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Research Article

The Reproducibility of the Use of Digital Pathology and Radiomics in Intraoperative Diagnosis in Neuropathology: The Experience of a Single Center

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Abstract

The relationship of pathology, represented by the rise of telepathology in the late 1960s, has evolved into the era of artificial intelligence assisted digital pathology. This field includes the application of digitized specimens to visualize, share, and conclude pathology information in a digital space. Radiomics, the extraction of quantitative features from radiological images, has been an effective technique in neuropathology and intraoperative diagnosis. Ongoing technological advancements, these methods offer enhanced diagnostic accuracy and expedited treatment decisions. However, evaluating their accuracies and reproducibility relative to traditional methods remains controversial. By and large, a group of specific techniques used for diagnosis, prognosis, and prediction of intracranial lesions. Digital pathology enables pathologists to assess radiologic images concurrently with frozen section slides, promoting real-time collaboration and informed decision-making regardless of geographical barriers. Our study investigates the reproducibility of digital pathology, AI, and radiomics in neuropathology and intraoperative diagnosis. By analyzing case studies, literature, and data analysis, this research sheds light on factors impacting the reliability of these techniques. Ultimately, this study aims to emphasize potential benefits and limitations of these technologies, mentioning their aspects to clinical practice.

Keywords: Artificial Intelligence; Digital Pathology; Intraoperative Diagnosis; Neuropathology; Radiomics

Abbreviations

WHO: World Health Organization; CNS: Central Nervous System; H&E: Hematoxylin and Eosin; AI - Artificial Intelligence

Introduction

The intersection of technology and pathology has a long-standing history, dating back to the rise of telepathology in the late 1960s. Since then, this interaction has improved remarkably, resulting in the development of artificial intelligence (AI). AIassisted digital pathology is a branch of pathology that relies on digitized specimens to visualize, comment, share, and conclude pathology information in a digital environment [1-3]. In the last years, radiomics consisted of high-throughput extraction of quantitative features from radiological images, has shown a superb development as a promising tool in both neuropathology and intraoperative diagnosis [4]. With the assistance of technological opportunities, more accurate and faster diagnoses, and more precise treatment decisions have improved [5]. Its reproducibility and accuracy should be tested, and compared with classical method, traditional light microscopy [6-8]. For diagnostic, prognostic, and

predictive purposes of intracranial lesions, specific methods are used in literature [9,10]. Some selected cases, the sole removal of the brain mass can achieve treatment. But in some others an intraoperative biopsy may be performed for diagnosis that will lead further steps of treatment.

Intraoperative consultation (frozen section), which is a common method as an invaluable intraoperative diagnostic technique. By definition it can be actualized as either by freezing the fresh tissue, making sections and evaluating sections by staining. Pathologists can use the cytology techniques also for microscopic evaluation by depending on tissue characteristics they are working on [11-13]. This procedure involves using a cryostat, an instrument that freezes and cuts the tissue into microscopic sections. This quick freezing procedure supplies a firm medium for cutting thin slices [14]. The material is taken into the macroscopy chamber after confirmation. It is prepared as three slides: one of them is an imprint (smear) slide, and the remaining two are squash slides. When the slides are prepared, they are stained with Hematoxylin & Eosin dye. Slides that are ready to be examined in a bright field optic microscope. Glass slides are scanned by device and automatically transferred into the patient's file with the help of protocol number. The pathologist uses that number to reach the images of slides and make the diagnosis.

In pathology, widely used radiomics in an auxiliary technics analyzing medical images for the diagnosis and prognosis of diseases. The texture and other features of an virtual image by radiomics can pave the way of pathologist to distinguish different types of tissues and lesions and even predict patient outcomes. Radiomics enhances the speed and efficiency of intraoperative diagnosis, which is critical in surgical settings. By automating the analysis of radiological images using AI algorithms, radiomics can provide real-time feedback to pathologists, allowing them to make more conscious decisions during the course of surgery [15-17].

Aim

The prominent idea of this research aims to explain the reproducibility of digital pathology, Artificial Intelligence, and radiomics in neuropathology and intraoperative diagnosis. Among the research goals are to define the elements that may have an effect on the reproducibility of these techniques. It provides suggestions for improving their reliability in clinical settings with the help of reviewing the literature by analyzing data and comparing case studies. Finally, the aim of this research is to develop our understanding of the possible benefits and limitations of these technologies in neuropathology and intraoperative diagnosis. So it promotes their responsible use in clinical settings.

Materials and Methods

In Yeditepe University Koşuyolu Hospital, intraoperative tissue evaluations performed in 966 cases between 2018-2022. Distribution of these cases annually is depicted in Table 1. Of the 966 selected patients, only neuropathology cases included, and the study persevered on 418 (43%) cases. Recent advances and developments in digital pathology softwares are increasingly taking place among pathologist practice. Use of digital pathology, AI, and radiomics in neuropathology and intraoperative diagnosis have the potential to develop the field by providing better diagnostic accuracy and improving treatment decisions. To investigate their utility in clinical settings, the reliability and reproducibility of these technologies should be carefully selected. Frozen and paraffin sections were evaluated thoroughly in all 418 cases.

Years	Number of Neuropathological Frozen Sections	Total Number of Frozen Sections
2018	87	179
2019	83	176
2020	90	194
2021	65	207
2022	93	210

Table 1: Years Number of neuropathological frozen sections, total number of frozen sections.

In our study, the frozen section and paraffin block results of 418 cases that received a diagnosis were compared. This comparison was evaluated with 7 different mismatch parameters. These parameters are: (Table 2)

- Tumor Upgrading
- Tumor Downgrading
- Histogenetic difference

- Histogenetic difference + Tumor Upgrading
- Histogenetic difference + Tumor Downgrading
- False positive (FP)
- False negative (FN)

Frozen section method

Upon arrival of the frozen sample, the name is double-checked on the container containing the material and the pathology request form that bear a unique barcode. The date and time of arrival noted on the pathology request form. Department secretary receives the sample signs and their name and surname on the relevant section of the request form. A photo of the pathology request form is taken and sent to the neuropathologist via WhatsApp. Immediately after that, our instructor is called via phone call to inform the frozen sample's arrival. A frozen number is given to the sample. (This number may vary from institution to institution.) A frozen record is dedicated in the relevant section of the hospital operating system. The frozen sample with the assigned number is taken to the macroscopic examination station. The necessary materials for the preparation stage are 3 slides, alcohol-filled vials, fine-tipped forceps, a ruler, a pencil, and a scalpel. The dimensions (length x width x depth) of the material is measured in cm using a ruler and written down. Then, the color, consistency (soft/elastic/hard), and texture of the material are noted on the back of the pathology request form, after being palpated by hand. The pathology secretary writes this description on the frozen report. One imprint and two squash preparations were prepared.

Three consecutive glass slides are selected and furnished with specific quates in each one. Frozen numbers, which the secretary has already recorded, and "imprints" for one slide and "squash" for the other two slides are written on the slides using a pencil. The tissue held with fine-tipped forceps, and the first smear prepared by rubbing the tissue in an "S'' shape on the slide labeled "imprint" and then immediately placing it into the alcohol-filled vial without delay. For the squash slide, a tiny piece of tissue is cut with a scalpel and topped on the slide with forceps. The other squash slide placed on top of tissue. The tissue smeared between the two slides. Afterwards, slides gently is pressed, and pulled out in opposite directions. Finally, the two squash slides dropped into the alcohol-filled vial without any delay.

After the smears are stained H&E process. During this step, the slides in the alcohol-filled vial are: **-** Washed with water. **-** Placed in Hematoxylin stain and left for approx. 30 seconds to 1 minute. **-** Washed under running water until the stain is gone. **-** Placed in alcohol for 10 seconds. **-** Placed in Eosin stain for approx. 15-30 seconds and washed with water. **-** Placed first in alcohol and then in acetone. The slides removed out acetone are left to dry in a 65-degree incubator. The dried specimens are covered with adhesive substances (balsam, consul mount, Entellan) and covered with a lamella for examination under a microscope. The same procedures are applied to hard tissues as well. However, since hard tissues do not leave cells on the glass slides and do not provide good results when squashed, sections are taken from hard tissues using a cryostat.

The necessary materials for this process are forceps, cryomatrix gel, plate, alcoholfilled container, glass slides, and a pencil. First step is adequate amount of cryomatrix gel is plastered on plate. Second step is , placement of tissue is on gel using forceps. Then plate is placed in the quick-freezing section of the cryostat. Once the gel has reached sufficient coldness and deep frozen, it is placed in the relevant section of the frozen device. Fourth step is the "trim" option selected from the panel of the frozen device and adjusted to 30 microns for section preparation. Fifth step is cryostat trimming that pursues until it reaches the target tissue. After the tissue is apparent, the "section" option is selected from the front panel of cryostat. Sequential 5 microns thickness is optimal for sectioning. Tissue section is adhered to glass slide and placed in an alcoholfilled container. After completing section phase, tissue is H&E stained, and cover slipped as in the above protocol.

Digital pathology

Imprint, squash, and sectioned material prepared from tissue and made ready for examination under a microscope means it is ready for scanning. The prepared glass slide placed in the tray inside the Aperio CS2 device connected to the computer. The program specific to the device opened on the computer, and the necessary parts to scanned on the glass slide are selected. All informative data (frozen number, imprint, squash, and section information written on the glass slides) was recorded. The scanning process has started. The image of the scanned lamella transferred to an application called SECTRA. Selected image, and protocol number of patient was entered on hospital information system. The lamella image appended to the patient's file via the protocol number. The doctor can then access the image and make a diagnosis. All the procedures completed in a minimum of 10-15 minutes. The pathologist who was requested to make an intraoperative diagnosis examines the radiology report of the case while the technician is performing the frozen section and loading it into the digital environment. After obtaining preliminary information with the radiology report,

the pathologist evaluates tissue image, makes a diagnosis, and prepares the report. Data extracted from radiologic images and MR reports in advance enhances higher reproducibility for each case. Therefore, pathologists and neuroradiologists are members of the diagnostic team while surgery is underway. The effectiveness and efficiency of this cooperation affects the precise and reliable diagnostics is also a subject of discussion in this preliminary study.

Results and Discussion

From the time the section taken for intraoperative diagnosis was sent to the pathologist, the shortest diagnosis time in the cases in this study was 7 minutes and the longest was 83 minutes, with an average time of 22 +/-9.26 minutes (Figure 1).

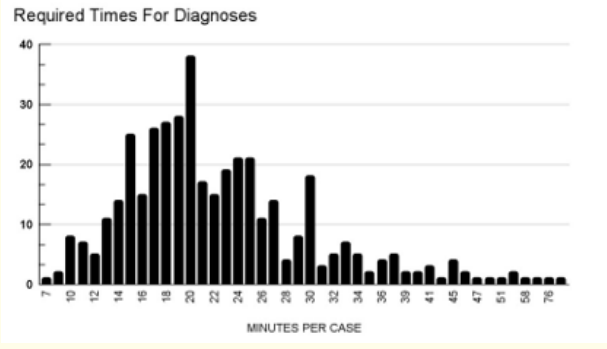

Figure 1

Variables	Number of Cases	Percentage	Percentage among Mismatches
Tumor Upgrading	12	2.8%	13.2%
Tumor Downgrading	14	3.3%	15.5%
Histogenetic Different	36	8.6%	39.5%
Histogenetic Difference + Tumor Upgrading	8	1.9%	8.9%
Histogenetic Difference + Tumor Downgrading	14	3.3%	15.4%
False Positive	3	0.7%	3.2%
False Negative	4	0.9%	4.3%

Table 2: Variables Number of cases Percentage, Percentage among mismatches.

Among intraoperatively diagnosed 966 cases, 418 (43%) were neuropathology cases. Frozen section, and paraffin section diagnoses were compared. Of 448 neuropathology cases performed, there are 12 cases where the degree of tumor increases compared to the diagnosis of frozen section and paraffin section diagnosis; the ratio of these cases to total cases is 2.8%, and accounts for 13.2% of incompatibilities. There are 14 cases with a decreasing degree of tumor(downgrading) in the same criterion; the ratio of these cases to neuropathology cases is 3.3%, accounting for 15.5% of mismatches. There are 36 cases with histogenetic difference between frozen section diagnosis and paraffin section diagnosis. So, the ratio of these cases to neuropathology cases is 8.6%, and accounts for 39.5%. Histogenetic difference is the most common among the detected mismatches. It roots fro the fact that the current WHO CNS-Tumors classification has changed. There are 8 cases in which the degree of tumor is increased along with the histogenetic difference when comparing frozen and paraffin sections. Therefore, calculated ratio of these cases to total neuropathology cases wa 1.9% and accounts for 8.9% of incompatibilities. For the same comparison, there are 14 cases in which the degree of tumor inconsistencies was due to histogenetic difference. So, the ratio of these cases to total neuropathology cases was 3.3% and accounted 15.4% of mismatches. Histological differences, such as distinction between glioblastoma and oligodendroglioma, were not accepted as mistakes. The similarity in tumor grades and the ability to detect the tumor were crucial for intraoperative diagnosis. These types of errors may not affect the treatment.

There are 3 cases characterized as tumor tissue in the frozen section, but no tumor tissue was present in the subsequent paraffin section. These cases account for 0.7% of neuropathology cases and 3.2% of incompatibilities. There are 4 cases in which no tumor tissue was present in the frozen section, only tumor diagnosed in the paraffin section. These cases accounted for 0.9% of the total neuropathology cases and encountered as 4.3% of the mismatches. False positive and false negative histopathologic differences compared (Table 3, Table 4).

False Negatives	
Intraoperative Diagnosis	Paraffin Section Diagnosis
Necrosis	Anaplastic Oligodendroglioma
Radionecrosis	Oligodendroglioma
Chronic Abscess	Glioblastoma
No Tumor	Ganglioglioma

Table 3: Comparisons of Intraoperative diagnosis and paraffin section diagnosis of false negative cases.

False Positives	
Intraoperative Diagnosis	Paraffin Section Diagnosis
Low Grade Neoplasm	No Tumor
Non-germinomatous Neoplasm	Lymphoplasmacytic Proliferative Inflammation
High Grade Glial Tumor	Lymphocytic Vasculitis

Table 4: Comparisons of intraoperative diagnosis and paraffin section diagnosis of false positive cases.

The first case, initially diagnosed intraoperatively as necrosis but later diagnosed as anaplastic oligodendroglioma in the paraffin section, resulting in a false negative result, is attributed to a sampling error. In the case of anaplastic oligodendroglioma, the sample taken from the necrotic area in the center of the tumor, pathologist misdiagnosed as necrosis. It is impossible to determine the cause of the necrosis, whether it is due to tumor-originated necrosis or not.

The second false negative case was initially diagnosed as radionecrosis intraoperatively but later diagnosed as oligodendroglioma in the paraffin section. The reason for this mistake is also a sampling error. Radionecrosis commonly occurs in patients after radiation therapy. In this case, the tumor sampling site had undergone necrosis due to radiation therapy, which prevented the pathologist from observing the tumor cells.

The third false negative case was initially diagnosed as a chronic abscess intraoperatively but later diagnosed as glioblastoma in the paraffin section. The central necrosis of glioblastoma can trigger chemotaxis. Inflammatory cells like neutrophils and polymorphonuclear cells, following chemotaxis, can mislead the pathologist into diagnosing a high-grade glial tumor as an abscess. It is difficult to distinguish between a chronic abscess and an inflamed high-grade glial tumor section. This error could have been avoided if the samples have been collected from various parts of the tumor.

In the last false negative case, tumor cells were not detected during the intraoperative diagnosis, but the paraffin section diagnosis revealed ganglioglioma (Figure 2). Some types of glioneuronal tumors bear a close histological resemblance to brain tissue. To prevent such errors due to this similarity, pathologists should examine radiological images. Giving a diagnosis of "no tumor" without reviewing radiological images is entirely a pathologist's mistake. In cases like these glioneuronal tumors radiological imaging is crucial for preventing pathologist errors.

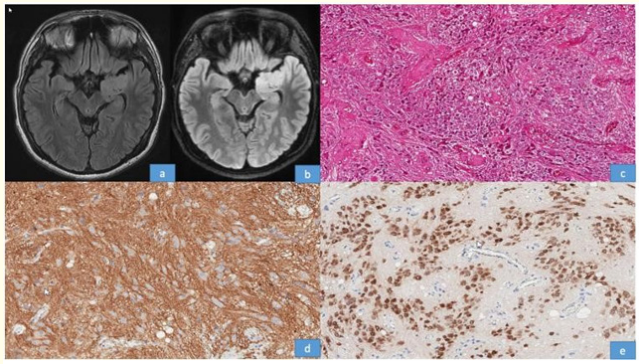

Figure 2: False negative case which is a. FLAIR-T2 heterogeneous hyperintense in the left posterolateral medulla oblongata, heterogeneous hypointense on T1-weighted examination, a lesion with a mass effect with minimal edema area around it showing ring-style contrast involvement after intravenous contrast material, the widest diameter of which measured 13 mm, was detected. b. 3D FLAIR revealed a lesion of 13 mm in diameter. c. Densely packed ganglion cells with prominent nucleoli and abundant perikarya. (H&E, x200) d. Large dysplastic ganglion cells immunoreactive to synaptophysin. (Synaptophysin, x200, biotinylated streptavidin complement) e. Large dysplastic ganglion cells immunoreactive to nuclear Neu-N. (Neu-N, x200, biotinylated streptavidin complement)

Overall 3 cases among false positive cases was interpreted as low grade neoplasm, non-germinomatous neoplasm and high grade glial tumor in intraoperative diagnosis and paraffin sections resulted in tumor negative, Lymphoplasmacytic Proliferative Inflammation and lymphocytic vasculitis respectively.

The probable cause of the first false positive result, in which there is no tumor in the paraffin section diagnosis but a low grade neoplasm in the intraoperative diagnosis, is the pathologist's error due to personal observations which is completely subjective.

Another false positive result was lymphoplasmacytic proliferative inflammation on paraffin sections as diagnosed a non-germinomatous neoplasm during surgery, a well defined common error. Germ cell tumors bear an abundance of lymphocytic infiltration. Therefore, correct diagnosis is dependent on biopsy site.

In the third false positive case, intraoperative diagnosis was a high grade glial tumor. But, paraffin sections showed lymphocytic vasculitis (Figure 3). This case should alert the medical team, since the mode of therapy and life expectancy will change definitely. If the infiltration damages the endothelium in lymphocytic vasculitis, local ischemia and infarction occur due to thrombosis. Although the necrosis seen in intraoperative diagnosis seems to be caused by high grade glial tumor, it is most likely caused by infarction. On MRI, necrosis in the tissue is not a clue for glial tumors, but vasculitis should take part always in the differential diagnosis.

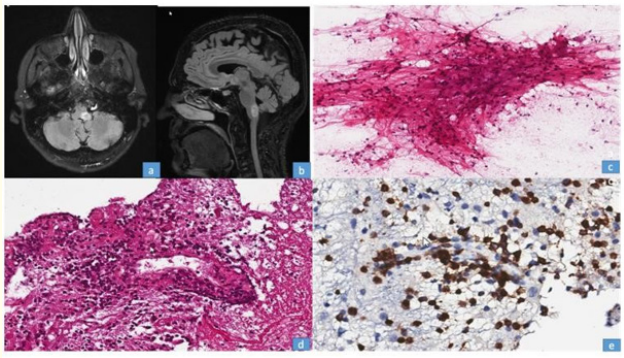

Figure 3: a. False positive case: Axial section: FLAIR-T2 heterogeneous hyperintense in the left posterolateral medulla oblongata, heterogeneous hypointense on T1-weighted examination, a lesion with a mass effect with minimal edema area around it showing ring-style contrast involvement after intravenous contrast material, the widest diameter of which measured 13 mm, was detected. b. Sagittal section: FLAIR-T2 heterogeneous hyperintense in the left posterolateral medulla oblongata, heterogeneous hypointense on T1-weighted examination. c. Squash preparation showing hypercellularity, atypia and capillaries interpreted as a high grade glial tumor. (HE, x200) d. Intense intramural and perivascular CD3+ lymphocytes consistent with vasculitis. (HE, X400) e. Intense lymphocytic infiltrating vascular wall and around consistent with vasculitis (CD3, X400, Biotinylated streptavidin complement.).

As a summation, there are 4 false negative and 3 false positive cases in our study. The main reason for false interpretations is limited samples. The intraoperative diagnoses are often based on a small sample of tissue, such as frozen sections. This limited sample may not fully represent the entire lesion, leading to misinterpretation and potential false results. Other reasons can be sampling errors, tissue artifacts, heterogeneity, pathologist bias, tissue changes and complex cases. Given these challenges, pathologists must carefully consider the context, clinical information, and potential limitations when providing intraoperative diagnosis. Collaboration with surgeons, using digital pathology and radiomics effectively, communication of uncertainties, and a comprehensive approach to diagnosis can help minimize false results and improve patient care. Increasing numbers of false negative cases directly impacts sensitivity of the diagnostic method. On the other hand, numbers of false positives have a negative influence on specificity of the diagnostic method.

Overall accuracy was calculated as %98.4, specificity was calculated as %99, positive predictive value was calculated as %99.29, negative predictive value was calculated as %85 (Table 5).

Parameter	Value
Overall Accuracy	98.4%
Specificity	99%
Positive Predictive Value	99.29%
Negative Predictive Value	85%

Table 5: Diagnostic accuracy of intraoperative diagnosis.

Conclusion

The practice of intraoperative diagnosis as a part of medical interventions and surgical procedures holds a significant importance. This procedure involves the immediate assessment and analysis of samples, enabling surgeons to make quick decisions based on diagnostic findings during surgery. Also, it offers surgeons to modify their approach and techniques if needed, eventually leading to improved patient outcomes. Comprehending the histopathology and stage of the mass during the surgical procedure significantly augments the succession rates. Based on the diagnosis, a complete excision of the tumor could be choice of manipulation. Therefore, this particular data helps prevent unnecessary extension of the duration of the operation and reduces the likelihood of tumor

recurrence. Thereafter, it helps to avoid overt anesthesia exposure of patient and potential risks of surgery. Pathologists contribute to successful intraoperative consultations by integrating additive knowledge based on pathological characteristics of lesions and their clinical and radiological context. Furthermore, the practice promotes research and innovation because the data is able to be shared and saved for advanced medical understanding.

The use of intraoperative diagnosis in neurosurgical cases holds a greater significance when compared to other surgeries due to the complex and sensitive nature of the nervous system. Even minor misleading during neurosurgical procedures can lead to irreversible damage and give rise to long-term disabilities or even death. After the removal of the tumors the follow-up treatment is tailored specifically for each tumour. These factors signify the importance of definite diagnosis of the neuropathological process. For example, determining whether the glioblastoma is wild or mutant during surgery may change the course of the surgery. If the tumor is IDH wild-type, resection can be an aggressive one. In contrary, if it is an IDH-mutant tumor, a limited resection could be applied. This type of tumor identification per surgery may affect the treatment modalities and patients' life expectancies.

Teamwork is essential in the realm of intraoperative diagnosis with digital neuropathology. This collaborative approach maximizes the expertise of a multidisciplinary team, including pathologists, surgeons, radiologists. The real-time nature of intraoperative diagnosis demands quick and well-informed decisions, and a team of experts working together can provide a more comprehensive and accurate assessment. Integrative data of the patient's medical sources, i.e., digital pathology images, radiomics, and medical data will be beneficial. Teamwork contributes quality assurance through peer review, reducing the risk of misdiagnosis and upholding the highest standard of patient care. Communication among team members ensures that everyone in the field cooperate in order to avoid misunderstandings and errors. In our study, pathologists checked radiomics, and reports to get the whole picture of each case. Almost they coordinated with other members of the team. In complkex situations, the team collectively discusses and decides on the best course of action, ensuring patients receive appropriate treatment and follow up. Overall, teamwork optimizes the diagnostic process by harnessing the collective expertise and resources of a diverse group of specialists.

In assessing the correlation between intraoperative diagnoses and definitive neuropathology diagnoses from other research studies, ranging 53% to 92% has been reported [18-20]. Modi et al. conducted at least 252 case studies, while Cheunsuchon et al. examined 698 cases. However, none of these investigations utilized digital pathology or artificial intelligence techniques. In distinctive studies, Kurdi et al. and Al-Ajmi et al. used radiomics, although instructions mainly provided by surgeons rather than direct interpretation of results. In contrast, our research relies on digital pathology, allowing pathologists to review radiomics data and frozen section slides instantly. This approach enhances diagnostic accuracy. As a consensus note, all of these studies revealed discrepancies between frozen section results and permanent sections did not adversely impact patient outcomes.

There are four false negative and three false positive cases in our study. The main reason for false interpretations is limited samples. The intraoperative diagnoses are relied on a small tissue sample, such as frozen sections. This limited sample may not fully represent the entire lesion, leading to misinterpretation and potential false results. Among other reasons can be sampling errors, tissue artifacts, heterogeneity, pathologist bias, tissue changes and complex cases. Given these challenges, pathologists must carefully consider the context, clinical information, and potential limitations when providing intraoperative diagnosis. Collaboration with surgeons, using digital pathology and radiomics effectively, communication of uncertainties, and a comprehensive approach to diagnosis can help minimize false results and improve patient care. The increasing numbers of false negative cases directly impacts sensitivity of the diagnostic method. On the other hand, numbers of false positives have a negative impact on specificity of the diagnostic approach.

The emergence of digital pathology marks a transformative change in intraoperative diagnostics, presenting a spectrum of promising advantages alongside unique challenges. One key advantage is the collaboration it enables among medical professionals via eliminating geographical barriers for consultation, and accelarate knowledge diffusion. This digital approach streams diagnostic workflows, enhancing efficiency by expediting slide preparation, scanning, and analysis. Digital archiving addresses storage challenges, ensuring easy retrieval of patient data and images, and also used as a valuable educational

resource. Additionally, recently developed quantitative analyses facilitated by sophisticated software tools enhances research capabilities and clinical decision-making. Integration with artificial intelligence will potentiate automating pattern recognition, and enhancing diagnostic accuracy. However, digital pathology presents challenges, including initial investment for infrastructure, technical complexities, regulatory compliance, data privacy, and the need for orientation training. Striking the right balance between its advantages and challenges is crucial. As digital pathology shapes the landscape of medical diagnostics, a detailed understanding is essential to harness its potential while addressing its conflicts.

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