to have better survival outcomes compared to those with right-sided primary tumors.

Treatment effectiveness is strongly influenced by technical factors, particularly the achievement of an adequate ablation margin (A0 ablation), which is essential for both overall survival and local tumor control. In this regard, advanced software for assessing ablation margins starts to be an important part of the procedure as it provides more accurate and effective results than traditional image comparison methods.

Rozprawa doktorska

Predyktory przeżycia u pacjentów poddawanych termoablacji mikrofalowej przerzutów raka jelita grubego do wątroby

Wstęp

Rak jelita grubego (CRC) jest jednym z najczęściej występujących nowotworów złośliwych na świecie i stanowi istotny problemem zdrowotny również w Polsce. Pomimo postępu w diagnostyce i leczeniu, około połowa pacjentów rozwija przerzuty odległe, z czego w większości przypadków lokalizują się one w wątrobie. Pacjenci z przerzutami do wątroby z raka jelita grubego (CLM) stanowią wyzwanie kliniczne wymagające indywidualnie dopasowanego podejścia terapeutycznego. Przez wiele lat standardem leczenia pozostawała resekcja chirurgiczna, uznawana za jedyną opcję radykalną. Jednak rozwój technik obrazowania oraz minimalnie inwazyjnych metod leczenia, takich jak przezskórna termoablacja – w szczególności ablacja mikrofalowa (MWA) – doprowadził do istotnego rozszerzenia wskazań i możliwości terapeutycznych w grupie pacjentów z chorobą oligometastatyczną. Najnowsze badania, w tym wieloośrodkowe badania randomizowane, wskazują na porównywalną skuteczność oraz lepszy profil bezpieczeństwa ablacji względem resekcji w wybranych przypadkach. Ablacja podobnie jak leczenie chirurgiczne pozwala na uzyskanie najlepszych wyników odległego przeżycia u pacjentów onkologicznych w przypadku doszczętnego zniszczenia zmiany nowotworowej.

Czynniki wpływające na całkowity czas przeżycia (OS) u pacjentów onkologicznych od dawna znajdowały się w obszarze zainteresowań badaczy. Zarówno parametry związane bezpośrednio z chorobą takie jak stopień zaawansowania, liczba zmian przerzutowych czy stężenie markerów nowotworowych, jak również parametry laboratoryjne wskazujące na zdolność do odpowiedzi antynowotworowej przez układ immunologiczny pacjenta. Jednymi z najczęściej badanych wskaźników są markery swoiste dla nowotworu, w przypadku raka jelita grubego jest to antygen karcynoembrionalny (CEA). Z kolei do nieswoistych dla nowotworu parametrów uwzględnianych w modelach predykcyjnych zaliczyć można biomarkery pochodzące z morfologii krwi obwodowej, są to między innymi: stosunek limfocytów do monocytów (LMR), stosunek neutrofili do limfocytów (NLR), stosunek płytek krwi do limfocytów (PLR) czy oparty na badaniach biochemicznych na przykład stosunek albumin do globulin (AGR). Markery te były badane w kohortach pacjentów leczonych zarówno systemowo, chirurgicznie jak i lokoregionalnie. Jednak zdecydowana większość prac dotycząca znaczenia tych biomarkerów w predykcji wyników leczenia miejscowego u pacjentów z CLM była oparta o kohorty poddawane zabiegom ablacji prądem o częstotliwości radiowej (RFA). Jest to związane z faktem, że RFA jest metodą znacznie dłużej dostępną i przez lata powszechniej stosowaną w porównaniu do MWA. Obecnie jednak MWA zajęła miejsce RFA i stała się podstawową metodą leczenia ablacyjnego CLM ze względu na krótszy czas zabiegu oraz lepsze efekty ablacji zmian położonych przy dużych naczyniach. Wynika to z mniejszej podatności MWA na tak zwany „heat-sink effect" czyli na pochłanianie ciepła, a przez to ograniczenie rozmiaru strefy ablacji, przez krew płynącą w pobliskim naczyniu. W dostępnej literaturze brakuje prac badających rolę prostych biomarkerów z krwi obwodowej u pacjentów z przerzutami raka jelita grubego do wątroby leczonych MWA.

Niniejsza rozprawa doktorska składająca się z cyklu publikacji skupia się na czynnikach wpływających na skuteczność zabiegu i długość przeżycia po nim mierzoną między innymi jako czas całkowitego przeżycia i czas przeżycia wolnego od progresji lokalnej (LTPFS) oraz bada potencjalne zastosowanie biomarkerów w roli predyktorów u pacjentów z przerzutami raka jelita grubego do wątroby leczonych termoablacją mikrofalową.

Pierwsza publikacja z cyklu rozprawy doktorskiej *(**Franke J**, Rosiak G, Milczarek K, Konecki D, Wnuk E, Cieszanowski A. Biomarkers of Survival in Patients with Colorectal Liver Metastases Treated with Percutaneous Microwave Ablation. Cancers 2025, 17, 1112.)* jest pracą oryginalną, stanowiącą retrospektywną analizę pacjentów z CLM zakwalifikowanych do leczenia przy pomocy MWA. Zgodnie z moją wiedzą jest to pierwsza praca, która ocenia taki zakres wskaźników laboratoryjnych pochodzących z krwi obwodowej w tego rodzaju grupie pacjentów. Celem pracy była ocena potencjalnej roli predykcyjnej LMR, NLR, PLR, AGR oraz stężenia CEA na OS. Wstępnie do tego badania została zakwalifikowana grupa pacjentów poddanych 262 zabiegom MWA, wyłoniono z niej kohortę 57 pacjentów, posiadających pełne dane kliniczne i wyniki laboratoryjne. Głównym punktem końcowym badania był OS liczony od daty wykonania zabiegu natomiast do analizy związku pomiędzy poszczególnymi biomarkerami został wykorzystany test log-rank, dzięki któremu określono optymalny poziom odcięcia, który umożliwił zamianę zmiennych ciągłych na binarne. Dzięki zdefiniowanym poziomom odcięcia możliwe było podzielenie pacjentów na podgrupy z wysokim lub niskim poziomem danego biomarkera. Następnie w oparciu o ten podział i zdefiniowane poziomy poszczególnych biomarkerów stworzono model proporcjonalnego ryzyka względnego Cox'a celem analizy wieloczynnikowej i wyłonienia czynników o istotnym statystycznie związku z długością całkowitego przeżycia.

Druga praca prezentowanego cyklu *(**Franke J**, Rosiak G, Konecki D, Milczarek K, Cieszanowski A. Technical Aspects, Methodological Challenges and Factors Predicting Outcome of Percutaneous Ablation for Colorectal Liver Metastases. Pol J Radiol. 2025;90:279–285)* stanowi przegląd najnowszych publikacji dotyczących metod leczenia małoinwazyjnego u pacjentów z rakiem jelita grubego z przerzutami do wątroby takich jak MWA, RFA czy nieodwracalna elektroporacja (IRE). W czytelny sposób prezentuje czym różnią się poszczególne metody oraz jakie mają wady i zalety względem siebie. Przedstawia aktualny stan wiedzy na temat czynników wpływających na skuteczność termoablacji u pacjentów z CLM, poruszając koncept ablacji A0, który powstał w analogii do resekcji chirurgicznej R0. Ponadto opisuje bieżące kierunki rozwoju lokoregionalnych metod leczenia, zwracając uwagę na coraz istotniejszą rolę oprogramowania potwierdzającego strefę ablacji w oparciu o badania przed i po zabiegowe. Praca ta może być zwięzłym przewodnikiem po metodach leczenia ablacyjnego w intensywnie rozwijającej się dziedzinie onkologii interwencyjnej.

Założenia i cel pracy

1. Ocena wartości prognostycznej prostych, laboratoryjnych biomarkerów, takich jak: LMR, AGR, PLR, NLR czy stężenie CEA u pacjentów z CLM poddawanych MWA.
2. Opracowanie modelu prognostycznego opartego na łatwo dostępnych biomarkerach i cechach klinicznych, u pacjentów z CLM pod kątem rokowania po MWA.
3. Przegląd czynników mających wpływ na efektywność MWA w tej grupie pacjentów między innymi pod postacią OS oraz LTPFS.
4. Ponadto prezentując aktualny stan wiedzy i najnowsze kierunki rozwoju termoablacji zmian przerzutowych do wątroby w „Polskim Przeglądzie Radiologicznym" („*Polish Journal of Radiology")* chciałem spopularyzować tę metodę leczenia pacjentów onkologicznych w Polskich ośrodkach i rozpowszechnić wiedzę o kluczowych aspektach tych zabiegów celem uzyskiwania jak najlepszych efektów leczenia.

Kopie opublikowanych prac

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Biomarkers of Survival in Patients with Colorectal Liver Metastases Treated with Percutaneous Microwave Ablation

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Simple Summary: According to international guidelines, thermal ablation and surgery are the two main radical treatment possibilities for colorectal liver metastases. The aim of this study was to assess the prognostic value of simple laboratory-based biomarkers in patients undergoing microwave ablation for colorectal liver metastases. In a cohort of 57 patients, with a mean follow-up time of 30.9 months, higher levels of carcinoembryonic antigen and lymphocyte-to-monocyte ratio were linked to worse survival, while higher neutrophil-to-lymphocyte ratio levels and left-sided primary colon cancer were positive prognostic factors. A multivariable analysis confirmed most of the findings, except the lymphocyte-to-monocyte ratio's significance.

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Abstract: Background/Objectives: To evaluate the prognostic value of easily obtainable biomarkers for patients undergoing percutaneous microwave ablation (MWA) for col- orectal liver metastases (CLMs). Prior studies showed that simple biomarkers, such as the lymphocyte-to-monocyte ratio (LMR), albumin-to-globulin ratio (AGR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR), as well as cancer- specific markers, like carcinoembryonic antigen (CEA), might have a prognostic role in various malignancies; however, none of these were assessed in patients undergoing MWA for CLMs. **Methods**: Based on the simple laboratory results, which were determined prior to the ablation, several biomarkers, including the LMR, AGR, PLR, and NLR, were calculated. The log-rank test's optimal cutoff points for continuous variables were deter- mined. Subsequently, univariable and multivariable Cox regression models were utilized to determine the association between various features and overall survival (OS). **Results**: This study included 57 CLM patients with a mean age of 63 ± 12.5 years at the time of ablation with a mean follow up of 30.9 months. The univariable model demonstrated that a high level of CEA (cutoff: 29.1 ng/mL; HR: 3.70) and a high LMR (cutoff: 5.32; HR: 4.05) were related to worse OS, whereas a high NLR (cutoff: 2.05; HR: 0.31) and primary left-sided colon cancer (HR: 0.36) were positive prognostic factors. The multivariable regression model confirmed these findings, with the exception of the LMR, which was no longer significantly associated with OS. **Conclusions**: This study demonstrates the feasibility of overall survival prediction and thus patient stratification based on easily obtainable biomarkers and clinicopathological features in CLM patients undergoing MWA.

Keywords: liver lesion microwave ablation; post ablation survival; survival predictor; ablation biomarker; blood-derived survival predictor; locoregional treatment predictor

1. Introduction

Due to the gradual buildup of evidence showing comparable efficacy to surgery in terms of the overall survival (OS) rates in liver tumor ablation, locoregional treatment has become one of the main treatment options for patients with both primary and metastatic liver cancer [1,2]. Radiofrequency ablation (RFA) has been the primary ablative modality for many years. With the advent of microwave ablation (MWA), most of the RFA limitations have been overcome. MWA can create larger ablation zones, the application time is shorter, and most significantly, it is suitable for lesions in close vicinity to vessels thanks to the lack of a 'heat sink effect' when compared with RFA [3]. Currently, thermal ablation and surgery are the two main radical treatment possibilities for colorectal liver metastases (CLMs). According to many recommendations, they should be considered complementary methods depending on the size and location of the lesions, the patient's comorbidities, and their preferences. According to the European Society for Medical Oncology (ESMO) guidelines, surgery or locoregional therapy is recommended as long as it is possible to eradicate the primary and oligometastatic disease. Similarly, current National Comprehensive Cancer Network (NCCN) guidelines for colorectal cancer state that locoregional treatment may be considered alone or complementary to surgery in case of the feasibility of an A0 ablation, which is defined as an ablation zone with margins over 10 mm [1,2].

Since the very beginning of ablative procedures, researchers have been looking for the predictive factors for local progression as well as overall survival, mainly focusing on the number and size of the lesions or the ablative margin [4–7]. Moreover, there have been studies trying to establish some readily available biomarkers, such as the lymphocyte-to-monocyte ratio (LMR), albumin-to-globulin ratio (AGR), platelet-to-lymphocyte ratio (PLR), neutrophile-to-lymphocyte ratio (NLR), and levels of cancer-specific markers, i.e., the carcinoembryonic antigen (CEA) and α-fetoprotein (AFP). The role of the aforementioned markers as independent predictive factors concerning survival has been demonstrated in patients with several malignancies [8–11]. However, most of these studies investigated patients treated with nonablative techniques. There are a few papers investigating biomarkers as OS predictors in patients treated with ablation, although a majority of them are based on cohorts with hepatocellular carcinoma treated with RFA [12–14]. The papers focusing on biomarkers in colorectal cancer patients undergoing ablation are limited [15–17]. To our knowledge, no study has investigated the LMR, PLR, NLR, AGR, and CEA in one cohort with colorectal liver metastases (CLMs) treated with MWA under CT guidance. Considering that colorectal cancer is one of the most commonly occurring malignancies, with the liver being the most common site of metastases, there seems to be a niche that was not thoroughly researched. Therefore, this study aims to provide a deeper insight into various clinicopathological predictors of survival.

2. Materials and Methods

This study included colorectal cancer patients with liver metastases who had been qualified for MWA by a multidisciplinary tumor board. The eligibility criteria for MWA were as follows: no extrahepatic disease, a platelet count > 50,000/mm^3, and an international normalized ratio < 1.5. The ablation procedures were performed under CT (Aquillon Toshiba, Otawara, Japan) guidance by three interventional radiologists with at least six years of ablative experience. All procedures were performed under general anesthesia. The Solero MWA applicator system (AngioDynamics BV, Amsterdam, The Netherlands) was used. The number of ablative sessions and application parameters was based on the lesion location and size to obtain an oncologic margin of at least 5 mm but preferably 10 mm. The technical success of the procedure was confirmed with a control triple-phase contrast-enhanced CT study performed at the end of the procedure. In case any unab lated tumor was visible while the control study was performed during the procedure, the ablation needle was reintroduced and an additional ablation session was performed during the same procedure to destroy the viable tumor tissue and achieve complete local control. Subsequently, all patients underwent a routine follow-up six weeks after the procedure to confirm the radicality of the ablation, and then every three months for a year to detect a possible early recurrence, which could be reablated. Further, a follow-up scheme, typically an MRI scan every 6 months, was implemented according to the referring physician's discretion.

Between 2017 and 2022, 262 patients underwent a CLM ablation using MWA. However, out of the 262 patients who were treated, 57 patients had a complete blood count with defined leukocyte subpopulations, CEA value, and an albumin level tested prior to the procedure. Only data from patients who met these inclusion criteria were used for statistical analysis (Figure 1).

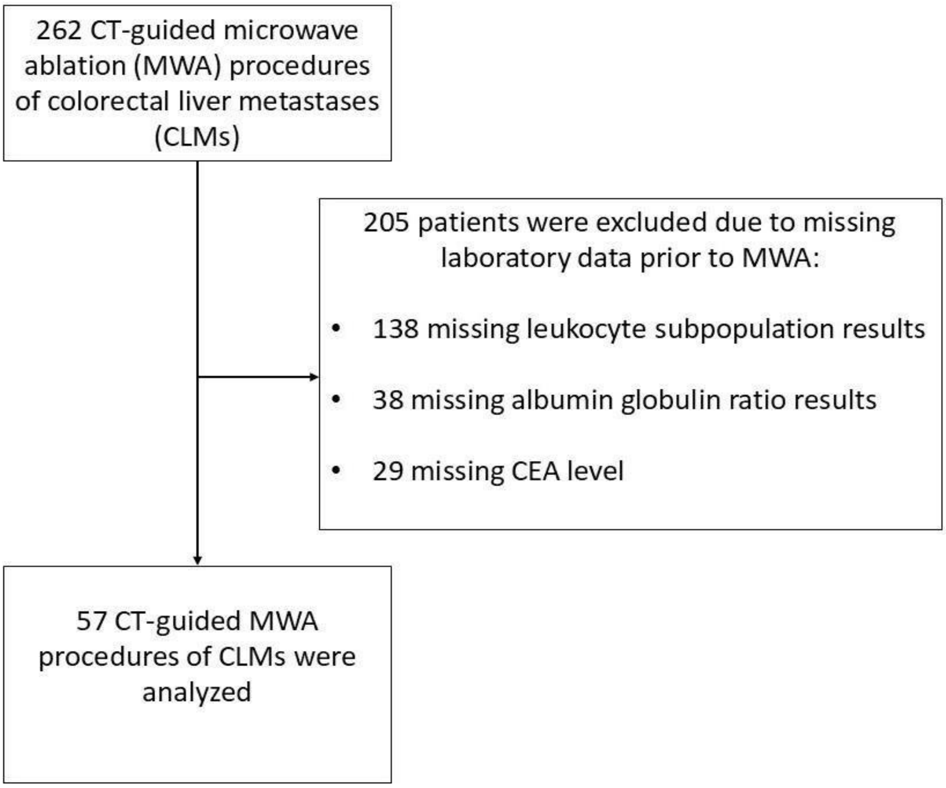

Figure 1. Patient selection flowchart of a study group consisting of patients with colorectal cancer liver metastases treated with microwave ablation.

The CEA density (ng/mL·mm^3) was calculated based on the total CEA serum level before ablation, divided by the total volume of the metastatic lesions located in the liver, similar to the method used by Hou et al. to calculate the CEA density in patients with colorectal lung metastases [16].

All the statistical analyses were performed using the statistical libraries available for Python version 3.9 and R version 4.2.3 (R Foundation for Statistical Computing, www.r-project.org). Right censoring was used when no event occurred during this study. Therefore the length of follow-up was defined as the time from ablation to death or the last available follow-up data. The optimal cutoff points for potential continuous predictors were calculated using a log-rank test. The value of a variable with the highest log-rank statistical value was accepted as a cutoff point. Furthermore, the variables were assessed using Cox regression models with a statistical significance level of a p-value < 0.05. A multivariable Cox regression model was created based on the variables that achieved significance in a univariable analysis. Furthermore, to avoid the bias resulting from possible collinearity all the variables in the multivariable analysis were checked using a variance inflation factor (VIF) analysis. For each variable in the model, the VIF was below 2 indicating that multicollinearity is not a significant issue in this model.

The Bioethical Committee accepted retrospective nature of this study (AKBE 6/2024). All procedures were performed in accordance with the declaration of Helsinki, as revised in 2013 and written consent for procedures were obtained from the patients.

3. Results

A total of 30 males and 27 females were included in this study with a mean age of 63 ± 12.5 years (29.5–87.9 years) at the time of ablation. In the majority of cases there was a single metastatic lesion (44/57) and only a few patients had more than two lesions (6/57). The mean diameter of the lesion was 20 ± 10.4 mm (5–59 mm), with all the lesions except one being below 50 mm. Moreover, the majority of patients (43/57) had lesions of a diameter below 30 mm. The mean follow-up period was 30.9 months ± 15.1 months (6.7–68.8 months).

A log-rank analysis was used to determine the most significant cutoff values for the biomarkers, LMR, AGR, PLR, NLR, CEA, and the CEA density (Table 1).

Table 1. Analyzed blood biomarker characteristics in the study group of patients with colorectal cancer liver metastases treated with microwave ablation.

Biomarker	Mean ± SD	Range	Cutoff Value
LMR	3.44 ± 1.84	1.34–10.05	5.32
AGR	1.66 ± 0.32	0.80–2.60	1.81
PLR	131.09 ± 74.68	18.64–383.02	122.7
NLR	2.36 ± 1.39	0.79–8.29	2.05
CEA [ng/mL]	30.47 ± 59.97	0.32–323.00	29.1
CEA density [ng/mL·mm^3]	0.0019 ± 0.01	0.000004–0.07	0.00046

Lymphocyte-to-monocyte ratio (LMR), albumin-to-globulin ratio (AGR), platelet-to-lymphocyte ratio (PLR), neutrophile-to-lymphocyte ratio (NLR), carcinoembryonic antigen (CEA).

In the univariable statistical analysis, the LMR, CEA, CEA-density, NLR, and primary tumor sidedness were statistically significant predictors of OS. The AGR and PLR were borderline non-significant. Moreover, several other features were not associated with OS (Table 2, Figure 2).

Table 2. Results of the overall survival univariable analysis of the blood biomarkers and clinical features in the study cohort.

Variable	HR	HR (95% CI)	*p*-Value
LMR (reference > 5.32)	4.05	1.62–10.12	0.003 *
AGR (reference > 1.81)	0.38	0.14–1.03	0.058
PLR (reference > 122.7)	0.49	0.22–1.13	0.094
NLR (reference > 2.05)	0.31	0.13–0.72	0.007 *
CEA (reference > 29.1 ng/mL)	3.70	1.68–8.14	0.001 *
CEA density (reference > 0.00046 ng/mL·mm^3)	2.55	1.16–5.62	0.020 *
Primary CRC location (reference left-sided)	0.36	0.15–0.85	0.019 *
Age	1.00	0.97–1.03	0.924
Gender (reference male)	1.34	0.60–2.96	0.472
Number of lesions	1.04	0.74–1.46	0.837
Diameter (reference > 30 mm)	1.07	0.46–2.50	0.875

* statistically significant (*p*-value < 0.05). The lymphocyte-to-monocyte ratio (LMR), albumin-to-globulin ratio (AGR), platelet-to-lymphocyte ratio (PLR), neutrophile-to-lymphocyte ratio (NLR), and carcinoembryonic antigen (CEA).

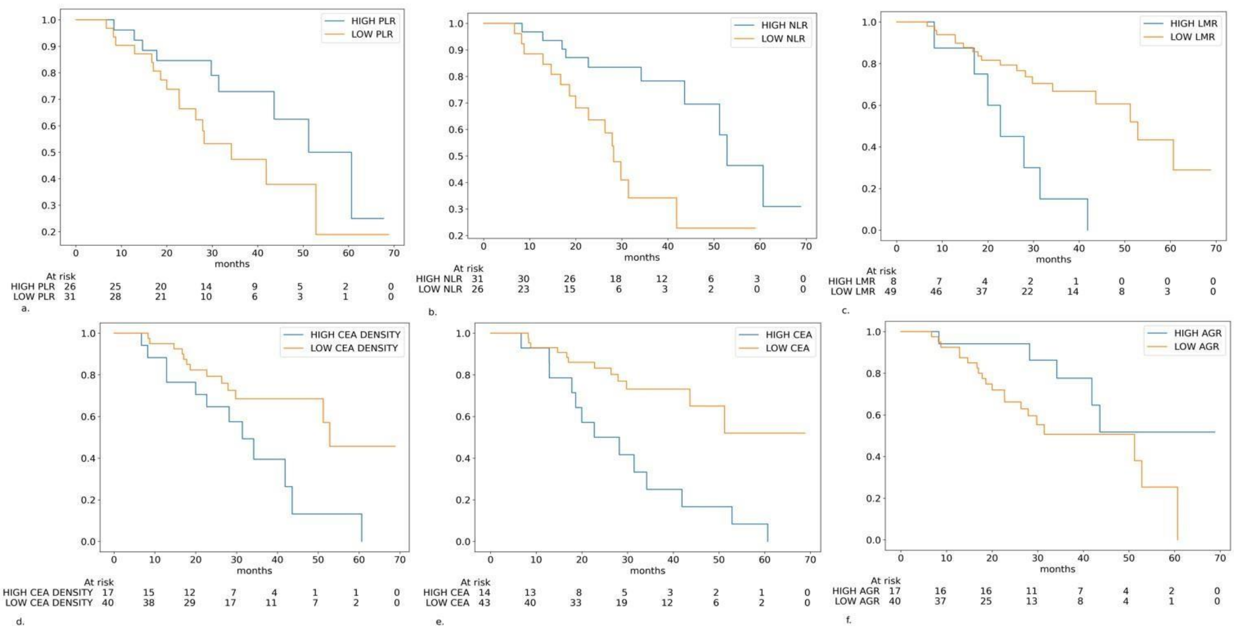

Figure 2. Kaplan–Meier curves in the different subgroups of patients based on the biomarkers levels: (**a**) platelet-to-lymphocyte ratio (PLR) level (cutoff: 122.7); (**b**) neutrophile-to-lymphocyte ratio (NLR) level (cutoff: 2.05); (**c**) lymphocyte-to-monocyte ratio (LMR) level (cutoff: 5.32); (**d**) carcinoembryonic antigen (CEA) density (cutoff: 0.00046 ng/mL·mm^3); (**e**) CEA serum level (cutoff: 29.1 ng/mL); (**f**) albumin-to-globulin ratio (AGR) level (cutoff: 1.81).

From the statistically significant variables, high levels of the NLR and primary left-sided tumor were protective prognostic markers, whereas high levels of the LMR, CEA and CEA-density were associated with worse prognoses. The strongest impact was demonstrated by the LMR (HR: 4.05) and CEA (HR: 3.70).

A multivariable Cox regression model using features that showed statistical significance in univariable analysis was created. In this model all the variables except the LMR remained associated with OS (Table 3).

Table 3. Results of the overall survival multivariable analysis of the blood biomarkers and clinical features in the study cohort.

Variable	HR	HR (95% CI)	*p*-Value
LMR (reference > 5.32)	1.03	0.31–3.41	0.96
NLR (reference > 2.05)	0.29	0.11–0.82	0.018 *
CEA (reference > 29.1 ng/mL)	4.10	1.60–10.54	0.003 *
Primary CRC location (reference left-sided)	0.25	0.10–0.64	0.004 *

* Statistically significant (p-value < 0.05). The lymphocyte-to-monocyte ratio (LMR), neutrophile-to-lymphocyte ratio (NLR), carcinoembryonic antigen (CEA), and colorectal cancer (CRC).

4. Discussion

The role and importance of the locoregional treatment of liver metastases originating from CRC as well as other gastrointestinal (GI) tumors keeps on increasing. The ablation of CLMs in case of small lesions is supported by international guidelines [1,2]. A recent randomized clinical trial demonstrated the non-inferiority of the CLMs ablation in the context of OS with a favorable safety profile when compared to surgical resection [18]. Ablation is also included as the treatment option in patients with oligometastatic neuroendocrine tumors (NETs) in case of the earlier resection of the primary tumor, as well as palliative treatment to relieve hormonal symptoms in the advanced stages [19–21]. In pancreatic cancer, the ablation of metachronous hepatic lesions is not included in the international guidelines; however, there are papers demonstrating decent results in oligometastatic patients treated with ablation or ablation combined with chemotherapy [22–24]. Nonetheless, the number of evidence supporting the role of locoregional treatment in the setting of metachronous metastatic pancreatic cancer is limited and probably should be studied more extensively. Another intriguing concept in the treatment of metastatic GI tumors is the management of patients with an advanced disease and liver-only metastases. There is increasing evidence that a highly specific subset of patients might benefit from surgical treatment of primary tumors and metastases, both in cases of NET as well as pancreatic cancer [25–27]. With further studies on this topic, one can expect that locoregional therapy will also have its role in case of unresectable but ablatable hepatic metastases in this highly selected group of patients. Having in mind the increasing role of MWA in the management of hepatic metastasis, different origin studies investigating the detailed predictors of OS are needed.

This study investigates the role of the various clinicopathological factors of OS predictors in patients undergoing the microwave ablation of liver metastatic lesions, mainly focusing on easily available biomarkers based on peripheral blood tests. The rationale of using biomarkers is based on the fact that the systemic inflammatory response was demonstrated to be a vital part of cancer initiation, growth, metastasis, and treatment response. Lymphocytes play a crucial role in the cancer immune response via the infiltration of the cancer microenvironment, recognition of neoantigens, and further stimulation of cancer-specific response. On the contrary, neutrophils and monocytes stimulate angiogenesis and suppress the immune response, thus leading to tumorigenesis and tumor promotion [28,29]. Therefore, the multiple markers based on the peripheral blood cell counts reflect the state of the host's anticancer immune response.

According to our knowledge, no study assessed the LMR, NLR, PLR, AGR, and CEA in a single cohort of patients with CLMs treated with MWA. There are few studies investigating these biomarkers in patients treated with RFA. Although these ablative modalities have some practical differences, they are both heat-based technologies. The aforementioned biomarkers are continuous variables with no widely accepted cutoff value, which can be recognized as abnormal. Therefore, the log-rank test's most significant cutoff points for each biomarker in the study population were determined. This analysis of the biomarkers demonstrated that the LMR, NLR, CEA and CEA density were associated with OS. Moreover, the analyzed biomarkers had a high impact on OS as the HR ranged from 0.31 to 4.05 in case of the strongest protective and negative factors, respectively. To further validate the results, the multivariable analysis was performed and to limit the risk of false positive findings all the variables in the model were checked for collinearity using the variance inflation factor. The NLR and CEA biomarkers remained significant predictors of OS with similar results to the univariable analysis of HR (0.29 and 4.1, respectively). The observed impact of both the NLR and CEA is really high, and although in accordance with other studies signifying the importance of the host immune system, as well as the overall tumor burden in predicting OS, the degree of the effect in this cohort is intriguing and probably requires further investigation with larger studies to better control potential confounding factors. However, in the multivariable Cox regression analysis, the LMR did not maintain its association with OS. One of the reasons for such a finding might be the fact that there is no widely accepted and optimal cutoff value for the LMR to be used in survival prediction as its cutoff points used in studies vary widely, and in some studies a too high cutoff resulted in the lack of the LMR's significance in the subgroup analysis [30–32]. Moreover the effect of the LMR on OS might have been diminished when paired with other possibly stronger survival predictors in multivariable analysis. Similar findings in which a certain biomarker was significant in univariate analysis but the significance did not persist in multivariate analysis can be found in other studies [12,15,33]. Both the CEA levels as well as CEA density can be interpreted as the biomarkers of the tumor burden and, in contrast to LMR, NLR or PLR, are not directly related to the patient's immune status. In this study, the high CEA level (>29.1 ng/mL) was one of the most significant predictors in the univariate analysis (HR: 3.70; p: 0.001) and the most significant predictor in the multivariate model (HR: 4.10; p: 0.003).

In general, the findings are in accordance with other studies based on nonablative treatment modalities, which report the LMR, NLR, and CEA as significant survival predictors [10,32–34]. It is worth noting that although in this study the PLR and AGR were not significant OS predictors, the obtained p-value was close to the significance level, and the hazard ratios were in accordance with the papers reporting the association of these biomarkers and OS [8,13,35].

Zhang et al. reported worse OS and disease-free survival (DFS) in patients with higher NLR after the RFA treatment of CLMs. The NLR threshold of > 5.0 was used as a cutoff point [36]. Chang et al. determined an NLR level of > 2.5 to be linked with worse DFS [37]. Moreover, a higher NLR was determined to be a poor prognostic factor in various other studies, including patients treated with nonablative modalities. However, the cutoff values used in these studies ranged from 1.9 to 7.26 [38]. Quite significant differences in the threshold levels reported by various papers can be possibly attributed to the character of the tumor microenvironment and the interaction between the tumor and host's immune system. Tumor cells are known to secrete various cytokines and chemokines, which might affect the infiltration of the tumor microenvironment as well as the counts of leukocyte subgroups [28,29]. The accordance in reporting higher NLR levels as a poor prognostic factor in cohorts treated with different modalities probably highlights the importance of the host's immune system anticancer response as the major factor determining the patient's prognosis irrespective of the treatment modality.

Facciorusso et al. investigated many possible biomarkers, including absolute counts of leukocyte subgroups, NLRs and LMRs in patients treated with RFA. In their study, the NLR with a threshold of 2.1 and the LMR with a threshold of 3.96 predicted survival in univariable models. However, in multivariable regression, only the LMR remained significant [15]. Such findings are in accordance with this paper, in which both the LMR and NLR are predictors of survival in the univariable analysis (HR:4.05 and 0.31, respectively) with cutoff values of 5.32 and 2.01, respectively. However, in opposition to the paper by Facciorusso et al., the LMR was no longer significant in the multivariable regression model. Contrary to the results of this study, the PLR and AGR have also been linked with patients' survival in several papers. However, most of them were based on a series of patients treated with nonablative modalities [8,10,11]. Although not in a cohort of CLM patients but in a series based on HCC patients treated with ablation, Wang et al. reported the AGR, NLR, and PLR in the univariable analysis to be associated with survival. In their multivariable analysis, the AGR and PLR remained significant. Notably, the LMR lacked such an association [13].

The role of the CEA serum level as a survival predictor is not fully understood. In most papers, a higher CEA level was reported to be linked with worse OS in patients with CLMs. However, some reports demonstrate a lack of such a link [5,6,15,16].

Hou et al. published an interesting approach. In their paper, the CEA density, defined as the total CEA serum level divided by the total volume of lesions, was a better OS predictor than the total CEA serum level. These results are in accordance with the literature, both in case of worse OS in the high CEA subgroup as well as the cutoff point used to stratify patients into subgroups, which commonly ranges from 29 to 35 ng/mL [5,15].

The impact of the sidedness of the primary cancer on the OS is also not fully elucidated, with papers supporting both theses, not only in cases of surgical resection but also thermal ablation. For example, Makowiec et al. and Zhou et al. [39,40] reported a lack of association between the sidedness of the primaries and OS in the case of resection and MWA, respectively. Interestingly, Dijkstra et al. [41] published an impressive series comprised of 520 patients with a total of 2101 CLMs who were undergoing local treatment and reported no association between the primary tumor sidedness and OS or local tumor progression-free survival. However, a difference in distant progression-free survival was observed. On the other hand, papers showed better OS in left-sided primary surgical and thermal ablation treatment [42,43]. In a reported cohort, sidedness was a significant predictor of OS. Left-sided colon cancer patients had better OS when compared to right-sided colon cancer counterparts (HR: 0.36)

This study has some limitations that should be taken into consideration. Firstly, it is a retrospective analysis from a single institution. The procedures were performed by three different interventional radiologists. However, this limitation is partially overcome due to the similar experience of the operators and the verification of the ablation zone with a contrast-enhanced CT scan immediately after the procedure. When analyzing the CEA serum concentration, one should remember that extrahepatic disease might affect the levels of this marker and that other non-oncological conditions are capable of increasing the CEA serum levels. The patients, before the ablation, were screened for extrahepatic disease and disqualified if any was present. Therefore, any potential extrahepatic lesions were radiologically occult and thus probably unable to affect the CEA levels significantly. Moreover, in some cases in the cohort, MWA was not the only treatment modality that patients underwent; thus, the observed OS may be confounded by other therapies and not linked only to the effect of MWA.

Some of the aforementioned limitations can be considered at least partially overcome; nonetheless, to address these limitations, future research should ideally involve prospective, multi-institutional studies with larger cohorts and longer follow-up periods. Such studies would allow for better control over potential confounders and provide more robust evidence on the predictive value of these biomarkers and the degree of the effect they have. It is worth noting that this study has several strengths. According to our knowledge, there is no other study investigating such a range of biomarkers in a single cohort of patients with CLMs who are undergoing thermal ablation. Moreover, the majority of papers focusing on the studied biomarkers come from cohorts treated with RFA, with a scarcity of data from cohorts treated with MWA. Both RFA and MWA are heat-based ablative modalities; however, currently, MWA is more frequently used in the setting of CLMs, thus increasing the value and adequacy of the findings of this study. Additionally, the ease of measurement, cost-effectiveness, and prognostic value of the investigated biomarkers make them promising tools, which can be utilized independently of the clinical setting, available laboratory equipment or healthcare funding models. While none of the biomarkers analyzed, apart from CEA and the CEA density—LMR, NLR, PLR, AGR—are specific to CLM, their value stems from their ability to reflect the systemic inflammatory response and tumor burden, both of which have a well-established role in cancer progression and treatment outcomes. These results suggest that the host immune response as well as the tumor burden play a major role in the OS prediction of patients treated with MWA. These findings can help refine patient selection for MWA, identifying those who may benefit most from the procedure or those who might require closer follow-up.

The prospective validation of these findings in larger, multicenter cohorts could lead to the development of standardized prognostic models integrating these biomarkers with clinical and radiologic factors similar to other scores or nomograms, like the surgical clinical risk score (CRS) or modified ablation CRS [5,13,44].

5. Conclusions

This study provides a deeper insight in efforts to create more individualized predictive models of OS for CLM patients undergoing MWA and the majority of the results are in line with prior studies based on RFA cohorts with HCC or CRC lesions. However, there are some discrepancies between the studies, which demonstrate that the role of biomarkers remains unclear, and further, that preferably multi-institutional studies based on larger cohorts and longer follow-up times are desired to provide necessary data to eventually elucidate the significance of these factors. Furthermore, such data may facilitate the creation of more sophisticated models and nomograms, which would hopefully improve patient selection or follow-up schemes.

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Institutional Review Board Statement: The Bioethical Committee accepted the retrospective nature of this study (AKBE 6/2024). All the procedures were performed in accordance with the Declaration of Helsinki, as revised in 2013, and written consent (form approved 05/2016) for the procedures was obtained from the patients.

Informed Consent Statement: This study was accepted by the Bioethical Committee (decision number AKBE 6/2024) and the Committee waived the requirement for written consent from participants.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest

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Review paper

Technical aspects, methodological challenges, and factors predicting outcomes of percutaneous ablation for colorectal liver metastases

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Abstract

Colorectal cancer is a prevalent malignancy, with colorectal liver metastases (CLM) being a common and challenging clinical issue. Traditionally, surgical resection was the only curative treatment; however, percutaneous ablation (radiofrequency, microwave, and irreversible electroporation) has emerged as a treatment option for select patients. Early trials demonstrated the efficacy of thermal ablation, leading to its inclusion in international guidelines. Currently, for small tumours, it is considered a viable alternative to resection. Recent studies demonstrate the non-inferiority of thermal ablation compared to resection in select cases and emphasize the importance of achieving an adequate ablation margin. Advancements in imaging techniques, ablative modalities, the use of image fusion, as well as ablation confirmation software, allow for a more patient-tailored approach. Additionally, tumour biology, including genetic mutations, influences both overall survival and local control, highlighting the need for personalised treatment strategies. As randomised trials continue to provide more data, the role of ablation in CLM management is evolving. This paper aims to provide a narrative review of factors predicting local control and overall survival in patients treated with ablation. Future research focusing on molecular markers, advanced imaging, and ablation verification techniques may further refine patient selection, and optimise treatment outcomes and follow-up imaging.

Key words: colorectal liver metastasis, liver ablation, microwave ablation, radiofrequency liver ablation.

Introduction

Colorectal cancer is one of the most common malignancies, affecting 1.93 million people each year [1], and about 50% of patients present with or will develop distant metastases in the course of the disease, with the liver being the most common site. For metastatic colorectal cancer approximately 75% of patients survive beyond one year, 30% beyond 3 years, and fewer than 20% beyond 5 years [2]. Therefore, patients with colorectal liver metastases (CLM) comprise a common and challenging clinical problem in everyday practice, requiring multidisciplinary care.

During the early days of locoregional treatment, surgery was the first-line treatment and the only curative option. One of the first randomised clinical trials on ablation was the CLOCC trial [3] which compared chemotherapy alone vs. chemotherapy and thermal ablation in patients with unresectable CLM. Subsequently, ablation was considered a treatment option only in small CLM in patients inoperable due to other comorbidities. However, increasing evidence and positive results of various studies resulted in the inclusion of percutaneous ablation in international guidelines [4,5] as a treatment offering comparable outcomes to surgery in the selected group of patients. Most recent prospective trials demonstrate non-inferiority of small CLM ablation when compared to resection [6,7].

This article aims to provide a current review of role of percutaneous ablation in CLM treatment and various factors affecting the results of this therapy.

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Ablation modalities

Currently, the primary ablation modality for liver locoregional treatment is a heat-based approach, with radiofrequency ablation (RFA) and microwave ablation (MWA) being the most commonly used techniques. RFA is based on alternating current, which is applied to the circuit. The rapid changes in the current cause continuous realignment of the water molecules, thus heating surrounding tissues, and subsequent necrosis around the ablative probe.

Due to its nature, RFA has some limitations – the energy application is longer because the heating process has to be strictly controlled to avoid charring the tissue, with the risk of rapid increase in resistance and subsequent inhomogeneity of the ablation zone. Furthermore, the so-called 'heat sink' effect caused by blood flow in adjacent vessels larger than 3 mm is a serious limitation of RFA.

Microwave ablation is a more recent technology based on the generation of an electromagnetic field, which results in constant realignment of the water molecules and subsequent tissue heating and necrosis. MWA overcomes RFA's main drawbacks by generating more consistent and homogenous ablation zones that are significantly less affected by the 'heat sink' effect and in a shorter time because the energy deposition is not dependent on tissue conductivity.

Even though MWA has some practical advantages over RFA, whether there is a significant difference in local tumour progression (LTP) or overall survival (OS) seems debatable.

Liu *et al.* [8] showed that OS was comparable between patients treated with MWA and RFA in a series of patients with liver metastasis, mostly of colorectal origin. Regarding LTP, the trend favouring MWA over RFA was visible but did not reach statistical significance ($p = 0.072$).

In the metanalysis of 16 studies done by Huo and Eslick [9] in 2015, 1-5-year OS rates were comparable; however, 6-year OS rates were better in the MWA subgroup. The authors consider this finding unexpected because there was no preceding trend for improved 5-year OS, raising the question of potential confounding factors. MWA had a significantly lower LTP than RFA (OR = 0.3, $p = 0.004$) but only in the subgroup of metastatic patients and not in HCC patients [9].

In a matched-cohort study based on 134 patients with CLM by Correa-Gallego *et al.* [10] MWA had lower LTP (6% vs. 20%; $p < 0.01$) when compared with RFA. An im- portant limitation of this study is the significantly shorter follow-up period for the MWA subgroup (18 months vs. 31 months, $p < 0.001$). However, it was partially overcome because the length of follow-up in both subgroups was longer than the median time to LTP.

Shady *et al.* [11] demonstrated comparable technique effectiveness for RFA and MWA with no difference in the LTP rates ($p = 0.84$). However, successful ablation of peri- vascular lesions using RFA is more challenging. For RFA, perivascular tumour location was one of the predictors of shorter local tumour progression-free survival (LTPFS) both in univariate and multivariate analysis ($p = 0.021$), whereas in the MWA subgroup, the perivascular location was not a predictive feature for LTPFS ($p = 0.43$).

Another ablative technique that was used in the treat- ment of CLM is cryoablation. It uses the Joule-Thom- son effect to generate very low temperatures at the end of the needle in alternating cycles of freezing and thawing, which leads to tumour destruction. However, it current- ly plays a minor role in locoregional treatment of CLM due to its less favourable safety profile and worse local control [12].

In contrast to the aforementioned ablative techniques, irreversible electroporation (IRE) is non-thermal based. It utilises high-voltage pulses to permanently disrupt cell membranes without damaging the tissue scaffold. Due to its mechanism of action, it does not damage temperature- sensitive structures such as blood vessels or bile ducts; moreover, it is not limited by heat sink effect [13]. How- ever, IRE requires very precise, parallel placement of the needles and generates smaller ablation zones when com- pared with other ablation modalities [13,14] (Table 1).

Table 1. Comparison of ablation modalities

Ablative technique	Mechanism of action	Advantages	Limitations
Radiofrequency ablation (RFA)	Heat based utilising alternating current	Widely studied	Longer application time when compared to MWA Heat sink effect Can damage adjacent bile ducts
Microwave ablation (MWA)	Heat based utilising electromagnetic field	Short application time Less prone to heat sink effect when compared to RFA	Heat sink effect Can damage adjacent bile ducts
Irreversible electroporation (IRE)	Cellular membrane destruction due to high voltage pulses	Does not damage adjacent blood vessels and bile ducts	Less data and experience when compared to RFA and MWA Requires insertion of multiple needles Requires general anaesthesia

Tumor specific factors

Studies have shown results favouring ablation of small metastatic lesions, because the risk of LTP increases with tumour size. Most studies demonstrate better local tumour control and longer OS in the case of lesions ≤ 3 cm [11,15-17]. In the case of medically inoperable patients or when surgical resection would result in insufficient liver residual volume, ablation of larger lesions is also feasible but requires the creation of multiple overlaying ablation zones; the use of a multiprobe stereotactic ablation approach in the case of large tumours has shown good results [18].

Lesions located in proximity to central bile ducts and main hepatic vessels pose a higher risk of complications due to potential thermal injury, which might lead to cholangitis, liver abscesses, vessel thrombosis, and subsequent failure of part of the liver. Therefore, additional care should be taken when qualifying and performing such procedures, which increases the risk of insufficient ablation margin and worse local tumour control. For perivascular locations, ablation with MWA results in longer LTPFS than RFA [11].

In central lesions located near major bile ducts and hepatic vessel IRE might be considered because it is not prone to the heat-sink effect and does not destroy adjacent structures [13,19]. However, when compared with thermal ablation modalities, the main downsides of IRE are general lack of experience and smaller amount of evidence.

Similarly to surgical resection, the oncological margin is one of the main features determining the success of locoregional treatment and the length of LTPFS. Based on earlier surgical experiences and knowledge that microsatellite lesions may be found within a 4 mm area around the primary metastatic tumour [20], the minimum ablation margin was one of the very first features that gained the attention of researchers. Initially, physicians performing ablations usually intended to achieve a margin of at least 5 mm.

In the paper by Shady *et al.* from 2018 [11], there was no single LTP for tumours ablated with margins over 10 mm. The authors demonstrated that for up to 3 lesions below 30 mm, CT-guided ablation provides comparable local tumour control to surgical resection. This finding led the authors to coin the term A0 ablation for ablation zones with margins over 10 mm. Even though there were local progressions (4/27 cases) in the subgroup with margins between 5 and 10 mm, the difference between this subgroup and the > 10 mm margin subgroup did not reach significance.

An earlier paper by the same group in the univariate analysis showed CEA level (cutoff > 30 ng/ml), tumour size (cutoff < 30 mm), and extrahepatic disease to be predictors of OS. Interestingly, prior liver resection, prior hepatic arterial chemotherapy infusions, and ablation margin were the significant features only for LTPFS but not OS. Based on their findings and surgical clinical risk score (CRS) [21] for OS and recurrence prediction in patients undergoing resection of CLM, the authors developed modified ablation CRS, which included node-positive primary tumour, disease-free interval < 12 months, more than one liver tumour, size of largest tumour > 30 mm, and CEA level > 30 ng/ml, with one point given for each feature. Patients are stratified into 3 subgroups based on the overall score. The modified ablation CRS was a significant predictor for both LTPFS and OS [16].

Recently published results of the randomised non-inferiority clinical trial comparing an ablation subgroup (92% treated with MWA and 8% with RFA) with a resection subgroup (consisting of 148 patients) showed no significant difference in OS between the treatment options and superior local control in per-tumour analysis in the ablation arm. In both subgroups the maximum diameter of the lesion was 30 mm, and the majority of patients (248/296, 84%) had no more than 5 metastatic lesions. The authors assumed a 5 mm margin as minimal to consider ablation as an A0 ablation. Local control was achieved in 95% of tumours with an ablation margin of at least 5 mm. Moreover, a favourable safety profile in the ablation subgroup was observed (number of adverse events in the ablation subgroup vs. control subgroup: 28 (19%) vs. 67 (46%), $p < 0.0001$; number of serious adverse events: 11 (7%) vs. 29 (20%) [7].

In a series of 365 patients and 15 years of follow-up, Han *et al.* [22] looked at the factors affecting LTPFS in CLM patients after RFA. In univariate analysis, tumour size > 20 mm, subcapsular and perivascular location of the lesion, and minimal margin < 5 mm were significant predictors of LTP. In the multivariable model, tumour size, subcapsular location, and minimal margin remained significant, but it should be noted that the model was heavily dependent on the margin feature. Unfortunately, the authors did not investigate the relationship between the abovementioned factors and OS. On the other hand, the subcapsular location of the lesion has been shown not to affect LTPFS or OS when compared with non-subcapsular location [16,23]. However, ablation of subcapsular lesions poses a threat of thermal injury to adjacent organs as well as the abdominal wall, intercostal vessels, nerves, or diaphragm; therefore, additional caution should be taken. Protective measures such as hydrodissection or pneumodissection can be used to decrease the risk of damaging adjacent tissues.

Laimer *et al.* [24], in a study consisting of 76 CLM lesions treated with RFA, showed that the ablation margin was the only independent predictor of LTP. In this series, the smallest margin that did not show LTP was 3 mm. The safety margin was assessed with 3D volumetric analysis, and the 3 mm safety margin did not show LTP only if 100% of the lesion had at least such a margin of ablation, whereas the 6 mm safety margin did not show LTP if 90-95% of the lesion had at least such a margin.

Knowing how important it is to obtain sufficient ablation margins, the next challenge is how to precisely determine them. Unlike surgery after ablation, there is no specimen, and the actual margin cannot be directly examined. Another obstacle is the fact that after ablation, due to tissue contraction, the ablation zone seems to be smaller when measured in imaging studies.

For a long time, the confirmation and radicality of the ablation zone were based on so-called eyeballing, i.e. comparing pre- and post-ablation scans with measurements based on anatomical landmarks. However, it was demonstrated that the conventional comparison of juxtapositioned scans is challenging and not precisely reader-experience dependent, thus demonstrating the need for more accurate verification options [25,26]. In recent years, various models based on rigid and non-rigid registration were developed [27-29]. One of the most noteworthy models was published in a study from 2022, including 68 patients with a total of 104 CLMs. A comparison of the traditional 2D method with 3D ablation confirmation software showed significant differences in terms of both sensitivity and specificity. The 2D method had a sensitivity, specificity, and accuracy of 20% (8/40), 86% (55/64), and 61% (63/104), respectively, whereas the 3D method achieved 93% (37/40), 42% (27/64), and 62% (64/104) sensitivity, specificity, and accuracy, respectively [30]. Recently, a paper evaluating 2 ablation confirmation softwares reported 100% LTPFS in the case of a confirmed ablation margin of at least 5 mm in patients with CLM, showing the importance of reproducible and accurate assessment of the ablation zone [31]. Based on the premise that the ablation margin is the most critical factor affecting the success of ablative therapy, the ACCLAIM trial, an ongoing randomised control trial, is currently investigating the efficacy of liver tumour ablation with software confirmation of the ablation margin (Table 2).

Imaging factors

Other factors that could affect the ablation outcome are related to imaging and precise visualisation of the tumour, as well as the post-ablation follow-up scheme.

It has been demonstrated that transcatheter computed tomography hepatic arteriography (CTHA) or computed tomography (CT) arterial portography provide operators with better visualisation of the lesions, and a decreased amount of iodine-based contrast agent allows for several intraprocedural contrast-enhanced studies [32]. Moreover, usage of intraprocedural CTHA was shown to provide better 2-year local control when compared with conventional CT fluoroscopy (8.9% vs. 32.8%, $p < 0.001$) [33]. In a recent paper, intraprocedural CTHA combined with conventional preprocedural imaging modalities: contrast-enhanced CT (CECT), contrast-enhanced magnetic resonance imaging (CEMRI), or ^{18}F-FDG PET CT, demonstrated superior accuracy compared to solely CECT, CEMRI, or ^{18}F-FDG PET CT. Moreover, it has been suggested that CTHA can show post-chemotherapy vanished lesions [34].

Another recent paper by Paolucci *et al.* [35] demonstrated that intraprocedural pre-ablation CECT, defined as a CECT study performed immediately before placing the ablation probe, significantly decreased the risk of incomplete ablation and residual disease on the first follow-up. However, pre-ablation CECT was not associated with improved LTPFS.

Every patient following locoregional treatment is at risk of LTP. Thus, a strict follow-up regimen is used to monitor the status of these patients. It was shown that most recurrences occur in the first few years. Han *et al.* [22] reported a minor difference between 5-year and 15-year LTPFS rates (73% vs. 72%). Similarly, in a cohort analysed by Shady *et al.* [16], 76% and 86% of all LTPs occurred within the first and second year. In the case of LTP, it was demon-

Table 2. Recent and ongoing major studies investigating ablation of colorectal liver metastases

Study	Year	Study type	Number of patients	Modality	Lesion type	Overall survival	Local control rate	Margin
van der Lei *et al.* [7]	2025	Prospective randomized	148	92% MWA, 8% RFA	CLM	92.7% 1-year, 78.5% 2-year, 51.2% 5-year	93% per tumour, 88% per patient	5% < 5 mm, 95% ≥ 5 mm
Tinguely *et al.* [6]	2023	Prospective	98	100% MWA	CLM	78% 3-year, 56% 5-year	83% initially, 92% after reablation	96% ≥ 5 mm
Shady *et al.* [11]	2018	Retrospective	154	52% RFA, 48% MWA	CLM	–	85% for 5-10 mm margin, 100% for > 10 mm margin	53% ≤ 5 mm, 47% > 5 mm
ACCLAIM trial	Expected completion 2027	Prospective	275	100% MWA	CLM	–	–	> 5 mm

CLM – colorectal liver metastases, MWA – microwave ablation, RFA – radiofrequency ablation strated that patients qualifying for reablation have better OS than those who are unable to undergo subsequent ablation (46 months vs. 31 months, $p < 0.001$) [36].

Primary cancer and patient factors

Shady *et al.* [16] reported a longer LTPFS in a subgroup of patients who had a history of resection prior to detection of new lesions which were ablated; however, history of prior resection was not associated with better OS in this subgroup. Similar findings in regard to local control were reported by Odisio *et al.* [37], who found that a history of hepatic resection significantly lowers the rate of LTP (6.1% vs. 36%, $p < 0.001$). Moreover, patients with prior liver surgery had better 3-year OS and recurrence-free survival at any site (78% vs. 48%, $p = 0.003$ and 23% vs. 9.1%, $p = 0.026$). The authors suggested that patients selected not to have surgery have tumours with worse biology or are in overall worse condition. Thus, their surgical counterparts have better results after surgery and subsequent ablation.

Several papers have demonstrated that certain primary cancer features impact the effectiveness of locoregional treatment. The sidedness of the tumour and its genetic characteristics affect both local control and OS.

Right-sided CRC (RSCRC), when compared with left-sided CRC and rectal cancer (LSCRC), has inferior disease progression-free survival as well as OS (median OS 29.4 vs. 40.3 months for RSCRC and LSCRC, respectively, $p = 0.042$) [15,38]. In patients following thermal ablation, LTPFS was better for RAS gene family wild-type tumours. RAS status is such an important factor that in subgroup analysis, even RAS mutated (mt) patients with ablation margin > 10 mm had worse LTPFS rates than RAS wild-type (wt) patients with margin < 10 mm (48% vs. 70%) (in the > 10 mm margin subgroup RAS mt vs. RAS wt: 48% vs. 94%, $p = 0.006$; in the < 10 mm margin subgroup RAS mt vs. RAS wt: 29% vs. 70%, $p \leq 0.001$) [23,38]. Similarly, in the paper by Shady *et al.* [39] KRAS status affected the OS. Patients with KRAS mutated tumours had worse OS after RFA than KRAS wild type ($p = 0.016$, HR = 1.8). OS was lower in the MSI and BRAF-mutated subgroups [38,40,41]. Moreover, lymph node metastasis of primary colon cancer and advanced stage were predictors of shorter LTPFS [42].

There are methodological differences between the analysed studies, including ablation modality, heterogeneity of the cohorts, number of treated lesions, minimal margin sufficient to obtain local control, tumour biology, or use of margin confirmation software. The aforementioned limitations highlight the need for further research and well-designed studies to provide more data on the role of ablation in the treatment of CLM and factors affecting the treatment outcome.

Conclusions

The role of percutaneous ablation in the management of patients with CLM is evolving and is recognised as a viable treatment option offering outcomes comparable to surgery in select cases. Currently the results from randomised clinical trials provide robust data supporting the role of thermal ablation. Further studies are expected to provide even more evidence supporting the use of ablation confirmation software, potentially leading to the establishment of a new standard for ablative therapies. The role of imaging in treatment planning and follow-up has also evolved, with techniques such as contrast-enhanced CT hepatic arteriography enhancing lesion visualisation and ablation margin assessment. Notably, achieving an adequate ablation margin remains one of the most critical determinants of LTPFS and OS. Importantly, emerging evidence suggests that margin requirements may not be uniform across all patients; for instance, smaller margins may suffice in tumours with favourable features, whereas high-risk lesions may necessitate more aggressive approach. Therefore, rather than a one-size-fits-all approach, one can consider a stratified strategy: aiming for >10 mm margins when technically feasible, especially for high-risk tumours, while in low-risk tumours with difficult location, margins of 5 mm may still offer local control. Additionally, further research into the importance of tumour biology and molecular characteristics could guide personalised treatment strategies to optimise long-term outcomes. As ablation continues to gain recognition in international guidelines, multidisciplinary collaboration remains essential to tailor treatment approaches and enhance survival rates for patients with CLM.

Disclosures

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2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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Wnioski

Przedstawione publikacje tworzące cykl rozprawy doktorskiej dowodzą, że:

1. Powszechnie stosowane wskaźniki laboratoryjne są powiązane z całkowitym czasem przeżycia u pacjentow z przerzutami raka jelita grubego do wątroby leczonych termoablacją mikrofalową:
   a) wysoki poziom CEA, koreluje z krótszym czasem przeżycia,
   b) wysoki poziom NLR z dłuższym czasem przeżycia.
   c) natomiast wskaźniki takie jak: AGR, LMR i PLR nie korelują istotnie z czasem przeżycia.
2. Pacjenci z pierwotnym lewstronnym rakiem jelita grubego poddawani termoablacji zmian w wątrobie mają dłuższy całkowity czas przeżycia w porównaniu do pacjentów z prawostronną lokalizacją zmiany pierwotnej.
3. Kluczowe dla czasu przeżycia oraz czasu przeżycia bez progresji lokalnej jest zapewnienie odpowiedniego marginesu ablacyjnego, optymalnie > 10 mm – wykonanie tak zwanej ablacji A0.
4. Tradycyjna ocena porównawcza obrazów przed i bezpośrednio po ablacji jest związana z mniejszą czułością w wykrywaniu zbyt małej strefy ablacji i przez to gorszymi wynikami kontroli lokalnej choroby, w porównaniu do oprogramowania oceniającego strefę ablacji.

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Warszawa, dnia 08.01.2024

AKBE/ 6 / 2024

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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 08 stycznia 2024 r. przyjęła do wiadomości informację na temat badania pt. "Biomarkery przeżycia u pacjentów poddawanych termoablacji mikrofalowej pod kontrolą tomografii komputerowej zmian przerzutowych raka jelita grubego do wątroby" Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U. z 2018 r poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

Oświadczenia współautorów publikacji

Warszawa, 05.05.2025
(miejscowość, data)

Lek .Dariusz Konecki
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Biomarkers of Survival in Patients with Colorectal Liver Metastases Treated with Percutaneous Microwave Ablation" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Zbieranie danych, pisanie manuskryptu, poprawki manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Jakuba Franke w powstawanie publikacji określam jako 75 %,
obejmował on koncepcję badania, zbieranie danych, analizę statystyczną, interpretację wyników, pisanie manuskryptu, poprawki manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Franke.

Dariusz Konecki
....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025
(miejscowość, data)

Dr n. med. Grzegorz Rosiak
(imię i nazwisko)

OŚWIADCZENIE

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Warszawa, 05.05.2025
(miejscowość, data)

Dr n. med. Krzysztof Milczarek
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OŚWIADCZENIE

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Warszawa, 05.05.2025
(miejscowość, data)

Dr n. med. Emilia Wnuk
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OŚWIADCZENIE

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Emilia Wnuk
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*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025
(miejscowość, data)

Prof. dr hab. n. med. Andrzej Cieszanowski
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OŚWIADCZENIE

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Warszawa, 05.05.2025
(miejscowość, data)

Lek. Dariusz Konecki
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OŚWIADCZENIE

Jako współautor pracy pt. „Technical Aspects, Methodological Challenges and Factors Predicting Outcome of Percutaneous Ablation for Colorectal Liver Metastases" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
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(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025
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Dr n. med. Grzegorz Rosiak
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OŚWIADCZENIE

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(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Technical Aspects, Methodological Challenges and Factors Predicting Outcome of Percutaneous Ablation for Colorectal Liver Metastases” oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Przegląd literatury, pisanie manuskryptu, poprawki manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Jakuba Franke w powstawanie publikacji określam jako 80 %,
obejmował on koncepcję badania, przegląd literatury, pisanie manuskryptu, poprawki manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Franke.

....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025
(miejscowość, data)

Prof. dr hab. n. med. Andrzej Cieszanowski
(imię i nazwisko)

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