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Liquid biopsy of circulating tumor DNA in cerebrospinal fluid for early diagnosis of brain malignancies: A review

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Abstract. Brain cancer is the most aggressive intracranial disease: once diagnosed, 70% of patients will not survive. Early and accurate diagnosis is essential to improving the survival rate of diagnosed patients. Currently, imaging scans and pathological biopsies are mainly relied on to confirm the diagnosis of brain tumors. However, imaging scans do not confirm the diagnosis or tumor grade, nor do assess response and monitor treatment effect. Similarly, pathological biopsies are highly invasive and difficult to repeat. To address these limitations, the field has proposed the use of cerebrospinal fluid (CSF) as a liquid biopsy method to detect circulating tumor DNA (ctDNA). This review focuses on how liquid biopsy of CSF ctDNA can facilitate and complement the clinical care of patients with brain tumors. Relevant reviews in the past five years show that ctDNA is highly expressed and its content in CSF is higher than that in plasma. By sequencing the ctDNA of CSF, the diagnosis and prognosis information of brain tumors can be obtained, the best treatment method can be selected, the treatment response can be monitored, and the tumor evolution can be tracked. Because ctDNA detection is still in the research stage and lacks standardized technology, its effectiveness and practicality require further investigation before they can be used in clinical practice.

Keywords: brain malignancies, circulating Tumour DNA, liquid biopsies, early diagnosis, cerebrospina fluid.

1. Introduction

Early and correct diagnosis and monitoring of brain tumors are essential for assessing disease evolution determining the best approach to treatment, and increasing the survival rate of diagnosed patients. Conventional MRI scans can help doctors examine brain tumors. However, this method depends on the experience of doctors, and the error rate is relatively high. In addition, the feature points on MRI scans are not well defined [1, 2]. Therefore, to accurately identify normal or abnormal features of MRI scans, it is not reliable to rely on the evaluation of medical professionals [3, 4]. Doctors are unable to prescribe drugs accurately based on an inaccurate diagnosis, and as a result the patient's chances of survival are reduced [5]. The diagnosis was confirmed by pathological confirmation of a biopsy or surgical resection. However, obtaining pathological specimens from tumor types affecting the CNS can be challenging because brain tumor resection or biopsy may place patients at risk for intracranial swelling in and around the tumor mass and possibly affecting neurological functions. Furthermore, the heterogeneity of the whole tumour is usually not predicted by

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pathological biopsy and may not truly reflect the real time activity of the tumor. For early diagnosis of tumor dynamics, the identification of tumor specific biomarkers is of great clinical significance. However, the existing brain tumor biopsy as a diagnostic standard is high-risk, time-consuming, and expensive. Therefore, it is urgent to use less invasive, faster and more accurate methods to monitor tumor evolution. Liquid biopsies can be obtained multiple times noninvasively during treatment and are easily repeated. This article reviews the clinical application of liquid biopsy in brain tumors. In this review, the author focused on CSF ctDNA as a tool for diagnosis and prognosis of brain tumors and monitoring tumor evolution.

2. Methodology

PubMed is one of the most authoritative free abstract medical literature databases in the world. This article referred to PubMed literature on the early diagnosis of brain tumors in the last five years, and the search keywords included brain tumors, early diagnosis, liquid biopsy, and cerebrospinal fluid. Considering the accuracy of reference sources and ensuring the timeliness of research, the authors selected review and experimental literature from 2018 to 2022. Due to editorial limitations, 23 literary texts were selected for critical analysis.

3. Circulating tumor DNA in the cerebrospinal fluid

ctDNA is rarely detected in the plasma of patients with central nervous system diseases because of the blood-brain barrier [6]. Central nervous system tumors are directly exposed to cerebrospinal fluid (CSF). CSF is produced by the choroid plexus and circulates with the brain and spinal cord [7]. Thus, CSF ctDNA has been applied to the study of brain tumors as a specific biomarkers [8, 9]. Gene mutations and molecular changes of CSF DNA have been detected in patients with brain tumors. This fact has been confirmed by several studies [10-15]. With the development of high through put sequencing technology, gene mutations and copy number variations of CSF ctDNA have been identified [16-24]. These investigations used lumbar punctures to acquire DNA methylation, cell-free DNA, and CSF ctDNA.

As shown in Figure 1, CSF ctNDA as a liquid biopsy approach can effectively outline the entire brain tumor genetic profile, and tumor characteristics can be determined to support all stages of brain tumors therapy. These stages include diagnosis, monitoring of tumor response, identification of early recurrence, etc.

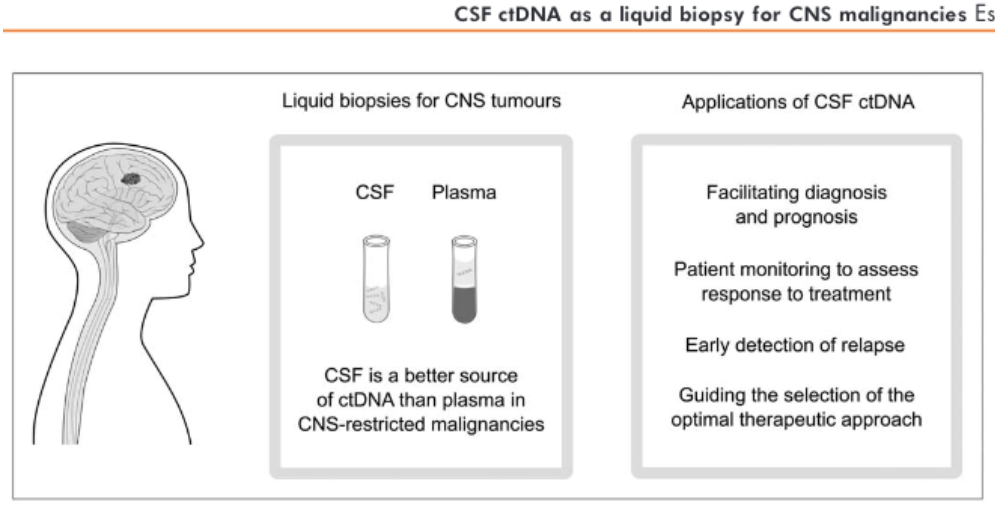

Figure 1. Liquid biopsies of brain malignancies [25, 26].

The use of CSF for liquid biopsy is superior to plasma in patients with brain cancer, and analysis of the application of CSF ctDNA may provide value for clinical nursing of such patients.

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4. cfDNA and ctDNA Biology

The concept of cell-free circulating DNA (cfDNA) is a concept that needs to be understood before studying cell-free circulating tumor DNA (ctDNA). CfDNA is usually composed of DNA double-stranded fragments with less than 200 base pairs. These fragments are released into serum or other body fluids, mainly from inflammatory processes or cell apoptosis and necrosis [27]. Circulating tumor DNA (ctDNA) which is a DNA fragment, is released into the blood stream by apoptotic or necrotic tumor cells. It carries the basic genetic information of tumor cells and information after gene mutation. Therefore, ctDNA biopsy can provide more information than conventional biopsy.

As much as 90% of the circulating cfDNA, or as little as 0.01%, is said to be made up of ctDNA [28–30]. CtDNA (its half-life is usually less than 1.5 hours) provides real-time and dynamic information about tumor evolution. This information is provided through point mutations, copy number variations (CNVs), chromosome rearrangements and DNA methylation patterns [31, 32]. Single base pair substitutions are the predominant specific mutations in these tumors [33]. ctDNA differs from normal cfDNA largely in the presence of specific mutations in tumor DNA but not in normal DNA.

5. CSF ctNDA as a diagnostic tool and monitoring tumor evolution

With the development of neuroimaging techniques and clinical evaluation, ctNDA in cerebrospinal fluid can determine the tumors mutation spectrum. The real-time dynamic monitoring of ctDNA can also be further used to study the mechanism of drug resistance [34, 35]. The genome and epigenome of primary brain cancer have been comprehensively studied, and CSF ctDNA has been applied in clinical diagnosis [36-39].

According to the anatomical location of the tumor, patients with diffuse midline glioma have a higher risk of tissue biopsy. Detection of tumor-specific mutations in cerebrospinal fluid ctDNA of patients with brain cancer is expected to become an effective tool for early diagnosis, which has also been confirmed by relevant studies [40, 41]. By analyzing IDH, ATRX, TP53, PIK3CA, pTERT mutations, H3F3A, and HIST1 H3B mutation status in CSF ctDNA, molecular diagnosis and prognostic evaluation of gliomas can be performed, such as when TERT promoter mutations increase the frequency of variant alleles and shorten the overall survival of patients [40, 42]. A longitudinal analysis of cerebrospinal fluid ctDNA from glioma patients revealed mutational changes. The evolution of the glioma genome was also shown in this analysis [43]. When the patient's CNS was infiltrated by B-cell malignant tumors, the dynamic changes of CSF ctDNA were expected to be a powerful monitoring tool to reproduce the evolution of tumors [44].

6. Discussion

Although lumbar puncture CSF removal is less invasive than pathological biopsy, CSF fluid biopsy may not be suitable for these patients. These patients are wrapped in the brain parenchyma and have nothing to do with cerebrospinal fluid. For patients with large tumors, obstructed CSF flow, or elevated intracranial pressure, lumbar puncture may result in herniation of the brain and is also not suitable for CSF liquid biopsy. These pose challenges to the applicability of CSF, but ctDNA still shows significant clinical and research potential in multiple types of brain cancer. Future research should concentrate on transferring these biomarkers from in vitro and animal studies to clinical trials as liquid biopsy technology advances in order to better address the majority of concerns when dealing with brain tumors.

7. Conclusion

The use of CSF ctNDA as a liquid biopsy is a less invasive and easily repeatable technique that can give useful information about the tumor burden and response to therapy. Additionally, CSF ctDNA can accurately define the genetic profile of whole brain malignancies. CtDNA analysis is a useful adjunct to tumor biopsies for confirming the diagnosis, finding mutations, tracking tumor progression, and assessing the efficacy of treatment. As oncology moves toward precision medicine, ctDNA studies

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provide a path to achieving this goal by adequately evaluating treatment responses and allowing geneticists and oncologists to select individual treatments for the patient based on the genetic profile. At present, ctDNA detection is still in the research stage, so it is necessary to establish standardized management and operation programs to implement ctDNA analysis in clinical practice. Therefore, in order to verify the effectiveness and practicability of ctDNA analysis in clinical practice, future research needs more patients to participate in larger research.

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References

[1] Latif, G., Butt, M. M., Khan, A. H., Butt, O., & Iskandar, D. A. Multiclass brain Glioma tumor classification using block-based 3D Wavelet features of MR images. In 2017 4th International Conference on Electrical and Electronic Engineering (ICEEE) (pp. 333-337). IEEE. (2017, April).

[2] Neetu Mittal and Satyam Tayal. Advance computer analysis of magnetic resonance imaging (mri) for early brain tumor detection. International Journal of Neuroscience, 0(0):1–16, PMID: 32241208. (2020).

[3] Sarah Ali Abdelaziz Ismael, Ammar Mohammed, and Hesham Hefny. An enhanced deep learning approach for brain cancer mri images classification using residual networks. Artificial Intelligence in Medicine, 102:101779, (2020).

[4] A. Al-Badarneh, H. Najadat, and A. M. Alraziqi. A classifier to detect tumor disease inmri brain images. In2012 IEEE/ACM International Conference on Advances in Social Networks Analysis and Mining, pages 784–787, (2012).

[5] Kazunori Arita, Makiko Miwa, Manoj Bohara, F. M. Moinuddin, and Koji Yoshimoto. Precision of preoperative diagnosis in patients with brain tumor — a prospective study based on “top three list” of differential diagnosis for 1061 patients. Surgical Neurology International, 11:55, (2020).

[6] Bettegowda C, Sausen M, Leary R.J,etal. Detection of circulating tumor DNA in early and late-stage human malignancies. Sci Transl Med, 6:224ra24 (2014).

[7] Ghersi-Egea JF, Strazielle N, Catala M,etal. Molecular anatomy and functions of the choroidal blood-cerebrospinal fluid barrier in health and disease. ActaNeuropathol; 135:337–361. (2018).

[8] Miller, A. M., Shah, R. H., Pentsova, E. I., Pourmaleki, M., Briggs, S., Distefano, N.et al. Tracking tumour evolution in glioma through liquid biopsies of cerebrospinal fluid. Nature565, 654–658 (2019).

[9] Killock, D. C. S. F. DNA provides a snapshot of the glioma genome. Nat. Rev. Clin.Oncol.16, 143–143 (2019).

[10] Schmitt-Gra¨ff A, Hummel M, Anagnostopoulos I,etal. Primary brain lymphoma in acquired immunodeficiency syndrome. Immunophenotype and molecular pathologic characterization in stereotactic biopsy, autopsy and cerebrospinal fluid cytology. Pathology; 16:75–80. (1995).

[11] Rhodes CH, Honsinger C, Sorenson GD. PCR-detection of tumor-derivedp53 DNA in cerebrospinal fluid. Am J Clin Pathol; 103:404–408. (1995).

[12] Swinkels DW, de Kok JB, Hanselaar A,etal. Early detection of leptomeningeal metastasis by PCR examination of tumor-derived K-ras DNA in cerebrospinal fluid. Clin Chem; 46:132–133. (2000).

[13] Shi W, Lv C, Qi J,etal. Prognostic value of free DNA quantification in serum and cerebrospinal fluid in glioma patients. J Mol Neurosci; 46:470–475. (2012).

[14] Yang H, Cai L, Zhang Y,etal. Sensitive detection of EGFR mutations incerebrospinal fluid from lung adenocarcinoma patients with brain metastases. J Mol Diagn; 16:558–563. (2014).
[15] Touat M, Duran-Pen˜a A, Alentorn A,etal.Emerging circulating biomarkers in glioblastoma: promises and challenges. Expert Rev Mol Diagn;15:1311–1323. (2015).
[16] De Mattos-Arruda L, Mayor R, Ng CKY,etal. Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. Nat Commun; 6:8839. (2015).
[17] Pan W, Gu W, Nagpal S,etal. Brain tumor mutations detected in cerebralspinal fluid. Clin Chem; 61:514 – 522. (2015).
[18] Wang Y, Springer S, Zhang M,etal. Detection of tumor-derived DNA incerebrospinal fluid of patients with primary tumors of the brain and spinal cord. Proc Natl Acad Sci U S A; 112:9704–9709. (2015).
[19] Pentsova EI, Shah RH, Tang J,etal.Evaluating cancer of the central nervoussystem through next-generation sequencing of cerebrospinal fluid. J ClinOncol; 34:2404–2415. (2016).
[20] Martı´nez-Ricarte F, Mayor R, Martı´nez-Sa´ez E,etal. Molecular diagnosis of diffuse gliomas through sequencing of cell-free circulating tumor DNA from cerebrospinal fluid. Clin Cancer Res; 24:2812–2819 (2018).
[21] Mouliere F, Mair R, Chandrananda D,etal. Detection of cell-free DNA fragmentation and copy number alterations in cerebrospinal fluid from glioma patients. EMBO Mol Med; 10:e9323. (2018)
[22] Miller AM, Shah RH, Pentsova EI,etal.Tracking tumour evolution in gliomathrough liquid biopsies of cerebrospinal fluid. Nature; 565:654–658. (2019).
[23] Seoane J, De Mattos-Arruda L, Le Rhun E,etal.Cerebrospinal fluid cell-free tumour DNA as a liquid biopsy for primary brain tumours and central nervous system metastases. Ann Oncol; 30:211–218. Revision of the implications of the study of CSF ctDNA on primary and metastatic brain malignancies. (2019).
[24] Le Rhun E, Seoane J, Salzet M,etal.Liquid biopsies for diagnosing and monitoring primary tumors of the central nervous system. Cancer Lett; 480:24–28 (2020).
[25] De Mattos-Arruda L, Mayor R, Ng CKY, etal. Cerebrospinal fluid derived circulating tumour DNA better represents the genomic alterations of braintumours than plasma. Nat Commun; 6:8839. (2015).
[26] Pentsova EI, Shah RH, Tang J, etal. Evaluating cancer of the central nervoussystem through next-generation sequencing of cerebrospinal fluid. J ClinOncol; 34:2404 ‑ 2415. (2016).
[27] Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer;11:426–437. (2011).
[28] Dawson SJ, Tsui DW, Murtaza M, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med;368:1199–1209. (2013).
[29] Wang J, Bettegowda C. Applications of DNA-based liquid biopsyfor central nervous system neoplasms. J Mol Diagn;19:24–34. (2017). doi:10.1016/j.jmoldx.2016.08.007
[30] Diehl F, Schmidt K, Choti MA, et al. Circulating mutant DNA to assess tumor dynamics. Nat Med.;14:985–990. (2008). doi:10.1038/nm.1789
[31] Diehl, F.et al. Circulating mutant DNA to assess tumor dynamics. Nat. Med.14, 985–990 (2008).
[32] Li J, Han X, Yu X, et al. Clinical applications of liquid biopsy as prognostic and predictive biomarkers in hepatocellular carcinoma: circulating tumor cells and circulating tumor DNA. J Exp Clin Cancer Res.; 37:213. (2018) doi:10.1186/s13046-018-0893-1
[33] Diaz LA Jr., Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. J Clin Oncol; 32:579–586. (2014). doi:10.1200/JCO.2012.45.2011
[34] Diehl, F., Schmidt, K., Choti, M. A., Romans, K., Goodman, S., Li, M., ... & Diaz Jr, L. A. Circulating mutant DNA to assess tumor dynamics. Nature medicine, 14(9), 985-990. (2008).

DOI: 10.54254/2753-8818/6/20230192

[35] Diaz LA Jr, Williams RT, Wu J, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature; 486:537–40. (2012).
[36] Sottoriva A, Spiteri I, Piccirillo SG,etal. Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. Proc Natl Acad Sci U S A; 110:4009–4014. (2013).
[37] Brat DJ, Verhaak RG, Aldape KD,etal. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med; 372:2481–2498. (2015).
[38] Ceccarelli M, Barthel FP, Malta TM,etal. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. Cell; 164:550–563. (2016).
[39] Capper, D., Jones, D. T., Sill, M., Hovestadt, V., Schrimpf, D., Sturm, D., ... & Pfister, S. M. DNA methylation-based classification of central nervous system tumours. Nature, 555(7697), 469-474. (2018).
[40] Martı´nez-Ricarte F, Mayor R, Martı´nez-Sa´ez E,etal. Molecular diagnosis of diffuse gliomas through sequencing of cell-free circulating tumor DNA from cerebrospinal fluid. Clin Cancer Res; 24:2812 – 2819. (2018).
[41] Azad, T. D., Jin, M. C., Bernhardt, L. J., & Bettegowda, C. Liquid biopsy for pediatric diffuse midline glioma: A review of circulating tumor DNA and cerebrospinal fluid tumor DNA. Neurosurgical focus, 48(1), E9. (2020).
[42] Juratli, T. A., Stasik, S., Zolal, A., Schuster, C., Richter, S., Daubner, D., ... & Thiede, C. TERT Promoter Mutation Detection in Cell-Free Tumor-Derived DNA in Patients with IDH Wild-Type Glioblastomas: A Pilot Prospective StudyTERT Promoter Mutations in Glioblastoma Cell-Free Tumor DNA. Clinical Cancer Research, 24(21), 5282-5291. (2018).
[43] Miller, A. M., Shah, R. H., Pentsova, E. I., Pourmaleki, M., Briggs, S., Distefano, N., ... & Mellinghoff, I. K. Tracking tumour evolution in glioma through liquid biopsies of cerebrospinal fluid. Nature, 565(7741), 654-658. (2019).
[44] Bobillo, S., Crespo, M., Escudero, L., Mayor, R., Raheja, P., Carpio, C., ... & Seoane, J. Cell free circulating tumor DNA in cerebrospinal fluid detects and monitors central nervous system involvement of B-cell lymphomas. Haematologica, 106(2), 513. (2021).