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CUSA Aspirates in Brain Tumors: Integrating Findings from a Single-Center Cohort and a 49-Center National Survey to Reassess Clinical Utility

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ABSTRACT

Objective: Cavitron Ultrasonic Surgical Aspirator (CUSA)–derived material is routinely generated during neurosurgical tumor resections but is often regarded as surgical waste. Although previous studies have demonstrated its potential for diagnostic and research applications, its real-world utilization and perceived value in routine neuropathology practice in Türkiye remain unknown.

Material and Methods: We conducted a retrospective single-center study evaluating CUSA aspirates received between 2021 and 2026, focusing on diagnostic yield, histologic quality, and suitability for ancillary testing. In parallel, a nationwide cross-sectional survey was also performed to assess submission practices, processing methods, and perceptions regarding the diagnostic and research utility of CUSA-derived material.

Results: Among 10 brain tumor cases, diagnostic tumor tissue was identified in 9 CUSA aspirates (90%). All diagnostically positive samples yielded sufficient material for immunohistochemistry. In one high grade diffuse glioma case, the aspirated material alone contained all features required for diagnosis and grading. Non-neoplastic CNS parenchyma was also present in five cases.

Survey results demonstrated that CUSA aspirates are not routinely submitted in most centers (63.3%), and when submitted the processing methods vary. Despite limitations, most respondents acknowledged at least partial diagnostic utility. Lack of standardized protocols and limited awareness were identified as the main barriers to broader utilization.

Conclusion: CUSA aspirates represent an underutilized resource with significant diagnostic and translational potential. While often overlooked in routine practice, these materials can provide sufficient tissue for histopathologic evaluation and ancillary testing. Bridging the gap between demonstrated utility and current practice will require improved awareness, interdisciplinary coordination, and standardized handling protocols.

Keywords: CUSA, Surgical aspirates, Neuropathology

INTRODUCTION

The Cavitron Ultrasonic Surgical Aspirator (CUSA), developed in the 1970s and first introduced for intracranial tumor removal in 1978, is a crucial tool in modern neurosurgery (1). CUSA operates by generating high-frequency ultrasonic vibrations (around 23 kHz) through a hollow titanium probe that emulsifies soft tissue within 1–2 mm of its tip (2). The system integrates three coordinated functions—fragmentation, irrigation, and aspiration—to safely disintegrate and collect tissue while minimizing thermal damage. Because ultrasonic energy preferentially disrupts water-rich tissues, structures with higher collagen content, such as major vessels, are relatively preserved, making CUSA especially valuable in resections near eloquent or vascular areas. It is widely used in the excision of glial tumors and other intra/extra-axial cranial and intramedullary spinal tumors, improving surgical precision, reducing traction-related injury, and lowering postoperative complication rates. During surgery, the aspirated tissue fragments and fluid are collected in a disposable reservoir, where the sediment often contains small but abundant cylindrical fragments of tumor and neural tissue.

Although aspiration materials have historically been regarded as biological waste, they have since been evaluated for a broad range of diagnostic, research, and molecular applications. Initially, CUSA samples were used for routine histopathological and cytological diagnosis, with early studies showing that even ultrasonically fragmented tissue could yield reliable diagnoses for meningiomas, gliomas, schwannomas, and metastatic carcinomas (2,3). Subse-

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quent work expanded their use to cell block preparations and immunohistochemistry supporting accurate classification of CNS tumors (2,4,5).

In research, CUSA aspirates have been successfully used to establish primary tumor cell cultures, including glioblastoma stem-like cells, which preserve the tumor's genetic and phenotypic heterogeneity (6). These samples have also been utilized for xenograft generation in immunocompromised mice (7). Molecularly, CUSA-derived DNA and RNA have proven suitable for oncogene amplification assays (e.g., MLPA), transcriptomic profiling (RNA-seq), and DNA methylation–based classification, often producing results comparable to conventional tissue samples (3,6,8,9). In addition, both the soluble and vesicular fractions of CUSA fluids have supported proteomic and extracellular vesicle (EV) analyses, enabling biomarker discovery through mass spectrometry and small non-coding RNA sequencing (10,11).

In addition, CUSA-derived cells have been examined through flow cytometry and immunophenotyping to study tumor-infiltrating lymphocytes and microenvironmental immune responses, while their compatibility with digital pathology has been tested to assess scanning fidelity of fragmented tissue (12,13).

However, despite increasing evidence regarding the diagnostic and research potential of CUSA-derived material, its utilization in routine neuropathology practice remains insufficiently understood in real-world practice. Specifically, there is limited data on whether these materials are consistently submitted, how they are processed across institutions, and how their diagnostic and potential molecular utility is perceived by practicing neuropathologists.

To address this gap, the present study combines a retrospective evaluation of CUSA aspirates from our institutional archive with a nationwide survey assessing current practices and perceptions across multiple centers. By integrating these complementary approaches, we aim to provide both practical evidence of diagnostic utility and a broader perspective on real-world utilization patterns.

MATERIALS and METHODS

Study Design and Case Selection

This study was designed as a single-center, retrospective observational analysis. All CUSA materials submitted to the pathology department of our institution between January 2021 and May 2026 were reviewed. A total of 10 consecutive cases in which CUSA aspirates were received for pathological evaluation were included in the study. No additional selection criteria were applied, in order to reflect routine neurosurgical practice. Clinical and pathological data were retrieved from the institutional pathology information system. All cases were anonymized prior to analysis.

Processing of CUSA Aspirates

CUSA aspirates were received in fluid-filled disposable collection containers as part of routine surgical specimen handling. Upon arrival at the pathology laboratory, aspirated material was filtered using a mesh and solid tissue fragments were collected and transferred into another container for formalin fixation. After the 24-hour fixation period, tissue fragments were wrapped in filter paper and submitted into cassettes. Then, routine pathology processing and embedding procedures were followed.

Histopathologic Evaluation

Hematoxylin and eosin (H&E)–stained sections prepared from CUSA-derived paraffin blocks were independently reviewed. For each case, the following parameters were recorded:

- Presence or absence of diagnostic tumor tissue within the aspirate
- Presence of non-neoplastic brain parenchyma
- Presence of histologic features relevant to tumor grading, including necrosis, microvascular proliferation, and mitotic activity
- Whether the final diagnosis could rely exclusively on CUSA material, without contribution from concurrent solid resection specimens

Survey Design and Data Collection

A cross-sectional, voluntary survey was conducted to assess current practices regarding the use of CUSA aspirates in neuropathology across Türkiye. This represents one of the first attempts to systematically evaluate national practice patterns regarding CUSA aspirates.

The questionnaire was designed by the study authors to capture information on institutional characteristics, submission practices, processing methods, perceived diagnostic utility, molecular applicability, and research potential of CUSA-derived material. To minimize duplicate institutional responses and better reflect center-level practices, only one neuropathologist from each institution was invited to participate. The questionnaire was distributed electronically, primarily through a closed WhatsApp group comprising approximately 100 practicing pathologists with

a predominant interest in neuropathology. Because neuropathology practice in most institutions is overseen by one or two dedicated pathologists, participants were repeatedly instructed that only one representative from each institution should complete the questionnaire to minimize duplicate responses. Participation was anonymous, and no identifiable personal data were collected.

Responses were collected over a defined study period and only fully completed questionnaires were included in the analysis. Because the survey was distributed mainly through a closed professional WhatsApp group and direct personal contacts rather than a predefined sampling frame, the exact number of eligible recipients who received or viewed the invitation could not be determined and a formal response rate could not be calculated. Data were analyzed descriptively, with categorical variables summarized as counts and percentages. No inferential statistical comparisons were performed, as the primary aim of the survey was to provide an overview of national practice patterns and perceptions.

RESULTS

Institutional Cohort Characteristics and Diagnostic Findings

The study cohort comprised 10 patients. The diagnostic spectrum included four meningiomas, two diffuse gliomas, one circumscribed glioma, one low grade glial tumor, NOS, one metastatic tumor, and one hemangioblastoma. Across the 10 cases, diagnostic tumor tissue was present in all but one of the CUSA aspirates. The only case in which diagnostic material was not identified in the aspirate was an ependymoma/subependymoma.

All aspirates that were positive for tumor tissue also provided sufficient material for ancillary diagnostic studies, particularly immunohistochemistry. The amount of tissue was considered potentially adequate for molecular testing. In most diagnostically positive cases, CUSA-derived material was also sufficient for ancillary studies. In fact, diagnostic immunohistochemistry studies were performed on CUSA-derived FFPE blocks in three of the cases. Figure 1 depicts an exemplary case demonstrating the high tissue yield of the CUSA aspirate, allowing preparation of multiple FFPE cassettes while maintaining excellent histomorphological quality and comparable immunohistochemical performance.

One diffuse glioma case (final diagnosis was glioblastoma, IDH wild type, WHO grade 4) demonstrated all histological features required for diagnosis and grading within the CUSA-derived material.

Non-neoplastic CNS parenchyma was identified in 5 of 10 cases.

All the features of the ten cases are summarized in Table I.

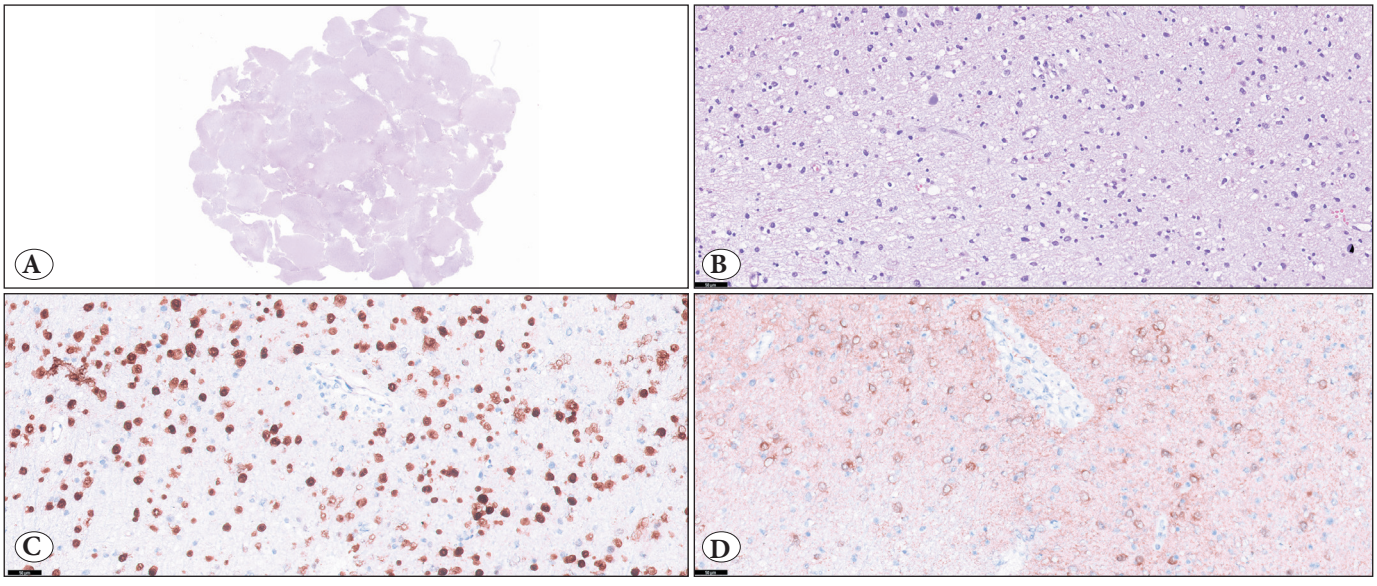


Figure 1: An "Astrocytoma, IDH-mutant, CNS WHO grade 2" case demonstrating substantial tumor yield in the CUSA collection. **(A)** Low-power view of a representative slide showing abundant tissue material mostly composed of tumor fragments. **(B)** High-power view demonstrating well-preserved histomorphological detail. **(C)** OLIG2 and **(D)** IDH1 p.R132H immunohistochemical stains demonstrating high-quality staining performance on CUSA-derived material.

Table I: Features of all ten cases with CUSA material.

Case Number	Age	Sex	Diagnosis	Presence of Diagnostic Material in Aspirate	IHC Performed on Aspirate	Presence of Features Needed for Grading in Aspirate	Diagnosis is Possible Just Using Aspirate	Presence of Non-Neoplastic Parenchyma
1	30	M	Meningothelial Meningioma, WHO Grade 1	Yes	Yes	N/A	Yes	Yes
2	51	F	Metastasis - Small Cell Carcinoma of the Lung	Yes	No	N/A	Yes	Yes
3	31	F	Transitional Meningioma, WHO Grade 1	Yes	Yes	N/A	Yes	Yes
4	10	M	Pilocytic Astrocytoma, WHO Grade 1	Yes	No	No	Yes	No
5	57	M	Meningothelial Meningioma, WHO Grade 1	Yes	No	N/A	Yes	No
6	66	M	Anaplastic Meningioma, WHO Grade 3	Yes	No	Yes	Yes	No
7	25	F	Low Grade Glial tumor, NOS	No	No	No	No	No
8	75	F	Glioblastoma, IDH wild type, WHO Grade 4	Yes	No	Yes	Yes	Yes
9	64	M	Astrocytoma, IDH mutant, WHO Grade 2	Yes	Yes	Yes	Yes	Yes
10	47	M	Hemangioblastoma, WHO Grade 1	Yes	No	N/A	Yes	No

Survey Results on National Practice

Respondent Characteristics

A total of 49 neuropathologists from different institutions completed the survey. The majority worked at university hospitals (n=28, 57.1%) or training and research hospitals (n=16, 32.7%), with smaller proportions at private (n=3, 6.1%) and state hospitals (n=2, 4.1%). Most respondents were experienced practitioners: 24 (49.0%) reported more than 20 years of practice and 14 (28.6%) reported 11–20 years of experience. Annual neuropathology case volume varied across centers; 21 respondents (42.9%) reported 101–500 cases per year, 15 (30.6%) reported 501–1000, and 6 (12.2%) reported more than 1000 cases annually.

Submission Practices and Barriers

Overall, only one-third of centers reported any form of submission of CUSA aspirates to pathology laboratories. CUSA aspirates were never submitted in 31 of 49 centers (63.3%). Routine submission was reported by only 5 respondents (10.2%), while 9 (18.4%) indicated rare submission and 2 (4.1%) reported selective submission for specific cases. Two respondents (4.1%) were uncertain about the practice at their institution (Figure 2).

Among the 31 centers where CUSA material was never submitted, the most commonly cited reason was lack of awareness regarding current practice (n=12, 38.7%), followed by the absence of a standardized protocol (n=8, 25.8%), perception of the material as surgical waste (n=4, 12.9%), and absence of a pathology department request (n=3, 9.7%).

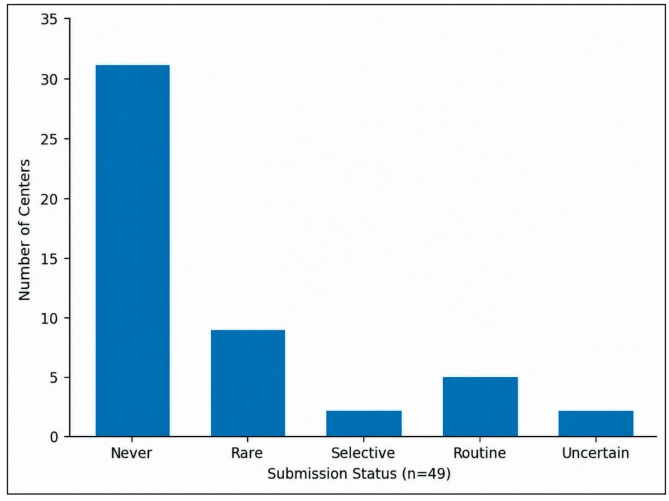


Figure 2: CUSA Aspirate Submission Practices

Logistic or time-related constraints were cited by only 2 respondents (6.5%), and a presumed lack of diagnostic value by 1 (3.2%) (Table II).

Processing Approaches for CUSA Aspirates

Among the 16 respondents who reported receiving CUSA material, processing methods were heterogeneous. Filtration through filter paper followed by routine paraffin embedding was the most common approach (n=6), followed by centrifugation with pellet embedding (n=4) and mesh/sieve-based particle collection (n=4). Cell block preparation was reported by one center. Notably, 4 respondents reported having no standardized method, with processing

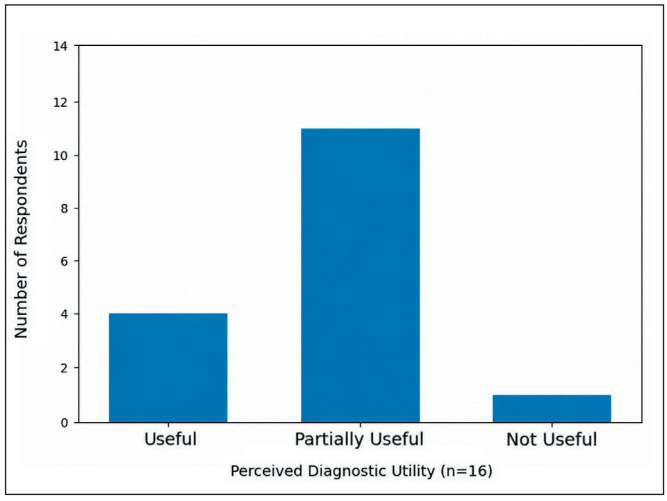


Figure 3: Perceived Diagnostic Utility

varying on a case-by-case basis. This variability reflects the absence of standardized handling protocols across centers.

Technical and Diagnostic Challenges

Among the 16 respondents with direct evaluation experience, mechanical artifact and cellular disruption were the most consistently reported challenge, described as "frequent" by 10 of 16 (62.5%). Difficulty with immunohistochemical evaluation was also commonly reported as frequent (11/16, 68.8%), representing the single most prevalent limitation. Excess blood and necrosis were rated as frequent by 8 of 16 respondents (50.0%), and loss of histologic architecture by 7 of 16 (43.8%).

In contrast, dominance of non-neoplastic brain parenchyma was less commonly reported as a frequent challenge, with most respondents rating it as occasional (8/16, 50.0%) or rare (7/16, 43.8%). Regarding nucleic acid quality for molecular testing, 5 of 16 respondents (31.3%) rated this as a frequent problem, while 5 (31.3%) had no experience with molecular testing on CUSA material.

Importantly, the predominant limitations were related to technical factors such as artifact and tissue quality rather than absence of tumor material.

Perceived Diagnostic Utility

Despite these limitations, most respondents from the centers that utilize CUSA aspirate acknowledged at least partial diagnostic utility. Overall diagnostic utility was considered partial by the majority of evaluators: 11 of 16 respondents (68.8%) found CUSA aspirates partially useful, 4 (25.0%) considered them useful, and 1 (6.3%) did not find them useful (Figure 3).

Table II: Summary of Nationwide Survey on CUSA aspirate practices (n=49).

Survey Component	Variable	n (%)
Submission Practice	Never submitted	31 (63.3)
	Routine submission	5 (10.2)
	Any submission (rare/selective/routine)	16 (32.7)
Barriers to Submission*	Lack of awareness	12 (38.7)
	No standard protocol	8 (25.8)
	Considered surgical waste	4 (12.9)
	No pathology request	3 (9.7)
Processing Methods †	Filtration + paraffin embedding	6
	Centrifugation + pellet embedding	4
	Mesh/sieve collection	4
	Cell block preparation	1
	No standard method	4
Perceived Diagnostic Utility‡	Useful	4 (25.0)
	Partially useful	11 (68.8)
	Not useful	1 (6.3)
Molecular Suitability‡	Sufficient in selected cases	8 (50.0)
	Sufficient in most cases	2 (12.5)
	Generally insufficient	6 (37.5)
Clinical Experience‡	Diagnosis supported by CUSA	7 (43.8)
	CUSA critical for diagnosis	4 (25.0)
Research Potential‡	Suitable	6 (37.5)
	Uncertain	8 (50.0)
	Not suitable	2 (12.5)
Standardization Need‡	Yes	7 (43.8)
	Uncertain	7 (43.8)
	No	2 (12.5)

*Based on responses from centers not submitting CUSA aspirates (n=31).
†Multiple responses allowed.
‡Based on respondents with direct experience evaluating CUSA aspirates (n=16)

Regarding the nature of the contribution, 8 respondents (50.0%) indicated that CUSA material contributes both morphologically and through ancillary testing, while 4 (25.0%) considered it valuable for better representing tumor heterogeneity and reducing sampling bias, and 4 (25.0%) considered it to provide no meaningful contribution.

High-grade glial tumors and metastatic tumors were most frequently identified as the categories in which aspirates are most valuable (11/16, 68.8% and 10/16, 62.5%, respectively), followed by recurrent tumors and CNS lymphomas (6/16 each, 37.5%), and low-grade glial or glioneuronal tumors (5/16, 31.3%).

Molecular and Ancillary Applications

Regarding molecular suitability, 8 of 16 respondents (50.0%) considered CUSA material to provide sufficient tumor cell content for molecular analysis in selected cases, while 6 (37.5%) generally found it insufficient and 2 (12.5%) considered it sufficient in most cases. When asked about contribution to integrated molecular classification — including next generation sequencing (NGS) and DNA methylation profiling — 7 respondents (43.8%) believed it could contribute to selected cases, while 6 (37.5%) had no opinion or experience, and 2 (12.5%) considered its contribution limited.

Molecular testing on CUSA material was considered appropriate in selected cases by 7 respondents (43.8%), while 6 (37.5%) were undecided and 1 (6.3%) considered it inappropriate. Overall, confidence in molecular applications remained cautious and largely case dependent.

Reported Clinical Experience

Seven of the 16 evaluators (43.8%) reported having encountered at least one case in which the final diagnosis was reached based on CUSA material, while 6 (37.5%) had no such experience and 3 (18.8%) were uncertain. Four respondents (25.0%) reported a case in which CUSA material was critical for diagnosis due to insufficient solid resection material, while 10 (62.5%) had not encountered such a scenario.

Notably, nearly half of respondents reported experience with a diagnosis supported by CUSA material, highlighting its potential clinical relevance despite inconsistent use.

Research Potential and Standardization

A considerable proportion of respondents remained uncertain regarding research applications, indicating a gap between potential and awareness. Six of the 16 active evaluators (37.5%) considered CUSA aspirates suitable for research purposes, while 8 (50.0%) were undecided and 2 (12.5%) did not.

Among those who expressed a view on the most valuable research aspect, 6 respondents indicated that both the tumor cell content and the admixed non-neoplastic brain parenchyma are valuable, while 4 emphasized tumor cell content alone.

Regarding the need for standardization, 7 of 16 evaluators (43.8%) expressed the need for national guidelines or a standard protocol, 7 (43.8%) were undecided, and 2 (12.5%) did not consider it necessary. Notably, among the 31 non-submitting centers, absence of a standardized protocol was the second most cited barrier after general uncertainty, underscoring the need for national guidance at a broader level. Overall, the survey revealed a marked discrepancy between the recognized potential of CUSA aspirates and their limited use in routine practice, largely driven by lack of standardization and awareness.

DISCUSSION

CUSA is a widely used tool in oncologic neurosurgery. The resection of many intracranial tumors requires a combination of direct piece by piece resection and various degrees of CUSA use (14,15). However, there is a long-standing belief that CUSA collections are disposable surgical by-products. Our survey findings confirm that this perception persists widely in Türkiye, where most centers do not routinely submit these materials to pathology laboratories. This represents a clear discrepancy between current practice and potential utility. In our limited series, diagnostically useful tumor tissue was identified in almost all cases, consistent with previous reports demonstrating that ultrasonically fragmented tissue often retains sufficient morphologic integrity for histologic evaluation (6,16,17). These findings support the view that surgical aspirates (including CUSA aspirates) constitute a meaningful component of the surgical specimen rather than biological waste.

Beyond basic histopathology, our results show that aspirated material is frequently suitable for extended diagnostic work-up. In most cases where tumor tissue was present, the material was sufficient for immunohistochemical and, when required, for potential molecular analyses. Notably, a subset of cases relied on CUSA-derived material for immunohistochemistry to establish the final diagnosis. This observation aligns with survey responses indicating that, although not universally recognized, a considerable proportion of neuropathologists have encountered cases in which CUSA aspirates contributed to or supported the diagnostic process. However, the survey also revealed that confidence in molecular applications remains cautious and largely case-dependent, reflecting understandable concerns about tumor cell content and nucleic acid quality. Together, these findings indicate that integration into routine practice remains inconsistent despite recognized diagnostic potential.

The role of CUSA aspirates appears to be variable. When surgically obtained diagnostic material is limited, necrotic, or otherwise suboptimal, aspirated material may become critical or even indispensable for diagnosis. Conversely, when sufficient tumor tissue is available in the primary specimen, CUSA material may be diagnostically redundant. In such cases, however, its value shifts toward research applications. Extensive literature indicates that aspirated tissue serves as an abundant source of tumor material, suitable for molecular profiling, biobanking, and experimental studies without interfering with routine diagnostic workflows (6–8,18,19). Despite this potential, our survey indicates that awareness of research applications remains limited, with a substantial proportion of respondents expressing uncertainty regarding its use in this context.

An additional, yet frequently overlooked, dimension of CUSA aspirates is the presence of non-neoplastic components. Our findings indicate that these specimens often contain significant proportions of near-normal or peritumoral brain parenchyma admixed with the lesion. This characteristic offers a distinct advantage for neuro-oncological research, particularly given the declining frequency of traditional autopsies. Consistent with this, our survey data suggests that researchers perceive both the malignant and non-neoplastic fractions as highly valuable, despite their current underutilization. As access to fresh, surgically derived non-neoplastic brain tissue is otherwise restricted, its availability within aspirates facilitates high-fidelity tumor–normal comparative studies and complex microenvironmental analyses.

Importantly, survey results indicate that the primary barrier to wider utilization of CUSA aspirates is logistical and conceptual. The lack of standardized handling protocols, limited coordination between surgical and pathology teams, and persistent perception of these materials as surgical waste were identified as key obstacles. The considerable variability in processing methods reported across centers further supports the need for standardization. Collectively, these findings underscore that the underutilization of CUSA material is driven more by practice patterns and awareness than by intrinsic limitations of the material itself.

We encourage close collaboration between neuropathology and neurosurgery teams to facilitate the routine collection of CUSA aspirates, particularly through effective communication with operating room nurses and surgical support staff. Establishing this practice as part of the routine surgical workflow requires persistence, coordination, and continued interdisciplinary engagement. With sustained implementation, collection of CUSA aspirates can become an integrated and standardized component of intraoperative tissue handling.

Following completion of surgery, aspirator containers should be transferred promptly to the pathology laboratory. A practical processing approach involves filtering the aspirated material through a mesh or sieve to recover solid tissue fragments, which should then be transferred into a separate container and fixed in 10% neutral buffered formalin. Although the aspirated material may occasionally be abundant and contain excessive blood clotting, identifiable tissue fragments should be preferentially collected and submitted for histopathological evaluation. Whenever feasible, the entire specimen should be processed to maximize diagnostic yield and the availability of material for ancillary studies.

Beyond specialized ultrasonic devices, the diagnostic research potential of conventional aspirator-collected tissue should not be overlooked. Standard aspiration remains the mainstay in various neurosurgical procedures; notably, this technique yields a volume of tissue comparable to CUSA, representing a robust and underutilized source for molecular and histological analysis. While conducting this study, we also encountered >50 cases in which standard surgical aspirator collections, rather than dedicated CUSA aspirates, were submitted for pathological evaluation. Many of these specimens yielded substantial amounts of tumor and non-neoplastic central nervous system tissue fragments. These observations suggest that not only CUSA-derived material, but also conventional surgical aspirator collections, may represent valuable sources of diagnostic and potentially research-grade tissue.

This study has limitations inherent to its retrospective, single-center design, small and heterogeneous cohort. The limited number of cases also restricts the precision and generalizability of the observed diagnostic yield, which may be influenced by local case mix, specimen handling practices, and institutional workflows. In addition, the survey component is subject to response bias and reflects voluntary participation among practicing neuropathologists, as it was specifically designed to evaluate perceptions and institutional practices among specialists most likely to encounter and interpret CUSA-derived material. A further limitation is that tissue quality was assessed descriptively rather than through a formal semiquantitative scoring system. Future studies may benefit from incorporating objective measures of cellular preservation, architectural integrity, artifact burden, and tumor cellularity. Nevertheless, the combined analysis of institutional data and nationwide

survey responses provides a comprehensive overview of both the potential and current utilization patterns of CUSA aspirates.

In conclusion, our findings suggest that CUSA aspirates represent an underutilized resource in contemporary neuropathology practice. Therefore, CUSA aspirates should not routinely be regarded as mere surgical debris. When appropriately collected, processed, and integrated into diagnostic workflows, they represent a versatile resource that can support routine diagnosis, may provide adequate material for ancillary testing, and may serve as a useful substrate for molecular and translational research applications. Bridging the gap between recognized potential and current practice will require increased awareness, improved interdisciplinary communication, and the development of standardized handling protocols.

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This manuscript was prepared with the assistance of natural language processing tools driven by artificial intelligence (AI) for language refinement and formatting. These tools were used solely to enhance clarity and structure and were not involved in the generation or analysis of data.

Conflict of Interest
Authors declare that they have no conflict of interest to disclose.

Ethics Approval
This study was performed in accordance with the Declaration of Helsinki and was approved by the Koç University Institutional Review Board (IRB) (Approval number: 2026.107.IRB2.047).

Authorship Contributions
Concept: **IK,** Design: **AHDK, IK,** Data collection and/or processing: **AHDK, SMA, IK,** Analysis and/or interpretation: **AHDK, SMA,** Literature search: **AHDK,** Writing: **AHDK, IK,** Approval: **IK.**

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