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Limitless potential within limited resources: The realm of liquid biopsy for brain tumors in low-middle-income countries

Dear Editor,

Central nervous system (CNS) tumors remain some of the most aggressive and lethal malignancies. Traditionally, diagnosing these tumors involved high-risk craniotomy procedures with large scalp incisions. While offering good visualization of the mass, these surgeries are associated with lengthy recovery times and significant costs. Minimally invasive surgical techniques, like microsurgery and endoscopy have emerged, causing less tissue damage and accelerating fast patient recovery. However, their ability to access certain tumors may be limited (Khalili et al., 2023). Pinhole craniotomy, utilizing advanced robotics and specialized instruments, promises minimal tissue damage and very rapid recovery, but this technique remains under development.

The gold standard for diagnosis remains histological examination of a biopsy sample obtained via an invasive procedure. Standard staining techniques like hematoxylin and eosin (H&E) aid in differentiating between neoplastic and non-neoplastic cells. Immunohistochemistry (IHC) utilizes antibodies to detect specific proteins on tumor cells, aiding in classification and subtyping of tumors. Fluorescence in-situ hybridization (FISH) utilizes fluorescent probes to identify chromosomal abnormalities in tumor cells, assisting in the diagnosis of specific CNS tumors. Additionally, molecular profiling techniques like, next generation sequencing (NGS) offer a deeper understanding of the tumor's genetic makeup (Otsuji et al., 2024).

Liquid biopsy involves investigating biological fluids to detect and analyse tumor biomarkers. Plasma is the most common source, but other fluids like cerebrospinal fluid (CSF), saliva, urine, pleural effusion and peritoneal fluid can also be used (Khalili et al., 2023). These fluids hold the potential to reveal tumor-specific biomarkers like circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), tumor-specific mRNA, microRNAs (miRNA), tumor specific proteins (TSPs), extracellular vesicles (EV), and tumor-educated platelets (TEP) (Khalili et al., 2023). Circulating Tumor Cells (CTCs) can be isolated using CellSearch assay, flow cytometry, or CNSide biotech (Diaz et al., 2024). Cell-free DNA (cfDNA), tumor-specific RNA (tsRNA), and microRNAs (miRNAs) are typically detected through polymerase chain reaction (PCR) techniques, including droplet-based digital PCR, quantitative PCR, and methylation-specific PCR (Khalili et al., 2023, Diaz et al., 2024). Additionally, next generation sequencing (NGS) and nanowire techniques can be employed. Nanoparticle tracking analysis is used to detect EVs, while mass spectrometry or enzyme-linked immunosorbent assay (ELISA) can identify tumor-specific proteins (Khalili et al., 2023).

Developed countries like USA, UK, China, Australia, Russia and Germany are actively exploring the use of liquid biopsy for gliomas (diffuse midline, diffused intrinsic pontine, low grade and high-grade gliomas), glioblastoma multiforme, meningioma, medulloblastoma leptomeningeal metastasis, brain metastasis, CNS lymphoma and many other body tumors (Khalili et al., 2023, Diaz et al., 2024). This approach holds promise for minimally invasive diagnosis, early detection, improved treatment planning, and identifying treatment-resistant tumors through detection of molecular heterogeneity (Masood et al., 2023). However, limitations exist. Sensitivity and specificity of some markers may be low, and the clinical application of certain markers like mRNA and tumor educated platelets (TEP) is still limited (Diaz et al., 2024). Additionally, the blood-brain barrier (BBB) can hinder the passage of some markers into the bloodstream, and specialized equipment and trained personnel are required for these analyses (Otsuji et al., 2024). While research flourishes in developed countries, there's a significant gap in low- and middle-income countries (LMICs) like Pakistan, Afghanistan, Bangladesh, Sri Lanka and Nepal. There is only one scientific study conducted in Pakistan on plasma PD-L1 role in glioblastoma multiforme management (Masood et al., 2023). Factors, like lack of awareness about liquid biopsy, reliance on traditional diagnostic methods, limited access to specialized centers and equipment, budgetary constraints, and a lack of enthusiasm for adopting new technologies contribute to this gap. Increased awareness and investment in research on liquid biopsy for CNS tumors in these regions are crucial.

Brain tumor diagnosis remains challenging, with traditional surgeries being invasive and expensive. Liquid biopsy offers a promising minimally invasive alternative which is cost-effective and efficient strategy (Fagery et al., 2023). This approach has the potential for earlier detection, better treatment planning, and identifying treatment resistance. Increased awareness and investment in liquid biopsy research are crucial for wider adoption and improved CNS tumor management globally.

Advocacy for training programs to educate healthcare professionals about liquid biopsy for CNS tumors is need of the hour. This will raise awareness and equip them to identify potential applications within resource-constrained set-ups. Since blood collection is readily available, emphasis should be directed towards research into CNS tumor markers detectable in blood, like cfDNA or ctDNA. This might be more feasible than relying on techniques requiring CSF or other less accessible fluids. This could involve adapting existing techniques or exploring new biomarker detection methods suitable for resource-limited settings. Prioritization of capacity building, starting with smaller regional centers and single fluid analysis and eventually expanding based on success and resource availability is a feasible recommendation. Encouragement of collaboration between LMICs and developed countries with ongoing liquid biopsy research is mandated.

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Ethical approval

Taken.

I, Dr. Haseeb Mehmood Qadri, certify that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium.

Please accept our submission.

Thank You.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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