

ORIGINAL ARTICLE

Concordance of Intra-Operative Frozen Section Consultation with Final Histopathology Interpretations of Surgical Specimens: A Retrospective Analysis.

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Abstract

Introduction: Intraoperative frozen section (IFS) consultation provides rapid histological assessment during surgery and can guide decisions regarding tumour diagnosis, margin status, metastasis, and other clinically relevant pathological findings. This retrospective study evaluated concordance between IFS consultation and final histopathology for surgical specimens at the University Malaya Medical Center (UMMC). **Methods:** A total of 109 IFS cases performed from January to December 2022 were reviewed. Concordance was defined as agreement between the IFS interpretation and final histopathology for the principal intraoperative diagnostic question, with final formalin-fixed paraffin-embedded histopathology used as the reference standard. Diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. **Results:** Of 109 cases, 106 (97.2%) were concordant, and three (2.8%) were discordant; all discordant cases were false negatives. Diagnostic accuracy was 97.2% (95% confidence interval [CI], 92.2%-99.4%), sensitivity was 89.7% (95% CI, 72.6%-97.8%), specificity was 100% (95% CI, 95.5%-100%), PPV was 100% (95% CI, 86.8%-100%), and NPV was 96.4% (95% CI, 89.8%-99.2%). Among the three discordant cases, two were attributed to interpretation errors and one to a technical error. **Conclusions:** IFS consultation demonstrated high concordance and diagnostic accuracy in this study. However, false-negative results remain possible, particularly in head-and-neck and lymph node specimens, emphasizing the importance of representative tissue sampling, optimal section quality, and cautious interpretation in minimizing discordant results. Continued institutional audit is recommended to support ongoing quality improvement.

Keywords: *Concordance; diagnostic accuracy; frozen section; histopathology; intraoperative consultation; surgical pathology*



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Introduction

Intra-operative frozen section (IFS), also known as "cryosection" or "intra-operative consultation," involves rapid freezing and sectioning of fresh tissue during surgery. It is an established component of surgical pathology practice in tertiary centres and provides real-time information that may guide the extent of surgery, margin assessment, evaluation of metastasis, and other immediate clinical decisions [1-4]. The value of IFS lies in providing a rapid and sufficiently accurate interpretation while recognizing that tissue quality and the time-sensitive intraoperative setting may limit morphological assessment.

Formalin-fixed paraffin-embedded (FFPE) permanent sections stained with Haematoxylin and Eosin (H&E) remain the reference standard for final histopathological interpretation [5]. Malaysian evidence on IFS performance is available but remains limited and heterogeneous. A multi-specimen audit from Johor reported high overall diagnostic accuracy, while Malaysian studies focusing on ovarian tumours and central nervous system lesions demonstrated organ-specific variation in concordance and diagnostic performance [3]. International studies likewise report generally high IFS performance, but accuracy varies according to specimen type, clinical indication, sampling adequacy, technical quality, and diagnostic complexity [2,4-5,8-9,11]. Thus, rather than an absence of Malaysian evidence, the relevant knowledge gap is the limited contemporary local evidence evaluating IFS across a broad range of surgical specimens and intraoperative indications in routine tertiary-care practice. Institution-specific audit is therefore important because discordance may arise from sampling, technical, interpretative, or communication factors and may influence intraoperative decision-making [6].

Accordingly, this retrospective study evaluated both agreement and diagnostic performance of IFS at UMMC. Concordance was assessed as agreement between the IFS interpretation and

final histopathology for the principal intraoperative clinical question, whereas diagnostic performance was evaluated separately using true-positive, true-negative, false-positive, and false-negative classifications and the derived measures of accuracy, sensitivity, specificity, PPV, and NPV. The study aimed to determine the concordance between IFS consultation and final histopathological interpretation across surgical specimens at UMMC and to describe factors associated with discordant cases.

Materials and methods

Ethical consideration

This retrospective analysis utilized archived histopathology reports and medical records from UMMC for cases performed between 1 January and 31 December 2022. Ethical approval was obtained from Universiti Selangor (UNISEL) (Ref No: UNISEL/FSK/RC/ET/1/2024/18) and UMMC (MREC ID N): 2023620-12569) before patient data and medical records were retrieved.

Data collection and analysis

The study included all patients who had IFS consultations from 1st January 2022 to 31st December 2022. This covered surgeries for cancer removal, suspicious metastasis, margin involvement, or other conditions requiring IFS consultation. Inclusion criteria were patients who underwent IFS consultation and received final histopathology interpretations within the study period. Exclusion criteria were patients who did not undergo IFS consultation or did not receive final histopathology interpretations due to insufficient tissue.

Electronic patient records were obtained from the I-Lab Laboratory Information System (LIS) and the I-Pesakit Hospital Information System (HIS). FS consultation records for 109 patients were collected, along with their final histopathology interpretations, including topography, and tissue/organ morphology. The data was entered into Microsoft Excel and organized by case ID,

tissue/organ type, FS consultation, final histopathology interpretations, concordant, discordant, and classification.

For each case, the IFS interpretation was compared with the corresponding final histopathology result. Concordance was defined as agreement between the two interpretations with respect to the principal intraoperative clinical question documented for the case, such as the presence or absence of a target lesion, margin involvement, or metastasis. Identical wording of the two reports was not required when the clinically relevant conclusion was equivalent. Discordance was defined as disagreement in this clinically relevant conclusion. Final FFPE histopathology was used as the reference standard. Concordance and discordance rates were calculated as the proportions of matched and mismatched cases, respectively, and were expressed as percentages.

Statistical analysis

Statistical analysis was performed using Microsoft Excel. For diagnostic classification, a positive result indicated the presence of the target pathological finding relevant to the intraoperative question, whereas a negative result indicated its absence. A true positive (TP) was a positive IFS result confirmed as positive on final histopathology; a true negative (TN) was a negative IFS result confirmed as negative; a false positive (FP) was a positive IFS result with a negative final histopathology result; and a false negative (FN) was a negative IFS result in which the target pathological finding was present on final histopathology. These categories (Table 1) were used to calculate overall diagnostic accuracy, sensitivity, specificity, PPV, and NPV (Table 2), with 95% confidence intervals reported for the diagnostic performance estimates.

Results

Distribution of sample

The 109 IFS cases represented 14 anatomical sites: breast (31, 28.4%), gallbladder (16, 14.7%), thyroid/parathyroid (13, 11.9%), head and neck (11, 10.1%), lymph node (11, 10.1%), skin (10, 9.2%), liver (5, 4.6%), gastrointestinal tract (4, 3.7%), chest (2, 1.8%), soft tissue (2, 1.8%), bone (1, 0.9%), lung (1, 0.9%), female reproductive organ (1, 0.9%), and kidney (1, 0.9%), as shown in Figure 1.

Concordance of intraoperative frozen section consultation

Among the 109 cases, 106 (97.2%) were concordant and three (2.8%) were discordant with the final histopathology interpretation (Figure 2). Of the 106 concordant cases, 80 were true negatives and 26 were true positives. All three discordant cases were false negatives, in which the target pathological finding was not identified on IFS but was subsequently demonstrated on final histopathology (Figure 3).

Analysis of all surgical specimens

IFS achieved an overall diagnostic accuracy of 97.2% (106/109; 95% CI, 92.2%-99.4%). Sensitivity was 89.7% (26/29; 95% CI, 72.6%-97.8%), specificity was 100% (80/80; 95% CI, 95.5%-100%), PPV was 100% (26/26; 95% CI, 86.8%-100%), and NPV was 96.4% (80/83; 95% CI, 89.8%-99.2%) (Figure 4). Among the three discordant cases, two (66.7%) were attributed to interpretation errors and one (33.3%) to a technical error. Because these percentages are based on only three discordant cases, they should be interpreted descriptively and with caution.

Analysis by anatomical sites

Site-specific comparison showed complete concordance (100%) between IFS and final histopathology in 12 of the 14 anatomical sites. Discordance occurred in two anatomical regions: one head-and-neck case and two lymph node

cases. The three discordant cases are summarized in Table 3.

Discussion

The principal finding of this study was a high concordance rate of 97.2% (106/109) between IFS and final histopathology. Concordance and diagnostic accuracy were treated as related but distinct measures. Concordance describes agreement between the IFS and final histopathology interpretations for the relevant intraoperative question, whereas diagnostic accuracy evaluates classification performance against final histopathology using TP, TN, FP, and FN results. In this binary dataset, overall diagnostic accuracy was also 97.2% because the 106 concordant cases comprised 26 TP and 80 TN results, while all three discordant cases were FN. Although the overall percentages were therefore numerically identical, sensitivity, specificity, PPV, and NPV provide additional information on diagnostic performance. The sensitivity of 89.7% indicates that false-negative results remain possible despite a specificity of 100%, emphasizing that a negative IFS result should be interpreted in the context of specimen adequacy, morphology, and the clinical question.

A strength of the present study is the inclusion of specimens from 14 anatomical sites rather than a single organ system. The observed overall diagnostic accuracy is consistent with findings reported in Malaysian studies, although although diagnostic performance has been shown to vary across different specimen types, including ovarian tumours and central nervous system lesions [3]. International institutional studies similarly report high overall diagnostic performance but show variation according to tissue type, indication, sampling adequacy, and technical quality [2,8]. The present study therefore contributes contemporary institution-specific evidence across a broad spectrum of surgical specimens and highlights local

diagnostic pitfalls that may not be apparent from organ-specific studies alone.

Only three cases were discordant, giving a discordance rate of 2.8%; all were false negatives. Two of the three discordant cases were attributable to interpretation error and one to a technical error. These absolute counts are more informative than percentages because of the very small denominator. Contemporary audits also identify interpretation, sampling, and technical factors as recurrent causes of frozen-section discrepancy [2,8]. Therefore, the error pattern observed in the present study should be regarded as descriptive and hypothesis-generating rather than representative of the wider population.

The head-and-neck group had one false-negative case. IFS demonstrated atypical cells in tissue from the left facial nerve trunk, whereas final histopathology confirmed malignancy in the attached fibrous tissue without invasion of the nerve bundles. Limited cellularity and freezing-related morphological distortion can make distinction between reactive atypia and neoplasia difficult. In diagnostically equivocal head-and-neck specimens, examination of additional or deeper levels and careful correlation with the gross and clinical findings may reduce false-negative interpretation [5].

Two false-negative cases occurred in lymph-node specimens. In one case, a small focus of atypical cells was subsequently confirmed as micrometastasis on permanent sections; the minute size of the focus and its exhaustion in deeper sections support a likely sampling limitation. The second case requires separate consideration: five lymph nodes were interpreted as negative on IFS, whereas intermediate-grade lobular carcinoma in situ (LCIS) was documented on final histopathology. Possible explanations include non-representative sampling between frozen and permanent sections, freezing-related morphological artefact, and interpretative difficulty. Variation in pathologist experience

may also contribute to such discrepancies; however, this could not be evaluated in the present retrospective study. The available records did not permit confirmation of which factor was responsible for this case, and these explanations should therefore be regarded as possible rather than definitive. This discordance reinforces the importance of representative sampling and cautious interpretation when the frozen-section findings do not fully correspond with the clinical or pathological context.

Discordance between IFS and final histopathology may arise from inadequate or non-representative sampling, freezing and sectioning artefacts, suboptimal staining, interpretive difficulty, and incomplete clinical or intraoperative communication [2,5,7,8]. Frozen sections generally provide lower morphological quality than FFPE sections, and the time-sensitive setting can further increase interpretive complexity [7]. When the findings are equivocal, obtaining additional representative tissue, examining deeper levels, seeking a second pathological opinion, or deferring a definitive diagnosis may be safer than over- or under-diagnosis.

Recommendation

Based on the observed discrepancies, several practical measures may reduce IFS errors: (1) clarify the clinical question, specimen orientation, and margin of interest with the surgical team before interpretation; (2) select representative tissue during gross examination and obtain additional or deeper levels when atypical cells or small foci are present; (3) optimize cryostat section thickness, freezing conditions, and rapid H&E staining to minimize technical artefacts; (4) correlate microscopic findings with the gross appearance and relevant clinical information; and (5) obtain a second-pathologist review or defer the diagnosis when uncertainty remains. Regular institutional audits comparing IFS with final

histopathology should be maintained as a quality-improvement activity [2,8].

Study limitations

This study has several limitations. First, it was conducted at a single tertiary centre, which may limit the generalizability of the findings to other institutions. Second, the retrospective design is susceptible to selection and information bias. Third, only three discordant cases were identified, limiting statistical power and preventing meaningful subgroup analysis of factors associated with discordance. Fourth, inter-observer variability among pathologists was not assessed. Fifth, surgeon-pathologist communication factors were not formally evaluated and therefore their potential contribution to diagnostic accuracy could not be quantified. Larger prospective multicentre studies are warranted to validate site-specific diagnostic performance and to examine modifiable contributors to discordance.

Conclusion

Intraoperative frozen section consultation demonstrated high concordance with final histopathology in this retrospective series, with a concordance rate and overall diagnostic accuracy of 97.2%. The three false-negative cases nevertheless illustrate that sampling, technical, and interpretative factors can affect diagnostic performance, particularly in challenging head-and-neck and lymph-node specimens. Careful representative sampling, optimal section preparation, effective surgeon-pathologist communication, and cautious interpretation of equivocal findings are important for maintaining diagnostic quality. Continued institutional audit of both concordance and diagnostic performance is recommended to support ongoing quality improvement.

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Authors' contributions

GK conceptualized and designed the study, developed the methodology, coordinated data collection, performed the statistical analysis, interpreted the findings, and drafted the original manuscript. DOBL provided expert input on histopathology and intraoperative frozen section interpretation, validated the frozen section and final histopathology data, and critically revised the manuscript for important intellectual content. NBB supervised the overall academic and scientific direction of the study, contributed to data analysis and interpretation, and critically reviewed and edited the manuscript.

All authors reviewed and approved the final version of the manuscript.

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Conflicts of interest

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

Table 1. Four diagnostic categories for statistical analysis.

Abbreviations	Category	Description
TP	True Positive	Target pathological finding correctly identified on IFS and confirmed on final histopathology.
TN	True Negative	Target pathological finding absent on both IFS and final histopathology.
FP	False-positive	Target pathological finding identified on IFS but absent on final histopathology.
FN	False-negative	Target pathological finding not identified on IFS but present on final histopathology.

Table 2. Formulas to calculate diagnostic accuracy

Statistical Analysis	Formula
Accuracy %	$\frac{(TP+TN)}{(TP+TN+FP+FN)} \times 100\%$
Sensitivity %	$\frac{TP}{(TP+FN)} \times 100\%$
Specificity %	$\frac{TN}{(TN+FP)} \times 100\%$
Positive Predictive Value (PPV) %	$\frac{TP}{(TP+FP)} \times 100\%$
Negative Predictive Value (NPV) %	$\frac{TN}{(TN+FN)} \times 100\%$

Table 3. Summary of discrepancy cases between intraoperative frozen section consultation and final histopathology interpretation.

No .	Case Id	Anatomical sites	Frozen section consultation	Final histopathology interpretations	Frozen section findings	Permanent section findings	Classification	Remarks
1	PT69 -2022	Head and neck	Left facial nerve trunk for tumour involvement: two cluster of atypical cells.	Left facial nerve trunk: positive for malignancy, in the attached fibrous tissue, no invasion into nerve bundles.	Negative	Positive	False-negative	Possible interpretative limitation related to limited cellularity and freezing-related morphological distortion.
2	PT20 -2022	Lymph node	Three lymph nodes are seen, in which one node shows a small focus (<1mm) of atypical cells with ductal formation. This focus of atypical cells exhausted and not detected in the deeper sections.	Three lymph nodes, one focus of micro-metastasis in one of the lymph nodes.	Negative	Positive	False-negative	Likely sampling limitation due to the minute (<1 mm) focus and exhaustion of atypical cells in deeper sections.
3	PT50 -2022	Lymph node	All 5 lymph nodes are negative for malignancy.	Intermediate grade LCIS	Negative	Positive	False-negative	Possible non-representative sampling and/or interpretative limitation. The exact cause could not be confirmed retrospectively.

LCIS = lobular carcinoma in situ; negative = absence of the target pathological finding; positive = presence of the target pathological finding.

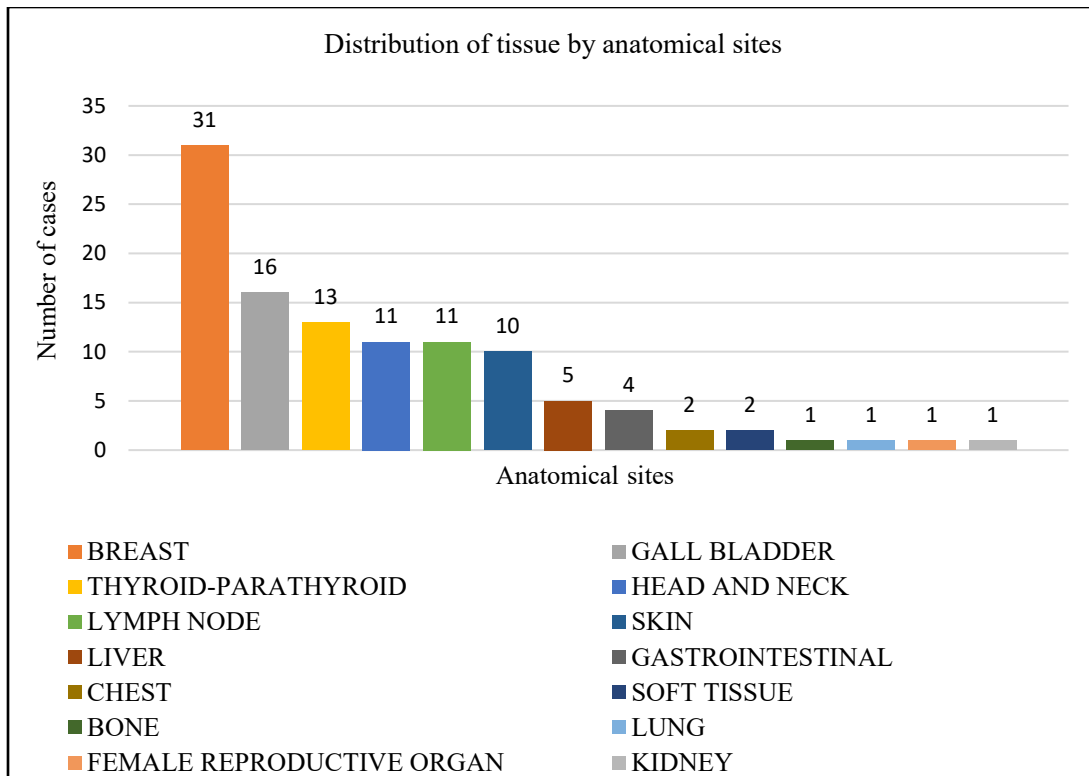


Figure 1. Distribution of frozen section specimens by anatomical sites.

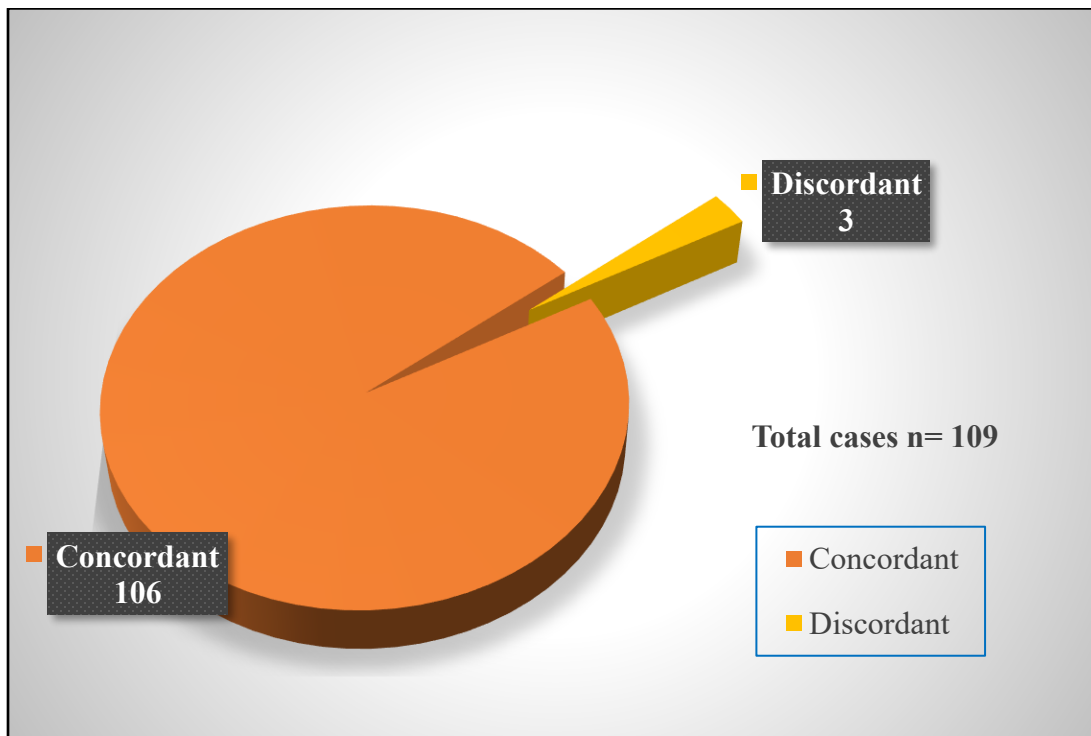


Figure 2. Concordance of intra-operative frozen section consultation for all surgical specimens.

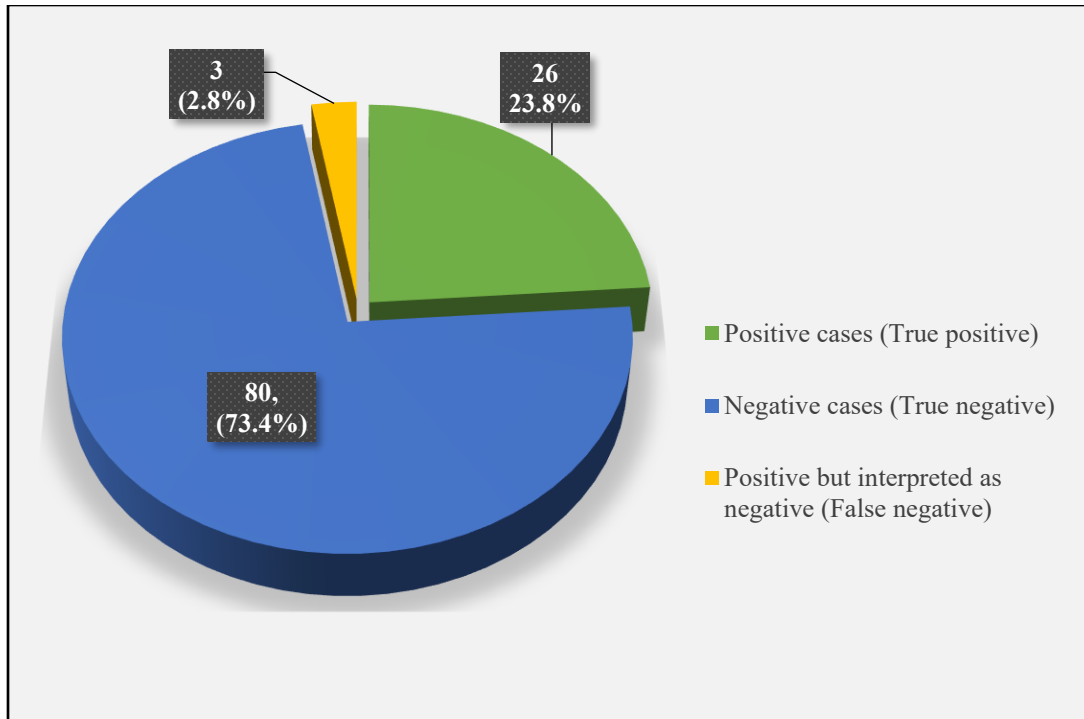


Figure 3. Distribution of intra-operative frozen section diagnosis for all surgical specimens.

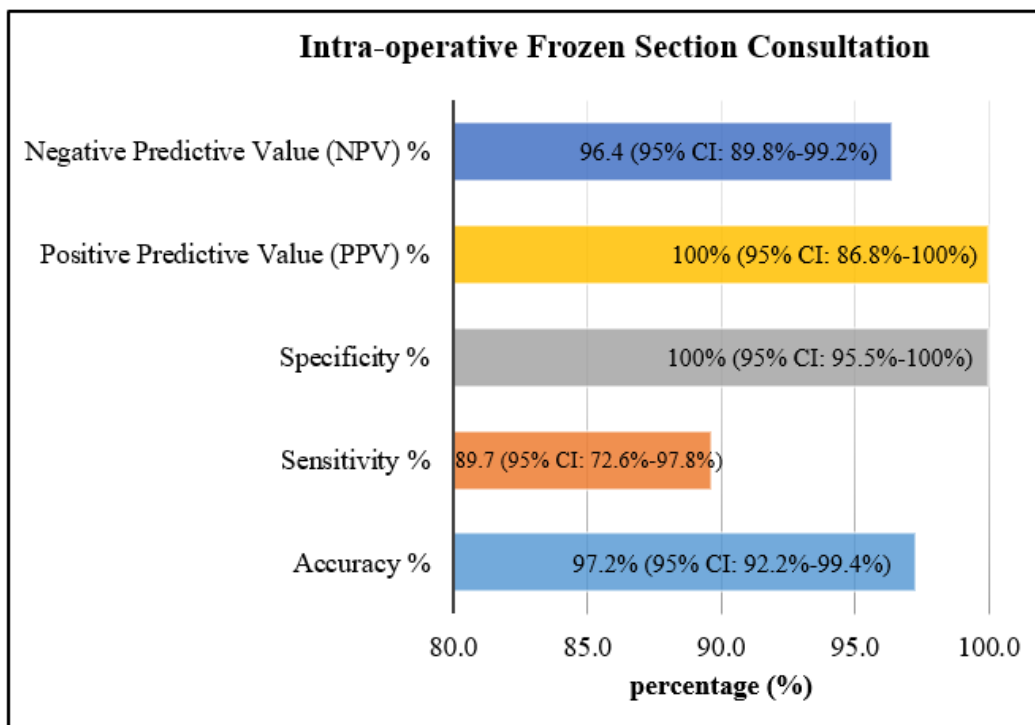


Figure 4. Error category and rate of intra-operative frozen section.

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