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Correlation of Intraoperative Frozen Section Report and Histopathological Diagnosis of Central Nervous System Tumors – A Six-Year Retrospective Study

Radiya Al-Ajmi[1], Hunaina Al-Kindi[2]*, Mina George[2] and Kurien Thomas[3]

[1]Department of Histopathology, Sultan Qaboos University Hospital, Muscat, Oman
[2]Department of Histopathology, Khoula Hospital, Muscat, Oman
[3]Department of Medicine, PIMS, Pondicherry, India

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ABSTRACT

Objectives: To evaluate the degree of agreement between the intraoperative frozen section (FS) reporting of central nervous system (CNS) tumors and final histopathological diagnosis based on permanent paraffin section. ***Methods***: All CNS tumor cases with a diagnosis at FS and subsequent permanent section (n = 261) taken from 2007 to 2012 were retrospectively reviewed. Twenty percent of FS were double-checked by a senior pathologist as part of the study and the intraobserver agreement between the pathologist and the agreement between final report, and initial FS report was estimated by the intraclass correlation coefficient (ICC). ***Results:*** A total of 261 cases were reviewed. The most common diagnosis was glioblastoma (grade IV) and meningioma (grade I–II) forming 45.6% of cases. Fifty-three cases were subjected to intraobserver agreement of histological diagnosis. There was nearly perfect intraobserver agreement on histopathology (ICC = 0.9). Out of 261 cases, 224 cases showed a strong agreement between the FS diagnosis and final histological diagnosis (ICC = 0.747). A discrepancy between the FS and final diagnosis were found in eight cases. The disagreement did not relate to any specific tumor type. However, in three cases, the discrepancy was in the grading of the glioma. In 29 cases, a definite opinion could not be given on FS as the samples examined were nonrepresentative. ***Conclusions:*** Histopathological slides classified by World Health Organization criteria of CNS tumors had excellent intraobserver agreement. Our results show a moderate to high degree of agreement in the intraoperative diagnosis of CNS lesions using FS. However, there are limitations, and some lesions are a diagnostic challenge. There is a need to improve our diagnostic skills and knowledge of possible errors and establish better communication with neurosurgeons.

Frozen section (FS) interpretation is one of the most challenging tasks in the field of pathology. The role of the pathologist in interpreting central nervous system (CNS) frozen sections along with clinico-radiological correlation is to assist the neurosurgeon in making the most accurate judgment regarding the nature of the CNS lesion. This enables the surgeon to decide further management on the operation table, in addition to determining the adequacy of the submitted tissue for diagnosis.[1–4] In some centers, pathologists only employ cytology smears prepared by the "squash method," while others employ both cytology and frozen sections.[5,6]

The soft consistency of most primary CNS neoplasms facilitates the preparation of smears, and smear cytology has been used with great success for the intraoperative diagnosis of CNS neoplasms,[7–11] especially astrocytomas, oligodendrogliomas, and small round cell tumors.[6]

Frozen sections are mainly useful for the more firm, rubbery neoplasms such as meningiomas, ependymomas, and most metastatic tumors from which it is difficult to prepare good cytology smears.[7,8] Studies have shown that a combination of the two techniques is most beneficial.[12]

In our center, we use a combination of both techniques whenever we get an intraoperative consultation in a suspected case of CNS neoplasm. Studies have reported the diagnostic accuracy of CNS intraoperative consultation in the range of 85% to 90%.[3,6,11,13–17]

*Corresponding author: ✉alkindihunaina@hotmail.com

The aim of this study was to evaluate the degree of agreement between the intraoperative FS reporting of CNS tumors and final histopathological diagnosis based on permanent paraffin section.

METHODS

A retrospective analysis of agreement between intraoperative CNS tumors reporting on fresh unfixed tissue and final histopathology reporting on formalin-fixed tissue was performed. The study was conducted in the department of histopathology in Khoula Hospital, Oman, using records from 2007 to 2012. Cases where both fresh unfixed tissue for intraoperative reporting and formalin-fixed tissue for final histopathology diagnosis were not available were excluded from the study. Cases of pituitary neoplasm and non-neoplastic lesions were also excluded. All other cases were analyzed to avoid any selection bias. Final histopathology reports based on the findings of formalin-fixed paraffin-embedded tissue were considered the gold standard used for the diagnosis of the tumors.[18] The diagnoses given on FS were compared to the final diagnosis given on permanent sections (and any additional material received), as indicated on the FS and final pathology report.[5]

The records of 261 cases where intraoperative fresh unfixed and later, formalin-fixed tissue samples were accessed. Intraoperative reporting was done based on both crush smears and frozen sections. The cytology smears were prepared at the time of intraoperative consult by the "squash method," (i.e., placing a small piece of tissue between two slides, gently squashing it, and pulling the slides away from each other). These squash smears were immediately fixed in 95% alcohol and stained with hematoxylin-eosin (H&E). FS slides were cut on a cryostat apparatus, fixed in 95% alcohol, and stained with H&E.

Fifty-three cases (20%) were randomly selected of the total 261 cases and were retrieved and reviewed by a senior consultant with many years of experience in neuropathology. The consultant was provided with the H&E stained slides of FS and squash preparation. Relevant clinical data and radiological findings were available in some cases as provided by the surgeon in the initial FS setting. The agreement between this pathologist and initial FS report was calculated.

Table 1: Intraclass correlation coefficient (ICC) interpretation values.

Strength of agreement	Agreement value
Almost perfect	> 0.8
Strong	0.7–0.8
Moderate	0.5–0.6
Fair	0.3–0.4
Poor	0.0–0.2

The tumors were classified according to the 2007 World Health Organization (WHO) classification of CNS neoplasms. Intraoperative reporting of a tumor as low grade was considered to be in agreement with a final grading as WHO Grade I and II, and high-grade would be in agreement with WHO Grade III and IV.[18]

Differences between FS or final diagnoses due to possible sampling errors (i.e., undergrading of tumors or composite tumors such as oligoastrocytoma in which only one component may have been sampled) were not considered discrepant as long as the general tumor cell type was consistent between FS and final diagnosis.[2]

Statistical analysis was performed with SPSS Statistics (SPSS Statistics Inc., Chicago, US) version 21.0. The agreement between the FS report and final histopathological diagnosis was analyzed via the intraclass correlation coefficient (ICC). The same type of analysis was also applied to measure the agreement between the reviewing pathologist's FS report and the final diagnosis report. The ICC two-way mixed effects model was used (the average measures ICC). The interpretation of ICC is shown in Table 1.[19]

RESULTS

In the 261 cases studied, 134 patients were female, and 127 were male. The majority of patients (n = 104) were aged 31–60 years old, 50 were <12 years, 53 were 13–30 years and the remaining 54 were > 60 years old.

Analysis of the 261 cases showed a strong agreement between the FS diagnosis and final histological diagnosis (ICC = 0.747) [Table 2]. This agreement increased to an almost perfect agreement when the pathologist reviewed the random 53 cases independently (ICC = 0.939) [Table 2].

Table 2: Intraclass correlation coefficient (ICC) analysis of the 261 cases with frozen section diagnosis and histological diagnosis and the random 53 cases independently.

Average measures	ICC	95% Confidence interval		F test with True Value 0			
		Lower bound	Upper bound	Value	df1	df2	Sig
All cases, n = 261	0.747	0.678	0.802	3.960	260	260	0.000
Random cases, n = 53	0.939	0.884	0.961	14.884	52	52	0.000

df: degrees of freedom; sig: significance

Table 3: Spectrum of central nervous system tumors.

Tumor	n
Craniopharyngioma	8
Meningioma, grade I–II	59
Glioblastoma	60
Astrocytoma, grade I–II	35
Astrocytoma, grade III	7
Ependymoma, grade I–II	14
Ependymoma, grade III	3
Oligodendrogliomas, grade II	7
Oligodendrogliomas, grade III	1
Mixed glioma (oligoastrocytomas), grade III	3
Carcinoma (metastatic)	20
Medulloblastoma	18
Lymphoma	3
Schwannoma	3
Choroid plexus papilloma	6
Central neurocytoma	4
Primitive neuroectodermal tumor (PNET)	3
Atypical teratoid/rhabdoid tumor	4
Hypothalamic hamartoma	3

Table 4: Cases in which there were discrepancies between the frozen section report and the final diagnosis (based on permanent section).

Frozen section	Permanent section	n
Low-grade glioma	Central neurocytoma	1
Malignant neoplasm	Microcystic meningioma (grade I)	1
Ependymoma	Medulloblastoma	1
Ependymoma	Choroid plexus papilloma	1
Low-grade glioma	Anaplastic astrocytoma (grade III)	3
Small round blue cell tumor	Glioblastoma	1
Total		**8**

Table 5: Cases where the frozen section reports were nonrepresentative and a final diagnosis was deferred to the permanent section.

Frozen diagnosis	Permanent diagnosis	n
Necrosis	Glioblastoma	12
	Medulloblastoma	1
	Metastatic carcinoma	1
Fibrous tissue	Meningioma	2
Glial tissue	Low grade glioma	10
	Hypothalamic hamartoma	2
Calcification	Choroid plexus papilloma	1
Total		**29**

Of the 261 cases studied, glioblastoma (WHO grade IV) and meningioma (WHO grade I–II) constituted the predominant tumors among the total cases (60 and 59, respectively) [Table 3]. A discrepancy between the FS and the final diagnosis was found in eight cases [Figures 1–5] and are summarized in Table 4. In 29 cases, a definite opinion could not be given on FS as the samples examined were nonrepresentative [Table 5].

Two discrepant cases were among the random 53 cases reviewed by the pathologist and the same diagnoses as the previous FS were given. The error was in misinterpreting microcystic meningioma (WHO grade I) as a malignant neoplasm or high-grade tumor, and misdiagnosing central neurocytoma (WHO grade II) as a low-grade glioma.

DISCUSSION

FS interpretation is one of the most challenging tasks for a pathologist. The pathologist tries to give the maximum possible information to the neurosurgeon; however, there are various limiting factors such as the

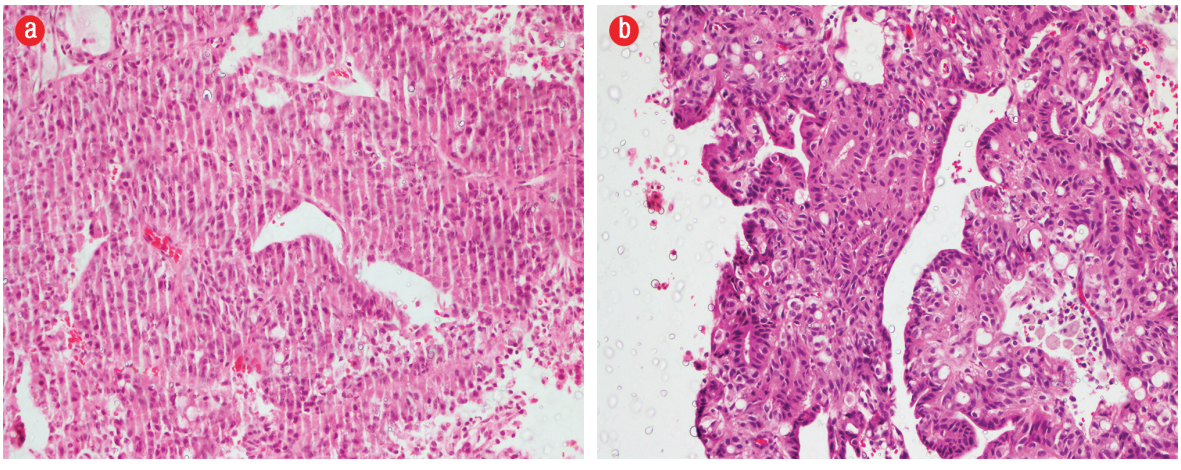

Figure 1: (a) Frozen section diagnosed as ependymoma with hematoxylin and eosin (H&E) staining, magnification = 200 ×. **(b)** Paraffin-embedded section diagnosis of choroid plexus papilloma with H&E staining, magnification = 200 ×.

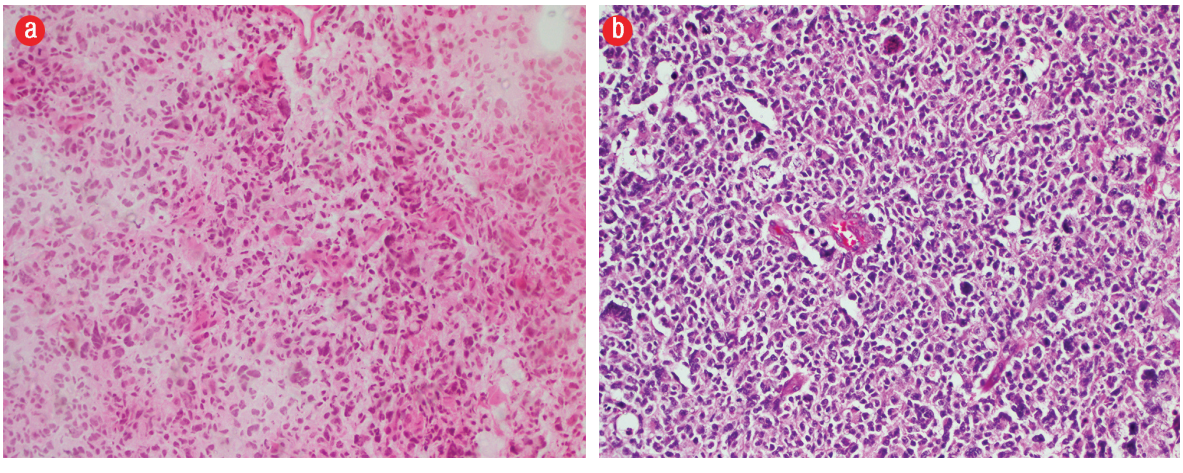

Figure 2: (a) Frozen section diagnosed as small round blue cell tumor with hematoxylin and eosin (H&E) staining, magnification = 200 ×. **(b)** Paraffin-embedded section diagnosis of glioblastoma with H&E staining, magnification =200 ×.

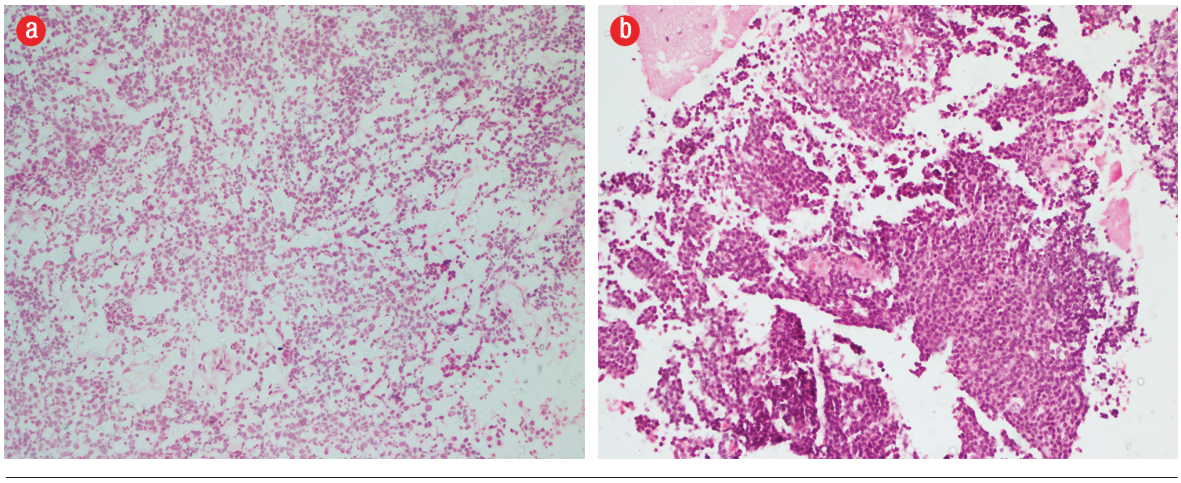

Figure 3: (a) Frozen section diagnosed as suggestive of ependymoma with hematoxylin and eosin (H&E) staining, magnification = 200 ×. **(b)** Paraffin-embedded section diagnosis of medulloblastoma with H&E staining, magnification = 200 ×.

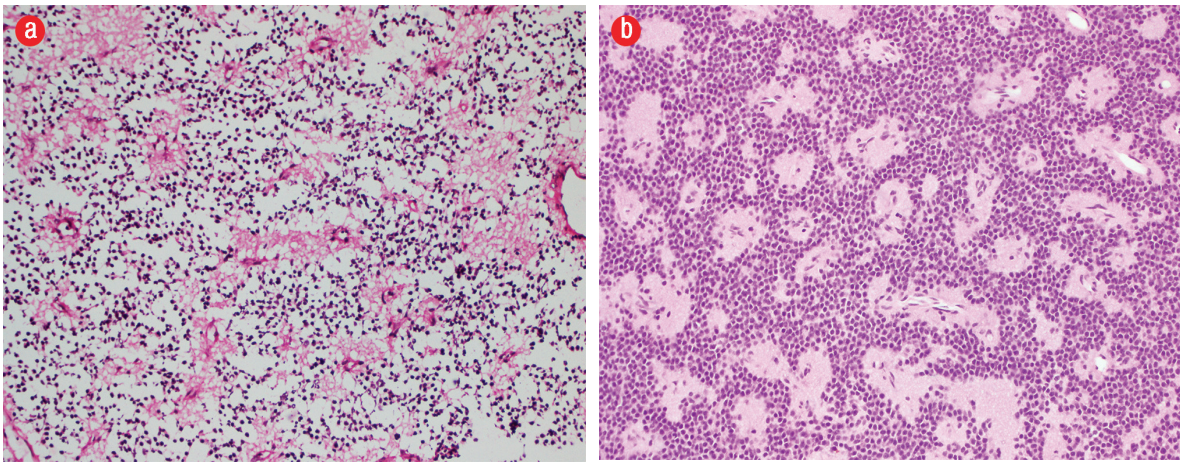

Figure 4: (a) Frozen section diagnosed as low-grade glioma favoring ependymoma with hematoxylin and eosin (H&E) staining, magnification = 200 ×. **(b)** Paraffin-embedded section diagnosis of central neurocytoma with H&E staining, magnification = 200 ×.

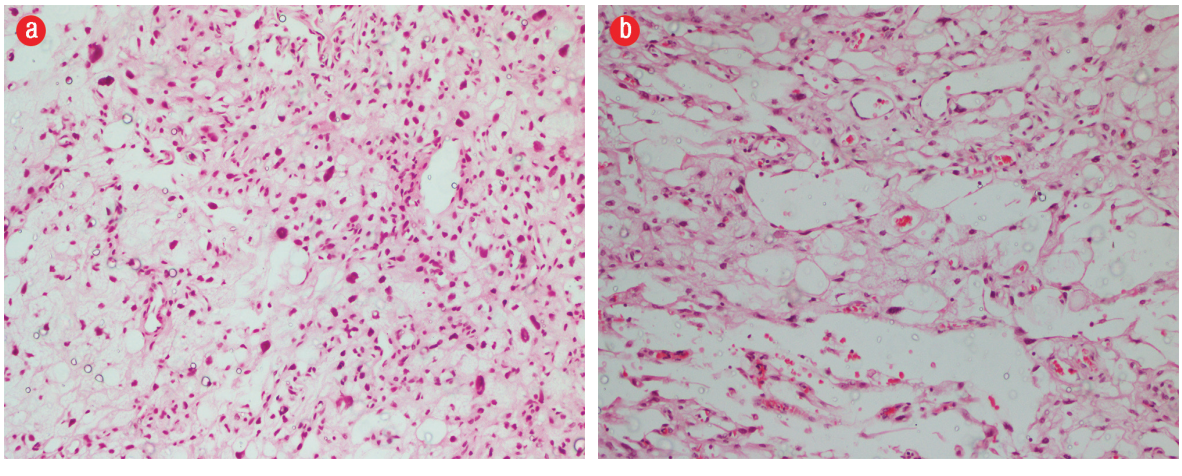

Figure 5: (a) Frozen section diagnosed as a malignant neoplasm with hematoxylin and eosin (H&E) staining, magnification = 200 ×. **(b)** Paraffin-embedded section diagnosis of microcystic meningioma with H&E staining, magnification = 200 ×.

fragile nature of CNS tissue, scant volumes of tissue sent to the pathologist, and like vascularity, necrosis, calcification, and unconventional cell morphology of the lesions. Surgeons commonly use cautery during the operative procedure causing burning of tissues, and this disrupts the morphology leading to difficulty in interpretation.[1] Another limitation is due to misleading clinical and radiological findings, and the experience of pathologist in interpreting and recognizing technical errors in frozen sections.[1] A precise diagnosis requires a good correlation of clinical, radiological, and histopathological data.

The agreement between the FS reports and final permanent section diagnosis was good (ICC = 0.747). This might reflect both the experience of the participating pathologist and the samples provided.

Only eight (3.1%) out of 261 cases showed discrepancies between the FS and final permanent section report. An evaluation of the eight discordant cases revealed various pitfalls, which led to misdiagnosis. The most frequent discrepancies occurred with grading. Three cases were reported as low grade on FS but eventually were graded as III. In the three cases mentioned, it was hard to comment on the grade even after studying the permanent section. Two of these cases were sent to a specialized neuropathology center abroad, and using a panel of immunohistochemical stain (especially cell proliferation index studies) the grade was confirmed as III. One case of choroid plexus papilloma was incorrectly diagnosed as ependymoma [Figure 1 a and b] due to the presence of pseudopapillae and

solid sheets of cells. This finding can be seen in both cases. Another case was diagnosed on FS as a small round blue cell tumor, and permanent section report revealed glioblastoma [Figure 2 a and b]. A small cell variant of glioblastoma, like this case, can be extremely difficult or impossible to differentiate from other small blue round cell tumors on FS. This pitfall is frequently encountered in frozen sections.[2,5]

Another case was of medulloblastoma being reported at the time of intraoperative consultation as ependymoma [Figure 3 a and b]. This error is commonly encountered as both these tumors occur in children and in the same location in the posterior fossa.

One case of central neurocytoma was reported on FS as a low-grade glioma favoring ependymoma [Figure 4 a and b]. In this case, the morphological features of central neurocytoma on FS were not evident, and even when the case was reviewed among the random cases the same diagnosis was given as the previous FS. Moreover, the clinical presentation and the site was also not typical, and it was a frontal intraventricular lesion and not in the foramina of Monro, which is the classical location for a neurocytoma. However, a report of neurocytoma was based on the immunoprofile (negative for EMA and positive for synaptophysin).

A case of microcystic meningioma (WHO grade I) was reported as a malignant neoplasm in FS [Figure 5 a and b]. The appearance of this tumor on FS was misleading, and this possibly explains the error.

Discrepant cases need to be reviewed by pathologists to familiarize themselves with the morphological changes and artifacts. The knowledge of possible errors could minimize misinterpretation and help to provide a more conclusive opinion to the operating surgeon.

Discrepancies between the FS and the permanent diagnoses were reported in many studies. Some studies showed discrepancies in ependymoma, glioblastoma, metastatic tumors, oligodendroglioma, meningioma, and astrocytoma.[17,20] A French study on 1 315 cases found most discrepancies were in gliomas, hemangioblastomas, and metastatic tumors.[17] Most of the discrepant cases were spindle cell lesions, astrocytoma versus oligodendroglioma, lymphoma, reactive versus neoplastic process, and tumor overgrading.[6] In a study by Rao et al,[1] 6% of cases were found to be discordant. These included angiomatous meningioma, Non-Hodgkins lymphoma, metastatic renal cell carcinoma, cerebellopontine angle fibrous meningioma, and craniopharyngioma. In 29 cases, a definite opinion could not be given on FS as the samples examined were nondiagnostic and included only necrotic, calcified, fibrous or glial tissue. This is due to heterogeneity of CNS neoplasms and sampling error. Twelve cases were given as glial tissue, and permanent section revealed 10 cases to be low-grade glioma and two cases to be hypothalamic hamartoma. The two cases diagnosed as fibrous tissue turned out to be a meningioma. One of the common difficulties involves a diagnosis of spindle cell neoplasm in FS. In their study, Plesec et al[2] encountered difficulties involving spindle cell lesions, most commonly confusing schwannomas and meningiomas with other lesions. However, despite these few cases of discrepancies and indefinite diagnoses, decisions regarding further patient management on the operating table were not affected in the cases involved in our study.

CONCLUSION

FS diagnosis is a very useful and highly accurate procedure. Gross inspection, sampling by a pathologist, FS complemented with cytological and histological review, and close cooperation with surgeon (with good communication between the surgeon and pathologist) can avoid certain limitations and provide rapid, reliable, and cost-effective information necessary for optimum patient care.

Disclosure
The authors declared no conflicts of interest. No funding was received for this study.

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