REVIEW ARTICLE

REVIEW OF INTRA-OPERATIVE FROZEN SECTION AND ITS ROLE IN SURGICAL EXCISION OF BASAL CELL CARCINOMA (BCC)

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INTRODUCTION

The frozen section (FS) examination is made while the patient is under anaesthesia on the operating table. The FS may be one of the most important procedures performed by the pathologist during his disgonstic practice. It is a difficult procedure. The pathologist has to arrive at a correct decision in a short time under pressure based on his experience, judgement and the knowledge of his specialty and allied disciplines. 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].

Basal cell carcinoma (BCC) is the most common skin malignancy arising from the basal layer of epidermis and its appendages[2]. The majority of these cancers occur on areas of skin that are regularly exposed to sunlight or other ultraviolet radiation including scalp[3]. The goal of treatment of BCC is complete removal of tumour and maximally preserve function and cosmetics at the site of treatment[4]. Surgical removal remains the standard mode of treatment for basal cell carcinoma and classically surgical excision is used as method of choice for treating BCC but is associated with recurrence and unacceptable cosmetic results due to wide margins excision[5]. In frozen section, when operating on a previously confirmed, or in cases of highly clinical suspicion of malignancy, the main purpose of the pathologist is to inform the surgeon if the surgical margin is clear of residual cancer, or if residual cancer is present at the surgical margin. This technique also used in for excision of BCC to get better cure rates and cosmetic outcomes in one step surgery with encouraging results[6,7]. With this improvised surgical technique and intra-operative pathologist consultation cure rates of 99% has been achieved for primary BCC with maximally preserved tissue[8]. The technique offer several advantages including better cure rate, maximal tissue preservation in cosmetically and anatomically sensitive areas with immediate reconstruction in most cases. This result in preserving time and resources along with improved quality of life of the patients.

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 -20° to -30° Celsius. Intra and intercellular water is frozen to produce a hard matrix to enable slicing of the tissue. In one study involving 700 laboratories worldwide, it was found that 90% of FS block turnaround 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[9].

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 use of this important technique[10]. 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

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decisions when requesting for a frozen section report.

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. He may want to know about an unexpected disease process requiring 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. Special stains and IHC stains cannot be used there and then. The 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.

The FS has its limitations, the sampling of specimen is limited and there are technical difficulties of getting good quality sections and staining; all of which can influence the interpretation of the section by the pathologist.

The FS should be planed before hand therefore, an appointment at least a day before the operation need to be made with the pathologist.

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 thoroughly between the surgeon and the pathologist and all the relevant information must be conveyed for the benefit of the patient. This information can be shared 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.

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 before FS examination. Preferably, the pathologist should only impart the information required on frozen section like adequacy of lesion, benign versus malignant, etc. Rarely, is specific histological subtype or grade required at the time of FS and it should be conveyed that such information may be changed at the final paraffin embedded tissue report.

The pathologist should be the final judge regarding requirement of FS. 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 than FS.

Application of Frozen Section

Both the surgeon and pathologist should be fully aware of the indications for FS. Following are some possible indications of FS;

- To establish whether the lesion is benign or malignant, presence of a lesion or skip lesion in surgically suspicious tissue area.
- For FS of bony lesion benign lesion need to be confirmed for curettage and packing whereas malignant bone lesion is usually diagnosed using preoperative biopsy.
- To know whether the representative site or enough material is obtained before the tissue is sent for histopathological diagnosis.
- 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 like evaluation for the presence or absence of endometrial carcinoma.

- The FS may also be utilized to ascertain the presence of another lesion spotted unexpectedly during an operation.
- Determining the organ of origin, important when dealing with tissue such as parathyroid glands that are too small and difficult to recognize.
- 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. The FS also has a role in assessing the extension of bone tumour in the marrow to help surgeon in deciding the operative manoeuvre. 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[11].
- The 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.
- Some times to see type of tissue inflammation, granuloma and fungus etc.
- 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%)[12].

Limitations of Frozen Section

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[13,14].

Sampling Error

- Poor sampling of tissue/limitation of the surgeons 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 theatre (OT) to evaluate the representative tissue taken.
- 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.
- 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 oedema and fibrosis are also important as sampling of these areas sometimes leave the pathologist with no diagnostic material.

Technical Problems of Frozen Section Technique

- Freezing artefacts, air drying artefacts are common and any water present in xylene solution used contributes to cloudy sections. All these can greatly jeopardize the reading of the slides.
- 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. 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.

- Depending on how good and how fast the tissue freezing process is, and its water content, will determine whether the cell morphology is preserved or not. The FS tends to cause the cells to be larger and appear bloated and the pathologist must take this into consideration.
- Likewise, due to the problem of fixation by freezing, the staining quality of the sections is also affected. This factor may affect his judgement.

Interpretative Errors in Frozen Section

Frozen section diagnosis sometimes can be very tricky. It would be the policy of the pathologist to give the closest possible diagnosis 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 drastically influence the intra-operative management. The followings are some difficulties that may be encountered in FS diagnosis.

- 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.
- 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.
- 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 may have been missed while sampling by the surgeon.
- 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%. Histological features of malignancy include variations in nuclear sizes of at least 4:1, disorganized duct distribution, incomplete duct lumen and infiltrating single cells[15].
- 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 artefacts produced by tissue freezing as mentioned above enhance the phenomenon. Likewise, wavy smooth muscles of the intestinal wall can be mistaken for hypertrophied nerve bundle.

Contraindications of Frozen Section

There seem to be no absolute contraindication to the use of FS diagnosis. Nonetheless, certain relative limitations and precautions should be kept in mind. The 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. 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, may hamper its final paraffin embedded tissue diagnosis. Although it is true for any site, FS should especially be 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 and 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 artefacts. 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 (2003)[16] 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 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. The 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 centres report an accuracy rate of 92% to 98% depending on type of cases studied. A large centre like Mayo Clinic Rochester, USA reported an overall accuracy of 97.8% on reviewing 24,880 frozen cases in a year[16]. A comparative overall accuracy of 97.56% was noted at a general hospital in Malaysia involving 215 FS specimens over 4 years duration[17]. Other reported cases include accuracy rate of 94% in central nervous lesion[18], 98.4% for tumours of the testis[19] and 91.1% for basal and squamous cell carcinoma of the skin[20]. Accuracy of FS in gynaecological cases can be as high as 97.5%[21]. In a study of 243 FS for ovarian tumours, an accuracy rate of 98.5% for malignant tumours was noted. DiNardo et al (2000) reported 98.3% accuracy in 80 patients that underwent head and neck surgery with 420 FS margins performed[22]. 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%, though the rate can drop to as low as 17% for encapsulated follicular carcinoma[23,24]. 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]. 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[26].

Trends in Frozen Section

The 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 lose some of its appeal.

Frozen Section Telepathology

In certain countries, the use of static and dynamic telepathology has help pathologists at remote areas and pathologists with limited experience to communicate with a distant pathology institute where diagnoses were made on digital images. Even though the remote pathologists can sample images sufficiently but the Internet is much too unreliable at times for such a time dependent task. This requires improvement of the systems[27,28].

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.

Frozen Sections in Basal Cell Carcinoma (BCC)

The BCC is a common skin cancer that arises from the cells of the basal layer of the epithelium or from the external root sheath of the hair follicle. Surgical excision is the standard mode of treatment for BCC[29]. Frozen section analysis has been used to increase the likelihood of complete excision of skin cancers and to minimize the risk for recurrence, however, its use remains controversial and commonly considered an optional tool, the reliability and effectiveness of which remain questionable[30]. Intra operative frozen section technique in assisting surgical excision of BCC with maximal tissue preservation in cosmetically sensitive areas with immediate reconstruction in most cases, eventually improves quality of life of patients. Success rate in BCC is assessed in terms of tumour free margin on histo-pathology report. Identifying a definite clinical margin may be difficult in various circumstances like sclerosing basal cell carcinoma that usually features ill-defined borders resembling small patches of scleroderma with peripheral growth and central sclerosis. A frozen section is always required for one or more specimen margins, according to the surgeon's subjective clinical judgment to avoid potential failure of the surgeon and consequently the whole procedure. In report of Manstein et al (2003)[31] on 60 consecutive cases in which frozen section diagnoses was compared with permanent sections. It was found that in 85% of the cases the frozen sections were accurate compared with the permanent sections, but in 13% of the total cases the margins were less than 1 mm.

However, some studies show contradictory result. Cataldo et al (1990)[32] in their review of 450 cases of BCC has shown frozen section to be most helpful in treating recurrent tumours where microscopic tumor foci extend beyond clinical margins in 45% of cases. They suggested that frozen section analysis may be of value in selected patients with primary tumors, but its routine use is not indicated for the majority of these lesions, since complete excision is possible without relying on frozen section in 90% of cases.

Bogdanov-Berezovsky et al (2008)[33] in their retrospective study of 169 cutaneous basal and squamous cell carcinomas excised showed false negative margins were found in 19 cases (11.2%) and false positive margins in 11 (6.6%). A significantly lower rate of false negative results was found in the residual tumor group. In conclusion they supported the use of frozen section margin control in selected patients suffering from non-melanoma skin cancer of the head and neck.

Nizamoglu et al (2016)[34] retrospectively reviewed excised non melanoma skin cancers with complete margin frozen section histological analysis. Sixty-nine patients were treated using this technique with a total of 70 lesions excised. Approximately 71% of the excision margins were clear after primary excision, 27% at second excision and 1% at third excision.

Ghauri et al (1999)[35] in their retrospective study showed that frozen section analysis were 91.1% accurate in detecting the presence or absence of tumor involvement at the surgical margins. The data also showed that the surgeons were able to estimate the margin of the skin tumor clinically and remove it entirely during the first excision 91.1% of the time. The lesions that had not been removed completely with the initial excision were those located on the periorbital region, forehead, and cheeks; were recurrent lesions; or were lesions that required more involved reconstruction than primary closure.

In our personal experience, an intra-operative frozen section was required to check a complete excision of the BCC in one or more specimen marginal spots. In particular, it is mostly required in the critical anatomical sites of the head, such as the nose, cheeks, eyelids, chin, lips and forehead. Thus, a potentially persistent disease from an incomplete primitive excision would demand a far more aggressive and disabling secondary surgery. Nonetheless, the effectiveness of an intra-operative frozen section biopsy is always correlated with the surgeon's subjective clinical assessment. Other authors consider the frozen section as an optional tool utilized to intra operatively assess one or more margins of a surgically excised specimen. Its advisability, reliability and effectiveness are as debated as Mohs micrographic surgery with a corresponding equal distribution of supporters and critics[32-35]. In conventional surgical excision for BCC at aesthetically important areas assisted with intraoperative frozen section technique resulted in high success rates in terms of tumor free margins.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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