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REVIEW ARTICLE

# INTRA-OPERATIVE FROZEN SECTION CONSULTATION: CONCEPTS, APPLICATIONS AND LIMITATIONS

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**Intra-operative frozen section plays an important role in the management of surgical patients and yet it must be used prudently to avoid the indiscriminate usage of this important technique. As it is subjected to many limitations in comparison to the paraffin embedded tissue sections, this review aims to highlight the important concepts and principle of intra-operative frozen section consultation as well as discussing the limitations of this technique. This will then allow the end-users of this technique to be more informed and more selective in their decisions when requesting for a frozen section report.**

***Key words*** *: Frozen section, concepts, applications and limitations*

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## Introduction

Tissue specimen taken from a patient by doing a biopsy or an operation is usually assessed by the pathologist on the following day after the specimen is adequately fixed in formalin. However, occasionally surgeons need pathologic information more urgently thus, they will request for an intra-operative consultation on the tissue that is being taken out.

The examination is made while the patient is under anaesthesia on the operating table. This involves gross inspection and, if it is a larger specimen, some dissection will be performed. Depending on the surgeon's inquiry and what the pathologist felt is necessary; a frozen section (FS) may be performed on the specimen and examined under the microscope. The examination report will then be conveyed as soon as possible to the operating surgeon via telephone or intercoms and the result will greatly influence the surgeon's intra-operational decision.

FS may be one of the most important procedures perform by the pathologist during his practice. It is a difficult procedure. The pathologist has to arrive at a correct decision in a shorter duration under pressure based on his experience, judgement and the knowledge of his specialty and clinical medicine. He should also have a keen awareness of the limitations of the method as the patient's life is often dramatically influenced by his report.

Likewise, the operating surgeon should also realize the limitations of FS and it is imperative for him to make a prior appointment for FS and should always ask himself whether the results of the FS examination will in any way influence the surgical procedure. If the answer is no, then FS examination is not indicated (1).

### *Historical setting*

Lang apparently first employed the use of freezing to harden tissues in the nineteenth century. De Riemer in 1818 (2) made the pioneering effort of using FS technique for histopathological diagnosis. With the advancement of a modern reliable FS technique, intra-operative problems could be addressed immediately. Interestingly, this development placed the pathologist back on the operating room team where he originated. Early FS techniques were difficult and demanding, and required as much art as science (3). It is a tribute to men like Hazard, Stevenson, and Dockerty that the procedure was accepted at all (4, 5).

The technique introduced by Hazard and Stevenson in 1949 is fascinating compared to modern procedures using the cryostat, in which the

fresh specimen was placed in a fixative ten times its volume and heated to about just the boiling point. The fixed block is then froze between pieces of dry ice and cut at 10-15 um with a microtome knife. Each section is transferred to a beaker of distilled water. The section is then carried by a glass rod into a beaker containing carbol fuschsin and toluidine blue solution. After repeated washing in a series of beaker containing distilled water, the section is mounted onto a clean glass slide and immediately covered with 30% of sucrose or cane sugar and coverslipped. This preparation will last for one hour and if the coverslip was rimmed with Permount or flexible colloidan, the section could be preserved for several days.

Dockerty in 1953 introduced a slight variation to the Hazard and Stevenson technique in which namely he froze the tissue, unfixed, directly to a Spencer microtome and all movements of the 10-15 um section except the first one was by glass stirring rod.

Teloh HA (6) basically perfected the technique in 1957 by directly placing the unfixed specimen onto the freezing stage of the microtome and subjected the tissue to intermittent release of carbon dioxide gas causing rapid freezing, then cutting the tissue at 25um and stained using a drop of aqueous thionin solution. The thionin stain will usually fade away after 48 hours. For permanent section, Teloh suggested the section to be subjected to a few drop of 95% alcohol and stained using the haematoxylin and eosin (H&E) technique used for paraffin embedded tissue section. Slides prepared by this method can be preserved indefinitely.

***The modern technique of frozen section***

The development of a cryomicrotome or popularly known as cryostat in 1959, has revolutionized the FS technique. The cryostat is a refrigerated box containing a rotary microtome. The temperature inside the cryostat is about -20º to -30º Celsius. The attending technologist will then process the tissue section by freezing it with frozen aerosol sprays and put onto the cryostat for sectioning. Intra- and intercellular water is frozen to produce a hard matrix to enable slicing of the tissue. The tissue sections are cut and picked up on glass slide, which are then ready for staining.

The overall effect of the cryostat was two fold: (a) it made possible sections from quick-frozen, unfixed tissue in the 5-10um range of thickness and (b) the use of a modified H & E stain produced permanent preparation.

The whole process, if all goes well, takes about 5-10 minutes. This is just to prepare the slides; the time the pathologist takes to study at it under the microscope and arrive at a diagnosis is in addition to this.

In one study involving 700 laboratories world wide, it was found that 90% of FS block turn around times were within 20 minutes, measured from the time the pathologists received the FS specimens to the time that pathologists returned FS diagnoses to surgeons (7).

***The concept of frozen section***

At times during performance of surgical procedures, it is sometimes necessary to get a rapid diagnosis of a pathologic process. The surgeon may want to know if the margins of his resection for a malignant neoplasm are clear before closing, or an unexpected disease process may be found and require a definite diagnosis to decide what to do next, or it may be necessary to determine if the appropriate tissue has been obtained for further workup of a disease process. This can be accomplished through use of a FS. It should be noted that FS technique is actually studying the tissue morphology by using a modified H&E stains to arrive at a conclusion and does not apply any other supportive methods of evaluation such as special stains or immunohistochemical stains used in routine diagnosis.

***A rapid technique compared to the paraffin-embedded technique***

FS provides rapid gross or microscopic diagnoses that can guide intra- or peri-operative management of a patient, including identification of an unknown pathologic process, evaluation of adequacy of margins, identification of lymph nodes metastases and identification of tissue.

***Not as a replacement for the more established routine technique***

Even though FS provides rapid diagnosis, it should not be used to replace paraffin embedded tissue technique. Comparatively, FS is still inferior to the later due to its limitations. The sampling of specimen is limited and there are technical difficulties of getting good quality sections and staining of tissue; which will all influence the interpretation of the section by the pathologist.

***An elective procedure***

FS should not be treated as an emergency

procedure due to the difficulty of the procedure and the availability of the technician. Therefore, an appointment at least a day before the operation need to be made with the pathologist. In most laboratories, FS is not done after office hours.

***Close cooperation and rapport between surgeon and pathologist***

Close cooperation between the surgeon and the pathologist is required if a meaningful frozen report is to be achieved. Preferably, the case should be discussed beforehand between the surgeon and the pathologist. The pathologist should not be treated as a mere technician and all the relevant information must be conveyed for the benefit of the patient. This information must be supplied verbally when making an appointment and the request form must be adequately and relevantly filled which include patient's particulars, relevant clinical history, previous tissue biopsy or fine-needle aspiration findings, purpose of the consultation and type of tissue or location of biopsy. The pathologist may also wish to have a look at the radiological findings of the case especially for bone and soft tissue tumours.

***The pathologist must be prepared and have a high suspicion index***

The pathologist should attend the FS fully prepared which include reading the literature about the suspected tumour and the possible histological variants and grading. With the relevant clinical information, the pathologist should have a high index of suspicion and look for the histological features concerned. If there are any prior pathology slides, then these slides must be reviewed if relevant. The pathologist should only impart the information necessary for the surgeon to know at the time of surgery. In some cases lesional tissue is adequate, in others, benign versus malignant will suffice. Rarely, is specific histological subtype or grade required at the time of FS and such information is likely to change at the final diagnosis.

***The pathologist should have the final say***

The pathologist should be the final judge of whether or not a FS should be done. After taking into consideration the reason(s) for FS, the clinical presentation of the case and all relevant investigations done on the patient, the pathologist should decide whether the FS is worth pursuing. If not, then it is wise and safe to wait for a proper histopathological report of the case rather then trying to make an unreasonable diagnosis that may have dire consequences to the patient.

***The application of frozen section***

Both the surgeon and pathologist should be fully aware of the indications for FS. This will allow the appropriate request to be attended to. As mentioned earlier, only those requests that will definitely influence the intra-operative management should be duly entertained.

(i) Establish the nature of a lesion

To establish whether a lesion that needs to be resected is benign or malignant is very important to the operating surgeon, as this will decide the type of operative procedure or further sampling that he has to make.

(ii) Establish the presence of a lesion

FS is sometimes utilized to confirm the presence of a lesion or skip lesion in surgically suspicious tissue area.

(iii) Confirm the presence of a benign lesion

This is quite important in the case of a bony lesion. A benign lesion need to be confirmed for curettage and packing. Malignant bone lesion is usually diagnosed using preoperative biopsy.

(iv) Confirm that sufficient tissue is present for diagnosis

FS is sometimes utilized to ascertain whether the representative site or enough material is obtained before the tissue is sent for histopathological diagnosis.

(v) Establish the grade of the lesion

Grading of a malignant tumour is best done after the tumour is removed. However, sometimes it may be necessary to do so intra-operatively to guide the surgical procedure e.g. during evaluation for the presence or absence of endometrial carcinoma.

(vi) Determine the presence of synchronous lesions

FS may also be utilized to ascertain the presence of another lesion spotted unexpectedly during an operation.

(vii) Determine the organ of origin

Determining the organ of origin using FS in operation should not replaced surgeon's skill in gross

anatomy. However, this procedure is important when dealing with tissue such as parathyroid glands that are too small and difficult to recognize.

(viii) Determine the adequacy of margins

Adequacy of surgical margins is very important on large resections in a case of malignancy. In a complicated operating site such as in the head and neck, margin clearance of a malignant lesion is very crucial as tumour recurrence can be very aggressive and difficult to treat.

FS also has a role in assessing the extension of bone tumour in the marrow to help surgeon in deciding the operative maneuver. In the case of a very infiltrative tumour such as desmoid tumour, FS plays a very important role in getting margin clearance.

Surgical margins for skin tumours such as basal cell carcinoma and squamous cell carcinoma sometimes need to be assessed for best cosmetic results. An audit of 64 cases of basal cell carcinoma treated from 1988 to 1994 in Hong Kong showed that the rate of complete excision increased after the introduction of FS examination, reaching 89% by 1994 (8).

(ix) Establish evidence of invasion

FS is used to establish the presence of tumour invasion to the lymph nodes and nerve. It is also sometimes used to ascertain metastasis at distant organs.

(x) Determine the presence of infection

This is basically looking at the presence of tissue inflammation, granuloma and fungal infection.

(xi) Acquire fresh tissue for special studies

Fresh tissue sometimes is required for special studies such as electron microscopy, genetic and molecular studies as well as for microbiological studies.

In a study done at University of Michigan Hospitals, Ann Arbor, USA on FS requests of 914 cases, it was noted that 95% were performed for appropriate reasons, which included evaluation of margins (46%), establishing a primary diagnosis (43%) and determining adequacy or viability of tissue (3%) (9).

***Limitations***

Limitations of FS need to be taken into consideration when requesting for this procedure, in order to avoid grave mistakes that will be detrimental to the patient's management. These limitations can be divided into three main categories namely sampling error, technical problem and interpretative error (10, 11).

***Sampling errors or limitations***

(i) Poor sampling of tissue / limitation of the surgeons

This is a very obvious limitation for the pathologist since he has to interpret whatever the tissue sent by the surgeon. Sometimes the pathologist and even the radiologist may be required to go into the operating theater (OT) to evaluate the representative tissue taken.

(ii) Poor selection of appropriate tissue after grossing

Tissue sample sent to the laboratory for FS is sometimes large and therefore the pathologist must use his discretion to sample the most representative tissue areas. This may greatly influence his interpretation. Sometimes the orientation of the tissue sent is not clear and communication with the surgeon in the OT is thus important.

(iii) Extensive tumour degeneration or necrosis

Sampling a large tumour is sometimes difficult. The surgeon must choose a viable area and avoid necrotic one. Recognizing areas of tissue reaction to tumour such as edema and fibrosis are also important as sampling of these areas sometimes leave the pathologist with no diagnostic material.

(iv) Poor assessment of capsular or vascular invasion

Assessment of capsular or vascular invasion is very difficult in FS and subjected to sampling errors. Therefore, assessing such a condition in endocrine neoplasm especially follicular carcinoma of the thyroid is controversial and requires good communication between both parties.

(v) Malignant component in ovarian teratoma

Searching for immature component in an ovarian teratoma is rather time consuming in FS and subjected to sampling error. It is not possible for all the tumours to be sampled either intra-operatively or in the pathology laboratory for FS. Therefore, a report of benign teratoma does not totally ruled out a malignant one until the tumour is adequately sampled later.

***Technical problems***

(i) Freezing artifacts / Xylene artifacts

Freezing artifacts causes much damage to the tissue structure of the FS. Inadequate xylene treatment and improper coverslipping of slides cause drying artifacts, whereas any water present in xylene solution used contributes to cloudy sections. All these can greatly jeopardize the reading of the slides.

(ii) Poor quality section

Frozen tissue section is not easy to cut compared to paraffin embedded section. The section is usually thick and occasionally folded. Air bubbles may easily get into the tissue sections. A thick section may render it difficult to visualize clearly the nuclear details for example in lymphoma cases and the cytoplasmic details of histiocytes, oncocytes and tumour cells. In addition, soft tissue such as brain and fatty tissues are difficult to cut and may cause numerous incomplete cutting and folding which may affect the interpretation of the slides.

(iii) Bloated cell morphology

Depending on how good and how fast the tissue freezing process is, and its water content, this step will determine whether the cell morphology is preserved or not. However, in most cases of FS the cell morphology is inferior to that of the paraffin-embedded section. FS tends to cause the cells to be larger and appear bloated and the pathologist must take this into consideration when examining the tissue sample.

(iv) Poorly stained section

Likewise, due to the problem of fixation by freezing, the staining quality of the sections is also affected. As pathologist depends on colours as well as morphology, studying cells and its surrounding tissues, this factor may affect his judgement. To obtain a better morphology and staining quality of the slide sections, some laboratories heat the tissue sample(s) in formalin for a brief period before subjecting it/them to freezing. However, this will increase the turn-around time of the procedure.

***Interpretative errors***

FS diagnosis sometimes can be very tricky. It is the policy of the pathologist to give the closest diagnosis as possible to the surgeon and avoid giving the definitive diagnosis if there is any doubt. It is preferable to delay the definitive diagnosis of the case especially if the finding(s) is not going to influence the intra-operative management. The followings are some difficulties that may be encountered in FS service.

(i) Tumours that are difficult to diagnose

Certain tumours may mimic the normal tissue or cells, such as well differentiated angiosarcoma or signet ring cells in diffuse gastric carcinoma. Malignant blood vessels in angiosarcoma may appear like ordinary blood vessels and assessment of normal tissue margin for sarcoma can be very tricky. Likewise, signet ring cells of the gastric carcinoma may appear like ordinary macrophages dispersed in the gastric tissue and thus may mislead the pathologist to report the lesion as chronic inflammation, rather than malignancy.

(ii) Heterogeneity of the tumour

Heterogeneity in tumours especially soft tissue sarcoma makes it fairly difficult to diagnose the lesion not only in FS but also in tissue biopsy specimen. A hemangiopericytoma-like area of vascular malignant peripheral nerve sheath tumour may be misdiagnosed as hemangiopericytoma. Most of the time, cases of soft tissue sarcoma require further evaluation using special stains and immunohistochemical stains.

(iii) Mixed tumour and biphasic tumour

Tumour that has various germ cell components such as teratomas and tumour with biphasic features such as mesothelioma and synovial sarcoma also add in to the diagnostic dilemma of the pathologist in terms of limited tissue sample and time available in frozen section.

(iv) Variable degrees of tumour differentiation

Tumours such as gliomas of the brain and chondrosarcoma of the bone may show varying degrees of differentiation and tumour grading in FS may not be accurate, as the higher grade cells of the tumour may miss sampling by the surgeon.

(v) Difficult assessment of chronic pancreatitis versus pancreatic carcinoma

Both chronic pancreatitis and pancreatic carcinoma caused destruction of the normal pancreatic tissue and elicited marked fibroblastic reaction of the stroma. In addition, majority of pancreatic carcinoma glands mimicked benign glands of the pancreas and this caused intra-operative diagnosis of pancreatic carcinoma very difficult in the setting of chronic pancreatitis. The ability to

diagnose pancreatic carcinoma is very much influenced by the experience of the surgeon and pathologist; and the accuracy rate can go as high as 98.3% (12). Histological features of malignancy include variations in nuclear sizes of at least 4:1, disorganized duct distribution, incomplete duct lumen and infiltrating single cells.

(vi) Difficulty in assessing ganglion cells and hypertrophied nerve bundles in Hirschsprung disease

Many cells in the gastrointestinal tissue may mimic ganglion cells and these include macrophages, endothelial cells and lymphocytes especially if they are in clusters. In addition, the artifacts produced by tissue freezing as mentioned above enhance the phenomenon. Likewise, artefactually wavy smooth muscles of the intestinal wall can be mistaken for hypertrophied nerve bundle.

***Contraindications***

There seem to be no absolute contraindication to the use of FS diagnosis. Nonetheless, certain relative limitations and precautions should be kept in mind as discussed above. In some circumstances, potentially inappropriate ordering of FS does occur.

FS is sometimes unnecessary but not harmful to the patient, for example, a FS of a large tumour for which further surgery or treatment is not anticipated prior to a diagnosis based on permanent sections. Such cases may be avoided by means of discussion with the surgeon either during, or after the procedure. Such practices result in increased charges without any benefit to the patient.

At other time, FS is not only unnecessary but also potentially harmful to the patient, for example, a FS on a small primary lesion that would be frozen in their entirety. Artifactual distortion or loss of tissue could hinder diagnosis. Although it is true for any site, FS should be especially avoided in cases of pigmented skin lesions and small breast lesions. In such cases the pathologist must be an advocate for the patient and clearly explained that the patient's interest (and ultimately the surgeon's) would be served by not performing a FS.

Sometimes, a FS may have a low sensitivity or specificity but could rarely be useful, for example, looking for a capsular invasion in a follicular lesion of the thyroid as mentioned above or breast re-excisions to look for ductal carcinoma in situ at the margin. Pathologist, surgeons and institutions usually develop preferences in their methods of examining such specimens. If a FS is performed, the surgeon must be aware of the possibility that there could be a change in diagnosis when permanent sections are made.

The final diagnosis of melanocytic tumours or margin clearance is often compromised because of freezing artifacts. If a clinician requests such an evaluation, the pathologist should inform him or her of the potential harm to the patient and that the evaluation should be made on well-fixed, well-oriented permanent sections. Prieto et al (13) studied two sets of lesions in which en face FS was used for analysis of surgical margins (13 malignant melanomas and 10 non-melanocytic lesions) and noted that if permanent histology is considered the gold standard for histologic evaluation, en face FS was not suitable for accurate surgical margin assessment of melanocytic lesions.

If a diagnosis of invasive breast carcinoma has been made previously, it is generally unnecessary to perform a FS, and the margins are evaluated grossly for involvement. FS is not needed for the evaluation of inflammatory changes. In cases of suspected malignancy arising in Inflammatory Bowel Disease, FS may be helpful.

Suspected cases of infectious diseases such as tuberculosis should best be avoided as handling of the fresh tissue may expose the pathologist and the technician to the infection.

***Accuracy of frozen section***

After discussing the limitations and pitfalls of FS, it should be noted that the technique is very reliable in good hands. Most centers reported an accuracy rate of 92% to 98% depending on type of cases studied. A large center like Mayo Clinic Rochester, USA reported an overall accuracy of 97.8% on reviewing 24,880 frozen cases in a year (14). A comparative overall accuracy of 97.56% was noted at a general hospital in Malaysia involving 215 FS specimens over 4 years duration (15).

Other reported cases include accuracy rate of 94% in central nervous lesion (16), 98.4% for tumours of the testis (17) and 91.1% for basal and squamous cell carcinoma of the skin (18). Accuracy of FS in gynaecological cases can be as high as 97.5% (19). However, if we look at borderline cases of ovarian tumours, this accuracy rate will fall due to diagnostic difficulty. Pinto et al (20) in studying 243 FS for ovarian tumours noted an accuracy rate of 98.5% for malignant tumours but only 78.6% for borderline tumours.

Utilizing FS to determine tumour grade is also less sensitive with accuracy of only 88.6% in 260

endometrial cancers studied by Quinlivan JA et al (21). Even though the accuracy rate is generally very high, in some surgery especially in the head and neck surgery, determination of the margin clearance may be quite costly and cannot reliably eradicate positive final margins. DiNardo et al (22) reported 98.3% accuracy in 80 patients that underwent head and neck surgery with 420 FS margins performed. However, 40% (8 of 20) of patients with positive final margins on the resection specimens, and 100% (15 of 15) with close (<15mm) margins were not detected by FS analyses. They concluded that patients with early-stage lesions and those undergoing re-resection for recurrence or salvage surgery after radiation failure derived the greatest potential benefit from FS margins.

For thyroid lesions, the overall accuracy rate of FS is > 90% (23), though the rate can drop to as low as 17% for encapsulated follicular carcinoma (24). Therefore, certain laboratories are reluctant to carry out FS on thyroid lesions, particularly when dealing with follicular neoplasm. In fact, some authors do not support the use of routine FS for thyroid nodules (25, 26). They recommended that FS be considered only when the clinical suspicion of malignancy is significant and the fine needle aspiration cytology results are suspicious or unsatisfactory and in patients with unexpected findings during surgery.

At times, diagnostic accuracy of FS may be much higher than that of fine needle aspiration cytology. In an audit of 31 parotidectomy cases in Singapore, it was noted that 88% of FS histology concurred with the final histology in contrast to 66.6% of fine needle aspiration cytology cases (27).

***Trend in frozen section***

FS technique has been the mainstay of rapid diagnosis in histopathology laboratories thus far. It has offered a very valuable service in patient management. However, it is believed that advancement in other techniques especially in the field of cytopathology, may make FS loss some of its appeal.

Increasing popularity of fine needle aspiration cytology

Since the introduction of fine needle aspiration cytology in Europe in late 1960's, this technique has been accepted for making diagnosis preoperatively. Even though it has its own limitations such as lost of tissue architecture and relied heavily on cell morphology, the technique has replaced some of the very important FS diagnostic procedure. This is particularly so in the diagnosis of breast cancer as request for FS by surgeon has declined tremendously in favour of fine needle aspiration. With the aid of radiological technique such as ultrasound and CAT scan, fine needle aspiration can be used to reach deep seated tumours in the body and has further popularized this technique. However, the main problem of getting adequate and representative sample remains.

Intra-operative cytology

This technique does not involve freezing of tissue. Samples are obtained by touch imprint of fresh specimen, scraping smear preparation and squash preparation (in case of glioma of the brain). These can add a great deal of information to FS and sometimes obviates the need for it altogether (28). Strong indications for this technique include lymphoproliferative lesions, central nervous system lesions and thyroid nodules. It can also be used for minute specimens and to sample tissue that would be difficult to cut with the cryostat.

Chonmaitri IS (29) claimed that imprint cytology also gives superior results in cases of isolated tumour cells, hemorrhagic tissue and infective cases. In their series of 80 cases done in Thailand, the total diagnostic accuracy of this technique was 90.6% for benign tumours and 93.7% for malignant tumours. In a large series of 2,250 intra-operative cytology performed along with FS, Scucchi LF et al (30) reported the diagnostic accuracy of each technique alone was 94.9% for FS and 96% for cytology. They noted that although specific diagnoses were more frequently formulated on the bases of FS examination, FS were not diagnostic in 113 cases in which cytology allowed a specific diagnosis.

Wakely PE et al (31) in studying the role of intra-operative cytology in pediatric surgical pathology involving 58 cases noted that 49% of the cases had diagnosis rendered by cytology alone without a concurrent FS examination. They concluded that intra-operative cytology serves as a useful supplement in FS diagnosis and, in some situations (particularly when tissue is limited), can replace histologic FS examination.

Mini Laboratory adjacent to Operating Theater

For an efficient FS services and better communication between pathologist and surgeon, a number of institutions have a mini laboratory adjacent to the operating theater. This is very

favourable but may however be an expensive venture. Pathologist can also offer intra-operative cytology services such as for brain tumours at the site and this is very helpful to the surgeon.

Frozen section telepathology

In certain countries, the use of static and dynamic telepathology has help pathologists at remote areas and inexperienced pathologists to communicate with a distant pathology institute where diagnoses were made on digital images (32, 33). Even though the remote pathologists can sample images sufficiently but the Internet is much too unreliable for such a time dependent task. This requires improvement of the system.

## Conclusion

The intra-operative consultation using FS is a very useful but one needs to be aware of its indication and limitations. Bearing the above in mind when requesting for this investigation, will make this technique a very reliable and accurate investigation and serves the patient's best interest.

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