SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Examination of molecular pathological alterations in solid tumors using liquid biopsy

by Szilvia Lilla Csoma

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University of Debrecen

Doctoral School of Clinical Medicine

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1. Introduction

Molecular diagnostics in cancer patients is primarily based on the analysis of nucleic acids isolated from histological samples, as proper examination of these sample types is essential to elucidate the genetic background fully. Small samples obtained by needle biopsy are not always suitable for high-sensitivity molecular testing, and the anatomical location of tumors often limits the sampling procedure. There are increasing efforts to incorporate liquid biopsy (LB) into clinical decision-making, as patients' peripheral blood contains circulating free nucleic acids derived from the tumor. The body fluids of cancer patients contain varying amounts of circulating tumor cells (CTCs), cell-free nucleic acid (cell-free DNA - cfDNA, cell-free RNA - cfRNA), and exosomes released by apoptosis, necrosis, and active secretion for which LB may be the most appropriate method of investigation.

Our work aimed to investigate two tumor types that occur with reasonable frequency in routine diagnostics, using tissue (FFPE) and LB as different sample types and

next-generation sequencing (NGS) and digital PCR (dPCR) as high-throughput sensitive technologies.

Biliary tract tumors (BTC) are rare malignancies with poor prognosis, and treatment options are still not fully understood. Groups that are distinct based on anatomical localization are treated in the same way, even though they have been shown to have different molecular patterns. It has been shown that in nearly 40% of patients, some abnormalities are detected that typically occur together, while others are mutually exclusive. The most frequently identified abnormalities include mutations in the *TP53* (44%), *KRAS* (17%), and *IDH1* (8.7%) genes. The rate of *KRAS* mutations can range from 9%-54%, occurring more frequently in extrahepatic cholangiocarcinoma (EHCC) and gallbladder-associated cholangiocarcinoma (GBC). Its occurrence in intrahepatic cholangiocarcinoma (IHCC) may be an early biomarker of progression. In GBC, mutations are generally less prevalent, with the most common genetic abnormality being the *ERBB2* gene (3%-38%). A significant proportion of mutations in the *PIK3CA* signaling pathway can be detected, with rates as high as 33%. Somatic

mutations in the *IDH1* and *IDH2* genes and fusions in the *FGFR2* gene are typical for IHCC, which presumably exclude the involvement of the *KRAS* and *BRAF* genes. In the future, these abnormalities may become therapeutic targets and diagnostic and prognostic biomarkers of disease.

Given that the prevalence of the disease has been increasing over the past decade, accompanied by a high mortality rate, and that, due to late detection, the majority of patients have metastases by the time the disease is diagnosed tumor resectability an option in less than 15% of cases-it is essential to develop a personalized treatment protocol based on genetic variations. As a result, many efforts have been made in recent years to understand the mechanisms underlying the development of biliary tumors. However, despite continuous progress, the diagnosis, treatment, and follow-up of cholangiocarcinoma remain a challenge for clinicians. The long-term solution is certainly the identification of biomarkers that facilitate earlier diagnosis, subtyping, and the selection of oncological therapy.

Primary cutaneous melanoma (PCM) accounts for almost 1% of all skin cancers, but due to its small size and often asymptomatic period, it takes a long time to diagnose and due to late identification and consequent lack of treatment, it can metastasize to many distant sites, making it the most dangerous form of skin cancer. Their classification, T-category, is based on the thickness of the tumor, known as Breslow-depth (BD. In addition, the histological classification of PCM also takes into account the Clark level, which has five groups. This is also based on the depth of the tumor.

The most common genetic abnormality in melanoma patients is the *BRAF* gene (44%), with the majority of mutations occurring in exons 11 and 15. Somatic point mutations account for 90% of the genetic abnormalities, namely the transversion of thymine at nucleotide position 1799 to adenine, which causes the conversion of valine at codon 600 to glutamic acid (*BRAF* c.1799T>A; p.Val600Glu). This is a pathogenic aberration that enhances the activation of the mitogen-activated protein kinase pathway, thus allowing activation of the signaling cascade even in the absence of an extracellular signal. As

a consequence of the mutation, the BRAF protein is activated independently of RAS and thus stabilized. These types of aberrations are more likely to respond to BRAF inhibitors.

Characterized by significant progression, it is imperative to identify a biomarker that enables the detection of high-risk melanomas in the earliest possible stages of the disease. Therefore, it becomes necessary to select personalized treatments for these tumor types. Reliable methods are needed for establishing the earliest and most accurate diagnosis or for potentially monitoring resistance to treatment. Studies to date have demonstrated that the similarity between tissue and plasma *BRAF* status is nearly 80%, indicating that the *BRAF* status obtained from LB analysis could be an appropriate biomarker for the disease.

2. Objectives

In our study, we apply two sensitive, high-throughput techniques to investigate two types of solid tumors. The majority of biliary tumors are inoperable, which is why, in addition to or instead of minimally invasive tissue biopsies, LB could be a suitable solution for routine diagnostics. Melanomas, due to their location on the body's surface and limited blood supply, present unique challenges. However, the use of LB in this type of tumor not only aids in establishing the diagnosis but may also provide insights into the extent to which cfDNA circulates in the peripheral bloodstream in tumors with such characteristics.

NGS can be an excellent tool for LB testing. It is now part of routine diagnostics for lung and colon adenocarcinomas. Taking this concept further, we also want to test it in the diagnosis of biliary tract tumors. DPCR is a more sensitive technology compared to traditional PCR techniques and has many advantages over NGS. It can produce results in a much shorter time, and it can detect mutations that may occur in samples with very

low variant allele frequencies with greater cost-effectiveness and accuracy.

We aim to quantify the cfDNA from LB of both tumor types, followed by molecular analysis. In the case of biliary tract tumors, we estimated the estimated tumor volume (ETV) and then examined its correlation with cfDNA yield. Additionally, we identified somatic mutations using NGS analysis and quantified tumor variant burden (TVB). We also investigated the distribution of mutations in the three subtypes of biliary tract tumors, as well as the genetic differences between DNA samples obtained from FFPE and LB from the same patient.

In melanoma patients, we retrospectively determined the *BRAF* status of 100 patients using StripAssay based on reverse hybridization and confirmed this status by dPCR to assess the diagnostic utility of the method. In a prospective study, we also determined the *BRAF* status of LB samples paired with FFPE samples, and in both studies, we searched for correlations between BD, tumor-derived DNA (tdDNA), cfDNA, and the p.Val600Glu genetic lesion *BRAF* p.Val600Glu variant

allele frequency (cfVAF) from LB and, taking into account the results obtained, we also searched for significant differences between groups based on Clark's classification.

3. Materials and Methods

3.1. Samples

A total of 38 patients diagnosed with biliary tumors had paired liquid biopsy (LB) samples collected alongside their FFPE samples, and next-generation sequencing (NGS) was performed. Additionally, a retrospective analysis was conducted to determine the BRAF mutation status of 100 patients diagnosed with melanoma, depending on their BRAF status, to set up and validate the effectiveness of the digital PCR (dPCR) protocol. The prospective cohort consisted of 34 individuals diagnosed with melanoma, from whom both FFPE and LB samples were available.

The tumor cell percentage was evaluated on hematoxylin-eosin stained sections from the FFPE samples, and in the case of melanoma tumors, histological classification was verified by a specialist pathologist. The cut-off value for tumor cell content was set at 5%. To confirm the diagnoses, the necessary immunohistochemical tests were performed on the tissue samples in all cases.

We obtained the necessary ethical approvals (60355-2/2016/EKU, 4648-6/2018/EÜ és IV/8465-3/2021/EKU).

3.2. Determination of tumor size

The tumor size was determined in collaboration with the Institute of Nuclear Medicine of the University of Debrecen Clinical Centre. In the case of biliary tumors, length (l) and width (w) values were measured with the help of a radiologist based on MRI and/or CT images taken at diagnosis, and ETV was calculated.

3.3. DNA isolation

The extraction of LB was performed via peripheral blood collection. Blood samples were taken in EDTA-containing anticoagulant blood collection tubes. During processing, plasma separation was uniformly carried out by centrifugation at 3000 x g for 10 minutes, followed by additional centrifugation of the obtained plasma at 16,000 x g for 10 minutes to isolate the supernatant suitable for cfDNA extraction. For the DNA isolation of FFPE samples, we used the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) with elution performed in 50

µl AE buffer. The cfDNA isolation was carried out using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Hilden, Germany) in 30 µl AVE buffer. DNA concentrations were measured using the Qubit dsDNA HS Assay Kit with the Qubit 4.0 fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). From the DNA concentrations obtained in LB, we calculated DNA yield.

3.4. StripAssay

The reverse hybridization-based *BRAF* 600/601 StripAssay (ViennaLab Diagnostics GmbH, Vienna, Austria) is a human in vitro diagnostic (IVD) certified method that detects nine clinically relevant mutations in the *BRAF* gene with a sensitivity of 1%. A biotin-linked adaptor sequence is bound to the assay, which is reacted with streptavidin-linked alkaline phosphatase, the substrate of which results in a color reaction.

3.5. Next-generation sequencing

NGS is a sensitive, high-throughput technology that enables the simultaneous analysis of multiple genes. In personalized medicine, NGS plays a key role in

identifying mutations, selecting appropriate therapies, and monitoring treatment progress. For patients with biliary tumors, we used a 67-gene Archer VariantPlex Solid Tumor Kit (ArcherDX, Boulder, CO, USA) for the comparison of the two sample types. Sequencing was performed on an Illumina MiSeq system (MiSeq Reagent Kit v3 600 cycles, Illumina, San Diego, CA, USA). The FASTQ files were analyzed using the Archer Local Virtual Machine software (version 7.0, ArcherDX). Based on the quality of the sequences, the variant allele frequencies (VAF) were set at 2% for both sample types. To determine the clinical significance of the identified mutations, we used the ClinVar,COSMIC and VarSome Premium databases, while the OncoKB database was employed to assess potential therapeutic options.

3.6. Digital PCR

Digital PCR (dPCR), based on traditional PCR technology, is a sequence-specific, high-throughput technique that enables the detection and quantification of nucleic acids through fluorescence measurement, with high accuracy and sensitivity. The advantage of this

method is that it allows for absolute quantification. Due to its sensitivity, it is also suitable for detecting small amounts of DNA. By knowing the absolute quantity of the target sequence, changes in copy number can be determined, making it applicable for the analysis of liquid biopsy (LB) samples from melanoma patients.

BRAF status was determined using the dPCR LNA Mutation Assay (Qiagen, Hilden, Germany) on the QIAcuity One dPCR system. The QIAcuity Software Suite was used for data analysis.

3.7. Statistical methods

In all cases, statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). A p-value below <0.005 was considered statistically significant.

Mann-Whitney, Kruskall-Wallis, ANOVA, and two-sample t-tests were used to compare ETVs, cfDNA yields, and TVB in three groups of biliary tract patients. Spearman's correlation analysis was used to examine the correlation between ETV and cfDNA yield, ETV and

TVB, while Pearson's correlation analysis was used to compare plasma cfDNA yield and plasma TVB.

Spearman correlation analyses were performed separately for melanomas in the retro- as well as prospective cohorts between BD, tdDNA, tumor-derived genetic variant allele frequency (tdVAF), cfDNA, and cfVAF. Furthermore, these parameters were statistically analyzed using the Kruskall-Wallis test in the Clark classification groups.

4. Results

4.1. NGS-based analysis of biliary tract patients

Based on the anatomical location of the tumor, we identified 21 cases as IHCC, nine as EHCC, and eight as GBC. The average ETV value in the studied patient population was 201,606.79 mm^3. Considering the tumor mass sizes, we did not find significant correlations between the values of the three groups ($p=0.53$), nor between IHCC and EHCC ($p=0.6346$), IHCC and GBC ($p=0.283$), and EHCC and GBC ($p=0.25$) individually.

The average DNA yield was 34.34 ng/ml of plasma. Statistically, we found no differences in the amount of isolated DNA among the three groups ($p=0.2177$), nor between IHCC and EHCC ($p=0.63$), IHCC and GBC ($p=0.09$), and EHCC and GBC ($p=0.18$) individually. However, we observed a significant correlation between ETV and cfDNA yield, which was confirmed by Spearman correlation ($r=0.8486$, $p<0.0001$ and $r=0.9059$, $p<0.0001$). Most of the gene variants we detected were

observed in cases 2, 24, 33, 35, and 37, while no nucleotide abnormalities were identified in patients 1, 5, 16, 20, 21, 23, 25. In five cases, only LB was found to be informative in the studies (12, 18, 26, 27, 36). When comparing the TVB values of the two sample types, no significant correlation was observed between the three subtypes (IHCC: p=0.9933; EHCC: p=0.7109, GBC: p=0.5102), nor was a significant difference found between the TVB values of cfDNA and liquid type samples (r=0.03061; p=0.8553). Statistically, there was no correlation between ETV and TVB values for any of the sample types (rs=-0.2914, pS=0.0759; rLB=0.08095, pLB=0.6290). 81.6% of patients (31/38) were identified as having some genetic aberration. In seven cases (1, 12, 20, 23, 25, 26, and 27), only LB analysis was performed due to inadequate tissue biopsy, of which three cases (12, 26, 27) showed some genetic aberration. Following bioinformatic analyses, the clinical characteristics of the detected differences were also verified. Some pathogenic mutation was described in 58% (43/74) of the detected aberrations. Most of them were also identified from LB samples paired with FFPE samples. In our study, 34 genes were affected, of which

FOXL2, *PIK3CA*, *KRAS*, and *TP53* were identified in all three distinct groups based on anatomical localization. We also identified differences in *CDH1*, *CDKN2A*, *H3F3A*, *FBXW7*, *MLH1*, *PTEN*, and *STK11* genes in both IHCC and GBC groups. *MET* gene aberrations were identified in intra- as well as extrahepatic groups. Two genes were identified as EHCC-specific variants, *HRAS* c.182A>G; p.Gln61Arg and *MAP2K1* c.308delT; p.Ile103Thrfs.

4.2. dPCR-based analysis of melanoma patients

For both the retrospective and prospective cohorts, FFPE samples derived from the tumors were surgically removed before the initiation of oncological treatment in all cases. LB was also performed before the start of oncological treatment.

In the retrospective study, the average BD value was 4.27 mm, the average tdDNA concentration was 17.39 ng/µl, and the average tdVAF value was 15.33%. In our prospective study, the average BD was 4.83 mm, the average tdDNA concentration was 18.75 ng/µl, the

average tdVAF was 20.2%, the average cfDNA value was 3.33 ng/µl, and the average cfVAF was 36.55%. The cases included in both the prospective and retrospective studies were grouped according to the internationally accepted Clark classification. The Clark I group was excluded from both cohorts due to the low sample size.

A retrospective study was performed to determine the effectiveness of dPCR. For routine diagnostics, 50 mutant (positive cases with p.Val600Glu mutation) and 50 negative (wild type without p.Val600Glu mutation) samples were selected as determined by StripAssay. These BRAF statuses were considered as real results and DNA isolated from FFPE blocks of the selected patients was re-determined for *BRAF* status by dPCR. The 1% mutant fraction was considered as the cut-off value. The FAM sensor of the dPCR detects the amplified products of BRAF c.1799T>A; p.Val600Glu (mutant partitions) based on fluorescence intensity (RFU). To separate valid from invalid partitions, the software uses a preset cut-off value of 85 RFU for FAM (mutant fractions) and 100 RFU for HEX (wild type). For the retrospectively selected samples,

diagnostic sensitivity was 99%, and diagnostic specificity was 98.5%.

In the prospective part of our study, we considered the StripAssay results from the patients' FFPE samples as valid and paired the liquid biopsy (LB) samples with the mutant and wild-type groups obtained from these results. A total of 34 LB samples were collected, of which 20 were found to be mutant and 14 wild-type. We performed StripAssay and dPCR analyses on cfDNA isolated from the LB samples, and then compared the results obtained and also compared them with the findings from the patients' FFPE samples. No differences were found between the two methods, and in this case, the sensitivity and specificity values were both calculated to be 100%.

Considering all cases, the actual diagnostic efficiency of dPCR showed a sensitivity of 98.6% and a specificity of 97%. Taking all these results into account, it can be concluded that the dPCR method we used is suitable for examining the *BRAF* status of melanoma patients.

Based on the values obtained in the retrospective cohort, we found a positive correlation between BD and

tdDNA concentration (r=0.36, p=0.002), while the values between BD and tdVAF (r=-0.04, p=0.7), and between tdDNA concentration and tdVAF (r=-0.06, p=0.52) did not show significant correlation. When considering only mutant cases (n=50), we identified positive correlations between all values (BD and tdDNA concentration r=0.31, p=0.02; BD and tdVAF r=0.37, p=0.009; tdDNA concentration and tdVAF r=0.33, p=0.018). In contrast, when examining only negative cases, a significant positive correlation was only found between BD and tdDNA concentration (r=0.33, p=0.02). No positive correlation was observed between BD and tdVAF (r=0.02, p=0.87), or between tdDNA concentration and tdVAF (r=0.01, p=0.93). In the prospective cohort, considering the entire population of 34 cases, we observed positive correlations between BD and tdDNA concentration (r=0.54, p=0.001), BD and cfDNA concentration (r=0.86, p<0.0001), tdDNA concentration and tdVAF associated with p.Val600Glu (r=0.76, p<0.0001), tdDNA concentration and cfVAF (r=0.59, p<0.0001), and tdVAF and cfVAF (r=0.65, p<0.0001). However, no significant relationship was found between BD and tdVAF (r=-0.12, p=0.5), BD and

cfVAF (r=0.006, p=0.97), tdDNA and cfDNA concentration (r=0.07, p=0.7), tdVAF and cfDNA concentration (r=0.008, p=0.96), or cfDNA concentration and cfVAF (r=0.13, p=0.47).

When considering only *BRAF* c.1799T>A; p.Val600Glu positive cases (n=20), significant relationships were found between BD and tdDNA concentration (r=0.57, p=0.008), BD and tdVAF (r=0.47, p=0.03), BD and cfDNA concentration (r=0.76, p<0.0001), BD and cfVAF (r=0.47, p=0.03), tdVAF and cfVAF (r=0.51, p=0.02), and cfDNA concentration and cfVAF (r=0.73, p=0.0003). No significant relationships were found between tdDNA concentration and tdVAF (r=0.41, p=0.02), tdDNA and cfDNA concentration (r=0.15, p=0.53), tdDNA concentration and cfVAF (r=0.07, p=0.77), or tdVAF and cfDNA concentration (r=0.35, p=0.12).

When analyzing only wild-type samples (n=14), a significantly positive correlation was observed only between BD and cfDNA concentration (r=0.77, p=0.002). No positive relationships were found between any of the other examined parameters: BD and tdDNA concentration

(r=0.15, p=0.6), BD and tdVAF (r=-0.09, p=0.75), BD and cfVAF (r=0.01, p=0.97), tdDNA concentration and tdVAF (r=-0.11, p=0.7), tdDNA and cfDNA concentration (r=0.41, p=0.15), tdDNA concentration and cfVAF (r=-0.27, p=0.35), tdVAF and cfDNA concentration (r=-0.29, p=0.3), tdVAF and cfVAF (r=-0.29, p=0.31), or cfDNA concentration and cfVAF (r=-0.33, p=0.24). Our observations indicate the strongest correlations (r>0.6) were experienced in the prospective cohort.

To analyze the associations between the groups based on the Clark classification, we used the Mann-Whitney statistical test.

In the retrospective cohort, when all cases were examined, a significant difference was observed in the BD values between Clark II and III (p=0.0022), Clark IV and V (p=0.0168), and also between Clark II and IV, Clark II and V, Clark III and IV, and Clark III and V groups (p<0.0001). When examining the groups of patients with the BRAF p.Val600Glu mutation, a significant difference was found in BD values between the Clark II and III (p=0.001), Clark II and V (p=0.0079), Clark IV and V (p=0.0039), Clark II and IV, and Clark III and V patients

(p<0.0001). Regarding the tdVAF values, a significant difference was observed between the Clark II and III (p=0.127) and Clark II and IV (p=0.0019) groups. In the negative cases, significant differences in BD values were found between the Clark II and IV (p=0.0069), Clark II and V (p=0.0485), Clark III and IV (p<0.0001), and Clark III and V (p=0.0018) groups. For the prospective cases (n=34), a significant correlation in BD values was observed between the Clark II and III (p=0.0131), Clark II and IV (p=0.0303), and Clark III and V (p=0.0063) groups. A significant difference in tdVAF values was confirmed between the Clark II and V (p=0.0357), Clark III and V (p=0.0048) groups, and a significant difference in cfDNA yield was observed between the Clark III and V (p=0.0170) groups. In the mutant cases (n=20), significant differences in BD values were found between the Clark II and III (p=0.0256) groups. In these two groups, significant differences in cfDNA yield were also observed (p=0.0256). Similarly, a significant difference in cfDNA yield was observed between the Clark III and Clark IV groups (p=0.0002). In the BRAF-negative patients, only

one significant correlation in BD values was found between the Clark III and V groups ($p=0.0238$).

5. Main findings and conclusions

In summary, the main findings of this Ph.D. work are as follows:

- Compared to traditional tissue biopsy, liquid biopsy is a non-invasive, repeatable procedure, making it a much more favorable sampling method.
- Qualitative and quantitative analysis of liquid biopsy can be successfully performed for both biliary tract tumors and melanomas.
- In biliary tract tumors, no significant correlation was found between the TVBs of anatomically distinct subgroups, either in tissue or liquid samples.
- A total of 74 genetic aberrations were identified, 44.6% of which were detected in both sample types (n=33).
- Among the 38 patients, pathogenic or likely pathogenic clinically significant alterations were observed in 20 (52.6%).

- According to the OncoKB database, specific therapeutic agents for certain biliary tract tumors were found in two cases. In both cases, an FDA-approved therapeutic agent, Ivosidenib, could be applied due to the presence of the *IDH1* p.Arg132 aberration.
- Our studies confirmed that dPCR allows for accurate determination of BRAF c.1799T>A; p.Val600Glu mutation status from both sample types in patients diagnosed with melanoma.
- Following the calculation of diagnostic sensitivity and specificity, it can be stated that the dPCR method can detect the presence of a mutation with nearly 100% accuracy and identify negative cases with 98.5% accuracy.
- Positive correlations were observed between BD and tdDNA concentration, BD and cfDNA concentration, tdDNA concentration and tdVAF, tdDNA concentration and cfVAF, and tdVAF and cfVAF.

- It was statistically proven that a significantly larger amount of cfDNA can be isolated from Clark V stage patients compared to other cases.

6. Publication list

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Candidate: Szilvia Lilla Csoma
Doctoral School: Doctoral School of Clinical Medicine
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List of publications related to the dissertation

1. **Csoma, S. L.**, Madarász, K., Chang Chien, Y. C., Emri, G., Bedekovics, J., Méhes, G., Mokánszki, A.: Correlation Analyses between Histological Staging and Molecular Alterations in Tumor-Derived and Cell-Free DNA of Early-Stage Primary Cutaneous Melanoma.
Cancers (Basel). 15 (21), 1-13, 2023.
DOI: http://dx.doi.org/10.3390/cancers15215141
IF: 4.5

2. **Csoma, S. L.**, Bedekovics, J., Veres, G., Árokszállási, A., András, C., Méhes, G., Mokánszki, A.: Circulating Cell-Free DNA-Based Comprehensive Molecular Analysis of Biliary Tract Cancers Using Next-Generation Sequencing.
Cancers (Basel). 14 (1), 1-13, 2022.
DOI: http://dx.doi.org/10.3390/cancers14010233
IF: 5.2

List of other publications

3. Chang Chien, Y. C., Madarász, K., **Csoma, S. L.**, Mótyán, J. A., Huang, H. Y., Méhes, G., Mokánszki, A.: Molecular Identification and In Silico Protein Analysis of a Novel BCOR-CLGN Gene Fusion in Intrathoracic BCOR-Rearranged Sarcoma.
Cancers (Basel). 15 (3), 1-17, 2023.
DOI: http://dx.doi.org/10.3390/cancers15030898
IF: 4.5

4. **Csoma, S. L.**, Bedekovics, J., Veres, G., Árokszállási, A., András, C., Méhes, G., Mokánszki, A.: A perifériás vérben keringő szabad DNS molekuláris vizsgálata epeúti malignitásokban.
Orv. hetil. 163 (50), 1982-1991, 2022.
DOI: http://dx.doi.org/10.1556/650.2022.32651
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5. Méhes, G., Mokánszki, A., Tóth, L., **Csoma, S. L.**, Lieber, A., Bittner, N.: Malignant pleural effusions for cancer genotyping: a matter of trans-pleural traffic of cell-free tumor DNA. *Mol. Cell. Probes. 61*, 1-7, 2022.
DOI: http://dx.doi.org/10.1016/j.mcp.2022.101793
IF: 3.3

6. Mokánszki, A., Méhes, G., **Csoma, S. L.**, Kollár, S., Chang Chien, Y. C.: Molecular Profiling of Merkel Cell Polyomavirus-Associated Merkel Cell Carcinoma and Cutaneous Melanoma. *Diagnostics. 11* (2), 1-11, 2021.
DOI: http://dx.doi.org/10.3390/diagnostics11020212
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7. Rezes, R., **Csoma, S. L.**, Németh, E., Jószai, I.: Fast liquid chromatographic determination of radiochemical and chemical purity of [11C]methionine by UPLC technique. *J. Radioanal. Nucl. Chem. 324* (3), 1237-1244, 2020.
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DEBRECENI EGYETEM
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