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ORIGINAL ARTICLE

What is the current clinico-radiological diagnostic accuracy for intracranial tumours?

Paulina Majewska[1] | Lisa Millgård Sagberg[1,2] | Ingerid Reinertsen[3] | Sasha Gulati[1,4] | Asgeir Store Jakola[1,5,6] | Ole Solheim[1,3]

[1]Department of Neurosurgery, St. Olav's University Hospital, Trondheim, Norway

[2]Department of Public Health and Nursing, NTNU, Trondheim, Norway

[3]SINTEF, Trondheim, Norway

[4]Department of Neuromedicine and Movement Science, NTNU, Trondheim, Norway

[5]Department of Neurosurgery, Sahlgrenska University Hospital, Gothenburg, Sweden

[6]Institute of Neuroscience and Physiology, Department of Clinical Neurosciences, Sahlgrenska Academy, Gothenburg

Correspondence
Paulina Majewska, Department of Neurosurgery, St. Olav's University Hospital, Trondheim, Norway.
Email: plmajewska@gmail.com

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Abstract

Objective: To determine the diagnostic accuracy of routine clinico-radiological workup for a population-based selection of intracranial tumours.

Methods: In this prospective cohort study, we included consecutive adult patients who underwent a primary surgical intervention for a suspected intracranial tumour between 2015 and 2019 at a single-neurosurgical centre. The treating team estimated the expected diagnosis prior to surgery using predefined groups. The expected diagnosis was compared to final histopathology and the accuracy of preoperative clinico-radiological diagnosis (sensitivity, specificity, positive and negative predictive values) was calculated.

Results: 392 patients were included in the data analysis, of whom 319 underwent a primary surgical resection and 73 were operated with a diagnostic biopsy only. The diagnostic accuracy varied between different tumour types. The overall sensitivity, specificity and diagnostic mismatch rate of clinico-radiological diagnosis was 85.8%, 97.7% and 4.0%, respectively. For gliomas (including differentiation between low-grade and high-grade gliomas), the same diagnostic accuracy measures were found to be 82.2%, 97.2% and 5.6%, respectively. The most common diagnostic mismatch was between low-grade gliomas, high-grade gliomas and metastases. Accuracy of 90.2% was achieved for differentiation between diffuse low-grade gliomas and high-grade gliomas.

Conclusions: The current accuracy of a preoperative clinico-radiological diagnosis of brain tumours is high. Future non-invasive diagnostic methods need to outperform our results in order to add much value in a routine clinical setting in unselected patients.

KEYWORDS
biopsy, clinico-radiological diagnosis, diagnostic accuracy, intracranial tumours

1 | INTRODUCTION

A histopathological diagnosis is still favoured in most patients with brain tumours. The need for a tissue diagnosis might be reduced in the future due to continuous improvements in pre-treatment diagnostics. An additional diagnostic value of special imaging protocols or techniques, including positron emission tomography (PET)[1] or radiomics based on artificial intelligence[2] in the preoperative workup

of patients with intracranial tumours is promising. However, it is not clear to what extent they outperform the current diagnostic standards. The aim of the current study was to determine the accuracy of a routine clinico-radiological diagnosis for a population-based selection of intracranial tumours.

2 | METHODS

The current study was a prospective cohort study. The data were collected as part of the Central Norwegian Brain Tumour Registry.

2.1 | Participants

All consecutive patients ≥18 years who underwent a primary surgical intervention for a suspected intracranial tumour (biopsy or resection) between 01.12.2015 and 25.07.2019 at the Department of Neurosurgery at St. Olav's University Hospital in Trondheim, Norway were eligible for the study participation. This department is the only neurosurgical unit serving a geographical catchment region with approximately 720 000 inhabitants.

Patients with missing data (i.e. no expected preoperative diagnosis filled out, and/or no postoperative histopathological diagnosis or inconclusive histopathological diagnosis) were excluded.

2.2 | Preoperative diagnosis

The primary surgeon recorded the expected clinico-radiological diagnosis in a questionnaire just prior to surgery using predefined groups: 'high-grade glioma' (WHO grade III-IV), 'diffuse low-grade glioma' (WHO grade II), 'metastasis', 'meningioma', 'pituitary adenoma', 'lymphoma', or 'other tumours'. 'Other tumours' included schwannomas, neurocytomas, haemangiomas, subependymomas, ependymomas, and epidermoid tumours. The expected preoperative diagnosis was discussed with neuroradiologists and colleague neurosurgeons, and/or neurooncologists and endocrinologists as part of clinical meetings. Routine imaging workup of all patients with newly diagnosed intracranial tumours included a structural MRI (T2-weighted/FLAIR, T1-weighted, contrast-enhanced T1 and DWI series) and CT thorax/abdomen/pelvis in patients with suspected intracranial metastases. In selected cases (54 out of 392 cases), MR spectroscopy and/or MR perfusion were used. PET scans are not routinely used in our department. Eight patients who underwent a PET scan preoperatively in the study period as part of another clinical study[3] were excluded from the data analyses.

2.3 | Postoperative histopathological diagnosis

The tumours were histopathologically classified by a neuropathologist based on the 2007 WHO-classification[4] (before May 2016) or the 2016 WHO-classification[5] (after May 2016). In cases with heterogeneity, for example in diffuse astrocytomas (grade II) with areas or molecular markers consistent with high-grade gliomas, the highest tumour grade was recorded. The histopathological diagnoses were then grouped according to the same predefined clinico-radiological groups estimated preoperatively.

2.4 | Data analysis

The accuracy of a preoperative clinico-radiological diagnosis (sensitivity, specificity, positive and negative predictive values) was calculated using the histopathological diagnosis as the final 'gold standard' diagnosis. Diagnostic mismatch rate was defined as the number of cases where the preoperative clinico-radiological diagnosis and the postoperative histopathological diagnosis were classified as a different tumour type category using predefined groups, divided by the number of total cases (n = 392). Data analysis was performed using IBM SPSS Statistics version 25.

2.5 | Ethical approval

The study was approved by the Regional Committees for Medical and Health Research Ethics (REC number 33132). Informed consent to research participation was obtained from all participants.

3 | RESULTS

Figure 1 shows a flow chart diagram of the inclusion process. In total, 392 patients were included in the data analysis, of whom 319 underwent a primary surgical resection and 73 were operated with a diagnostic biopsy only. 7 out of 392 patients had no sign of tumour cells on histopathology. In those cases, histopathology showed either a normal brain tissue or inflammatory changes suggesting an inflammatory rather than a neoplastic disease.

As seen in Table 1, the overall sensitivity, specificity and diagnostic mismatch rate of a clinico-radiological diagnosis for all tumours were found to be 85.8%, 97.7% and 4.0%, respectively. The same diagnostic accuracy measures for gliomas only were found to be 82.2%, 97.2% and 5.6%, respectively.

In the reported tumour type subgroups, the sensitivity and specificity of clinico-radiological diagnosis varied between 65.0%-94.9% and 96.5–99.2%, respectively. The preoperative diagnosis with the highest sensitivity was observed for metastases and the lowest for 'other tumours'. The preoperative diagnosis with the highest specificity was observed for lymphomas and the lowest for diffuse low-grade gliomas and metastases. The diagnostic mismatch varied between 1.3 and 6.6%. The highest diagnostic mismatch was observed for high-grade gliomas and the lowest for lymphomas. The positive predictive value of high-grade glioma diagnosis was 0.95 reflecting that when the diagnosis of high-grade glioma was expected

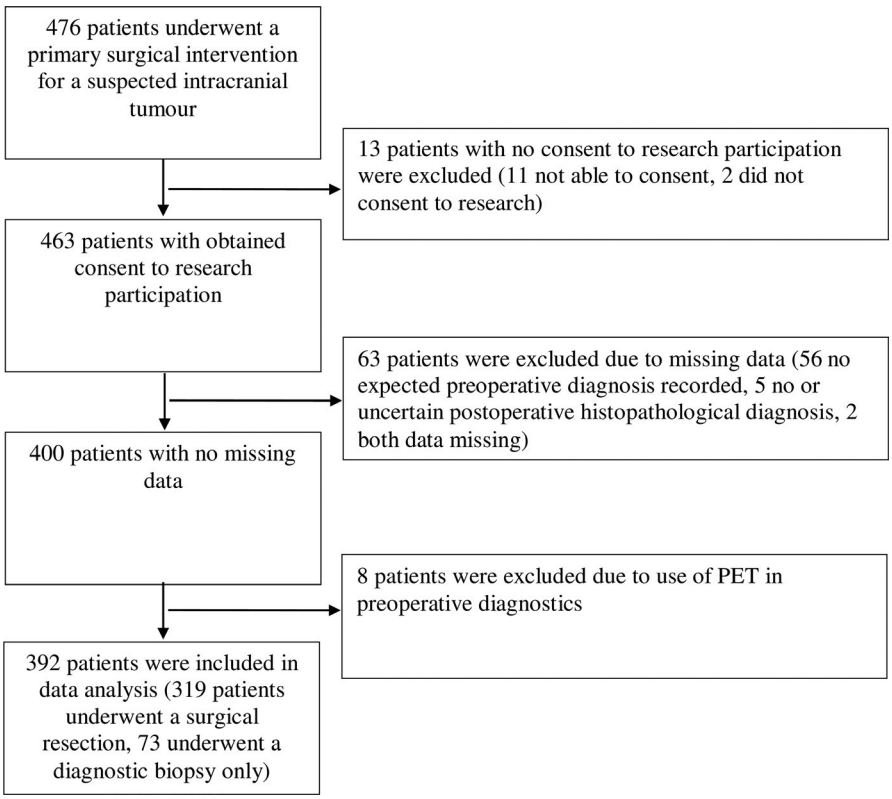

FIGURE 1 Flow chart of the inclusion process

TABLE 1 Clinico-radiological diagnostic accuracy in patients undergoing primary surgical interventions (tumour resection or biopsy)

	n	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value	Diagnostic mismatch (%)
High-grade gliomas	123	82.9	98.1	0.95	0.93	6.6
Diffuse low-grade gliomas	23	78.3	96.5	0.58	0.99	4.6
Metastases	79	94.9	96.5	0.87	0.99	3.8
Meningiomas	88	85.9	97.6	0.92	0.95	5.4
Pituitary adenomas	45	93.3	98.6	0.89	0.99	2.0
Lymphomas	6	66.7	99.2	0.57	0.99	1.3
Other tumours	21	65.0	97.6	0.59	0.98	4.1
All gliomas	146	82.2	97.2	0.87	0.96	5.6
All tumours	385[a]	85.8	97.7	0.86	0.98	4.0

[a]Seven patients had no sign of tumour cells on histopathology

preoperatively, this was confirmed histopathologically in 95% of the cases.

In patients who underwent diagnostic biopsies only, the overall sensitivity, specificity and diagnostic mismatch rate of a clinico-radiological diagnosis was 78.9%, 96.1% and 6.3%, respectively.

A subanalysis of the diagnostic accuracy for differentiation between diffuse low-grade gliomas and high-grade gliomas only was performed. The analysis included 146 histopathologically confirmed WHO II-IV gliomas. In 13 cases, a diagnosis of non-glioma was suspected preoperatively. In the remaining 133 cases, accuracy of 90.2% was achieved for differentiation between diffuse low-grade gliomas and high-grade gliomas.

Table 2 presents the frequency and type of misdiagnosed pathology in cases where the preoperative clinico-radiological diagnosis differed from the postoperative histopathological diagnosis for all primary surgical interventions. Figure 2 shows examples of cases with diagnostic mismatch.

The most common misdiagnosed tumour type among false-positive and false-negative cases was low-grade glioma when high-grade glioma was suspected and high-grade glioma when low-grade glioma was suspected.

4 | DISCUSSION

Our study suggests that the accuracy of preoperative clinico-radiological diagnoses of intracranial tumours is high and can provide benchmark data for future studies on non-invasive diagnostics of brain tumours.

TABLE 2 Cases with diagnostic mismatch (all primary surgical interventions)

	Cases with diagnostic mismatch n (%)	Frequency and type of misdiagnosed pathology	
		False positives	False negatives
High-grade gliomas	26 (6.6)	3 low-grade gliomas 1 metastasis 1 no tumour	10 low-grade gliomas 6 metastases 2 meningiomas 2 lymphomas 1 other
Diffuse low-grade gliomas	18 (4.6)	10 high-grade gliomas 2 others 1 no tumour	3 high-grade gliomas 2 others
Metastases	15 (3.8)	6 high-grade gliomas 2 lymphomas 2 no tumour 1 other	2 meningiomas 1 high-grade glioma 1 other
Meningiomas	21 (5.4)	2 high-grade gliomas 2 metastases 2 pituitary adenomas 1 other	2 pituitary adenomas 1 other
Pituitary adenomas	8 (2.0)	3 others 2 meningiomas	2 meningiomas 1 other
Lymphomas	5 (1.3)	2 high-grade gliomas 1 no tumour	2 metastases

There is limited literature on the current clinico-radiological diagnostic accuracy for intracranial tumours. The clinico-radiological diagnosis, considering factors such as patients age, tumour growth and previous medical history, may differ from a pure radiological diagnosis. A randomized controlled trial investigating high-grade glioma treatment found that mismatch between a pure radiological and histopathological diagnoses occurred in 23% of cases.[6] A multicentre randomized controlled trial investigating the effect of 5-ALA in resection grade of high-grade gliomas included only patients with typical radiological signs of glioblastoma, that is ring contrast enhancement, irregular tumour walls and tumour necrosis. Still, the histopathology of 10.6% of patients showed other tissue diagnoses, of which 38% and 21% were metastases and low-grade gliomas, respectively.[7]

A recent retrospective study investigating the accuracy of conventional MRI for the diagnosis of intracranial tumours, concluded that the MRI interpretation is generally accurate. The overall diagnostic error rate was 15.1%–27.4%. Similarly to our results, the diagnostic performance differed among tumour types, and gliomas and metastases were most frequently misdiagnosed for each other.[8] In this study, the authors excluded all patients with tumour-negative histopathology and evaluated the accuracy of a radiological diagnosis from radiological reports alone. The reports often included more than one differential diagnosis. When only one diagnosis was given in the radiology reports, the sensitivity and specificity for all tumours were 90.7% and 45.9%, respectively. The same diagnostic accuracy measures for gliomas only were 82.8% and 90.3%, respectively.

Many imaging techniques or sequences have been reported to increase accuracy of diagnostic imaging for intracranial tumours, including PET[9-11] and radiomics studies based on artificial intelligence.[12-14] In a study investigating the diagnostic accuracy of PET in patients with unclear brain lesions, the authors found that neoplastic lesions showed significantly higher (18)F-FET uptake than non-neoplastic lesions (NNL). They were able to diagnose an intracranial neoplasm with sensitivity of 57%, specificity of 92% and with 62% accuracy. The study found sensitivity of 80%, specificity of 65% and accuracy of 72% for the differentiation between high-grade and low-grade gliomas.[9] Sensitivity and specificity for the detection of a brain tumour were 87% and 68%, respectively in another study. The authors of the study found that gliomas had (18)F-FET uptake in 80% of World Health Organization (WHO) grade I, 79% of grade II, 92% of grade III and 100% of grade IV tumours. Although the sensitivity of (18)F-FET uptake is high, its specificity is limited by passive tracer influx through a disrupted blood-brain barrier and (18)F-FET uptake in non-neoplastic brain lesions.[10] The authors of a recent systematic review and meta-analysis on the performance of (18)F-FET versus (18)F-FDG-PET for the diagnosis and grading of brain tumours found that FET-PET demonstrated a pooled sensitivity of 94% and pooled specificity of 88% for the detection of neoplastic vs. non-neoplastic lesions. Furthermore, FDG-PET reached a sensitivity, specificity and accuracy of 60%, 91% and 74%, respectively for distinguishing between low- and high-grade gliomas. For FET-PET, they observed a sensitivity, specificity and accuracy of 80%, 82%

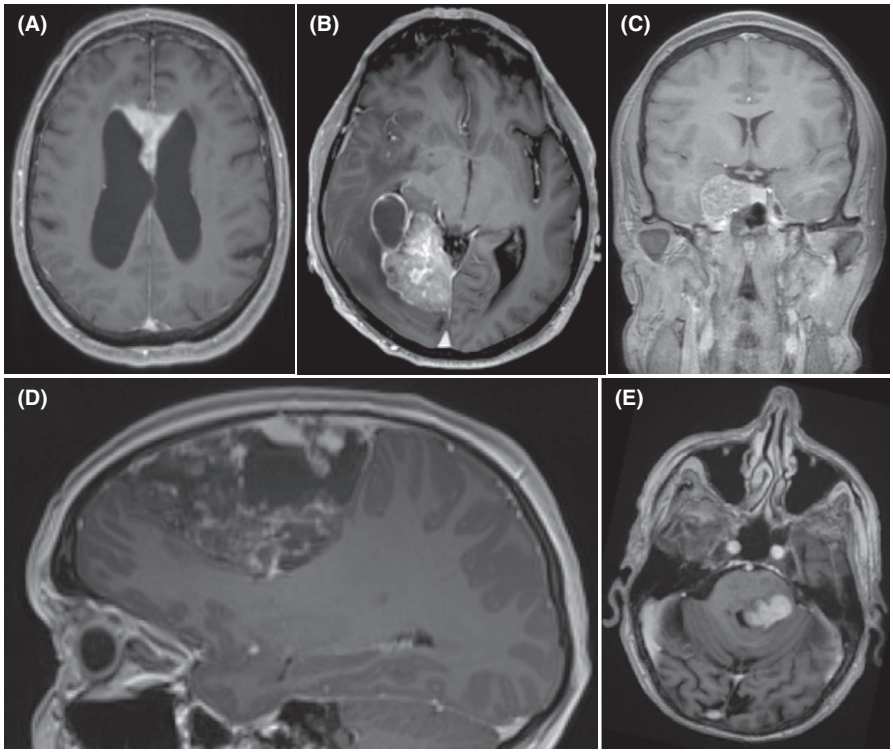

FIGURE 2 **Examples of cases with diagnostic mismatch.** (A) Periventricular location and a lack of surrounding oedema led to a preoperative estimated diagnosis of lymphoma. Histopathology showed a WHO IV glioma. (B) Dural attachment and intense rather homogenous contrast enhancement led to a preoperative diagnosis of meningioma. Histopathology showed a metastasis from a malignant neuroendocrine carcinoma. (C) Due to less intense contrast enhancement in the tumour than in the pituitary gland, a pituitary adenoma was suspected preoperatively. Histopathology showed a WHO I meningioma. (D) Sagittal view of a large frontal tumour with heterogeneous contrast enhancement, extra-axial appearance and some dural (tail) contrast enhancement. MR spectroscopy did not show any N-acetylaspartate, suggestive of non-neuronal tissue. The tumour had no surrounding oedema, and the patient had no other symptoms than papilloedema. The estimated preoperative diagnosis was a meningioma, but histopathology showed an oligodendroglioma. (E) Due to homogenous contrast enhancement, periventricular growth and a lack of surrounding oedema, a lymphoma was suspected preoperatively. Histopathology showed a WHO III anaplastic astrocytoma

and 81%, respectively.[11] Another systematic review concluded that the diagnostic value of amino acid PET imaging in suspected low-grade gliomas is difficult to interpret due to the lack of consistent results across studies.[1]

There are many promising reports on applying artificial intelligence for tumour grading.[15] The authors of a recent study achieved maximum accuracy of 92.9% or 98.3% for differentiating between four grades of gliomas using two different algorithms.[12] Another research group achieved 96.13% maximum accuracy for classifying between meningiomas, gliomas and pituitary tumours. The same authors reached 98% accuracy for differentiating between grade II-IV gliomas.[16] Another group found 87% accuracy, 89% sensitivity and 79% specificity when using machine learning algorithm for discrimination of metastases from gliomas, and 87% accuracy, 83% sensitivity and 96% specificity for discrimination between high-grade and low-grade gliomas.[14]

In comparison with the mentioned studies that used special radiological techniques, we present rather similar accuracy of a current clinico-radiological diagnosis for suspected intracranial tumours. There may be several explanations for this. First of all, in our real-life data the preoperative diagnoses were reached based on imaging but also clinical details of the patients, which would be particularly useful in differentiating between gliomas and metastases. Secondly, the preoperative diagnoses in our study were influenced by a team of multiple neurosurgeons and neuroradiologists that had discussed the medical history and imaging findings before surgery. Moreover, the results might be affected by possible differences in patient selection. Finally, it is possible that the add-on value of some of the mentioned novel techniques may not be so large after all, at least in unselected patients.

Histopathological diagnosis is still considered to be the gold standard for a diagnosis of intracranial tumours. However, indication for a tumour biopsy to reach a diagnosis among elderly, frail patients with many comorbidities is controversial, especially in the light of our results showing high accuracy of the clinico-radiological diagnosis of many brain tumours. Due to some degree of diagnostic mismatch in all assessed categories, one may argue that a certain diagnosis may always require a biopsy. Still, we present data from an unselected and consecutive patient series. If we had excluded all cases where the clinico-radiological diagnosis was uncertain at least to some degree, the accuracy of the preoperative diagnosis would have likely improved significantly.

Considering the large number of patients with suspected meningiomas treated with 'watchfull waiting', one might be particularly concerned about the reported diagnostic mismatch rate of 5.4% for the diagnosis of meningiomas in our study. In our department, only patients with symptomatic or growing meningiomas, or individual cases where the diagnosis of meningioma is particularly uncertain, for example in patients with other malignancies and a malignant radiological appearance of the intracranial tumour, undergo a tumour resection or biopsy. Therefore, the reported diagnostic mismatch rate for meningiomas is representative of those highly selected cases rather than all patients with stable and asymptomatic radiologically diagnosed meningiomas.

Finally, brain biopsy is not without risks and its accuracy is not perfect. The mortality and morbidity of brain biopsies are <1% and 3.5%, respectively.[17] The diagnostic yield of stereotactic brain biopsy is approximately 90%.[18] Therefore, some patients need to undergo more than one biopsy to obtain a tissue diagnosis. Moreover, considering the fact that gliomas are known for their regional histological heterogeneity, histopathological diagnosis derived from a secured tissue, may not be entirely accurate. In a case series where a biopsy of glioma was followed by its surgical resection within a short period of time (<3 months), the established histopathological diagnoses differed in as many as 38% of the cases.[19] In a study where the authors reviewed 500 brain or spinal cord biopsy cases that were submitted to their centre for a second opinion, they found some degree of disagreement between the original and reviewed diagnoses in 42.8% of cases.[20] These results demonstrate that an inaccurate histopathological diagnosis after biopsy is still a genuine challenge, especially in heterogeneous lesions.

5 | CONCLUSIONS

The current accuracy of a preoperative clinico-radiological diagnosis of brain tumours is high. Although special sequences, analysis algorithms or imaging methods may add diagnostic certainty in difficult cases, future non-invasive diagnostic methods need to outperform our results in order to add much value in a routine clinical setting in unselected patients. Our findings are also relevant when estimating the risks and benefits of diagnostic biopsies in management of patients with intracranial tumours not considered eligible for tumour resection.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Paulina Majewska https://orcid.org/0000-0002-7932-6497

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