A comprehensive review of biopsy techniques for oculoplastic and orbital surgeons from ophthalmic pathologists' perspective

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Abstract:

This narrative review aims to discuss different modalities for obtaining diagnostic orbital biopsies, compares the available updated methods, and provides recommendations on the choice of technique. It also highlights special precautions in the handling of orbital specimens from various pathologies. A search was performed in PubMed and Google Scholar with no language or study type restriction. The keywords orbital biopsy, core biopsy, fine-needle aspiration biopsy, and orbit were used, and titles and abstracts were screened for relevance.

Keywords:

Biopsy techniques, oculoplastic and orbit, ophthalmic pathology

Introduction

Orbital and periocular biopsy serves as a valuable diagnostic tool, and it is of particular significance when a clinical or radiological diagnosis of orbital pathology is not readily established. Contrary to external eye and adnexa, intraocular biopsy has fewer indications; an example of such is differentiating between masquerading uveitis and intraocular lymphoma.[1,2] The latter is also associated with a higher number of complications compared to extraocular biopsy.[2] An example of a dreaded complication includes the seeding and dissemination of malignant cells because of intraocular fine-needle aspiration biopsy (FNAB).[3] The indications of acquiring an ocular biopsy in general for suspected intraocular malignancy had been summarized by Eide and Walaas as the following: in situations of an inconclusive diagnosis, in cases of suspected recurrence, patient refusal to undergo treatment without a histopathologic confirmation, as well as for prognostic purposes.[4] A unique application of ocular biopsy had been highlighted in a case report by Dios E *et al*., which described three cases wherein a diagnosis of sarcoidosis had been established based primarily on conjunctival biopsy in patients with ocular manifestations of disease who were otherwise asymptomatic.[5] Regarding orbital biopsy indications, Mombaerts *et al*. recommend the acquisition of tissue biopsy in orbital inflammation with an uncertain diagnosis.[6]

Few studies in the literature have explored techniques of obtaining ocular biopsy and their respective advantages, disadvantages, special considerations, and notable precautions.[5] The choice of technique varies depending on several factors, such as the site, size, and suspected diagnosis.

Modalities

Fine-needle aspiration biopsy

FNAB is a diagnostic method that uses a very thin needle and syringe to take a sample of cells, tissue, or fluid from an abnormal mass in the body, which is considered to be minimally invasive and relatively fast.[7] It has been applied in orbital pathology for establishment of the diagnosis of malignant orbital tumors to decide the need for surgical intervention with a reported histopathological accuracy of 81% by Tijl and Koornneef.[7] The most common indication of FNAB is diagnostic uncertainty, such as when there is discrepancy among the

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results of noninvasive diagnostic tools.[8] The accuracy of FNAB can be high, however, limited cellularity can lower its diagnostic potential as pointed out by Singh and Biscotti in their review on FNAB.[8] This diagnostic technique was also found to be less beneficial for orbital tumors and inflammatory conditions with considerable fibrosis such as pseudotumor by Kennerdell *et al*. in 1979.[9] It was not recommended generally for diagnosing benign encapsulated orbital tumors and its yield was thought to be limited in the diagnosis of lymphoid tumors.[9,10] FNAB requires special arrangements between the orbital surgeon who needs to have adequate experience with the FNAB technique and the cytopathologist who has particular expertise in orbital pathology. Katavi has nicely summarized the application of FNAB in the diagnosis of orbital and adnexal tumors and concluded the importance of patient selection, experience, availability of ancillary testing, and imaging guidance.[10] In addition, several drawbacks to this technique application in the orbit in comparison to its use for intraocular tumors because of the complexity of orbital structures and difficulties that might be faced in reaching deep-seated retrobulbar lesions without causing damage to vital structures such as the globe or the optic nerve.[10,11] Gupta *et al.* in a study that has included 37 patients with orbital mass lesions, out of which 19 were located in the posterior aspect of the orbit-described the technique for ultrasound-guided freehand FNAB using a 25-gauge needle.[12] Similarly, this technique was reported by Rastogi and Jain to be successful in reaching accurate diagnosis for several orbital pathologies including histiocytosis X, cryptococcosis, non-Hodgkin's lymphoma, schwannoma, cysticercosis, and lacrimal gland epithelial tumors (adenocarcinoma and pleomorphic adenoma) without considerable complications.[13] However, the authors pointed the importance of parallel diagnostic radiological techniques to aid in the diagnosis.[13] Even though fine-needle aspiration cytology (FNAC) has been found to be helpful as a diagnostic technique in accurately diagnosing new primary lesions, recurrences, or metastases, some investigators such as Agrawal *et al*. were against undertaking radical decisions and/or procedures based on the FNAC alone.[14] In general, clinical examination and appropriate imaging studies can be enough for diagnosing most orbital lesions, which may limit the need for FNAB.

Core-needle biopsy and imaging-guided core-needle biopsy

Core-needle biopsy (CNB) is a type of procedure performed to take a tissue sample with a larger needle under image guidance by means of sonography, computerized tomography (CT) scan, or magnetic resonance imaging (MRI). It is commonly performed in oncology, and contrary to FNAB, it provides sufficient tissue sample for histopathology and immunohistochemical (IHC) and was found to be superior to FNAB in diagnosing soft-tissue lesions.[15,16] CNB has been accepted since the 90s as a diagnostic tool for orbital lesions and became more popular than FNAB in the oncology practice.[16] Many modalities of imaging can guide the procedure of CNB including ultrasonography (US), CT scanning, and MRI.[17,18] The advantages of the US-guided procedure over CT include the absence of ionizing radiation and real-time monitoring of the needle position. However, studies with CT-guided procedures have not shown a greater number of complications. Moreover, some lesions are easily accessible with CT-guided techniques depending on their location. CNB is superior to FNAB because it provides sufficient tissue for proper histopathological examination and IHC staining, thus, CNB was recommended as an alternative for FNAB, in challenging histopathological diagnoses such as rhabdomyosarcoma, lymphoma, and even in inflammatory diseases.[16] Similar to any other medical procedure, CNB has disadvantages and complications. In a study conducted in 2013 by Yarovoy *et al*., 50 CNB samples of orbital lesions were evaluated using 18-gauge and 20-gauge needles (11 of which were US guided, and the remaining number of biopsies were obtained without the help of imaging), only two patients had mild retrobulbar hematoma, without compromise of the visual acuity, and there were no cases of globe or optic nerve injury, ocular motility alteration, or infection. The study concluded that a CNB of an orbital mass lesion is evidently safe.[16]

In the mentioned study by Yarovoy *et al*., three biopsies among the total of fifty were reported to be nonrepresentative. Of those three nonrepresentative biopsies, one case of false-negative lacrimal gland adenocarcinoma was missed by CNB. Furthermore, the amount of tissue it provides is sufficient for histology and immunohistochemistry, which may result in an improvement in the quality of orbital oncology diagnostic studies.[16] In this sample, the histopathological diagnosis was successfully established in 94% of the procedures.[16]

Bata *et al*. recommended CT-CNB, which might be specifically indicated for lesions that are located at the lateral orbital aspect as an easier alternative to excisional biopsy since it is less invasive and allows access for radiotherapy treatment, if required, without any delay.[19] Another study by Nyquist *et al*. has been conducted to evaluate the value of different types of biopsies for head-and-neck lesions, and the researchers recommended CNB as a superior consideration over excisional biopsy in lesions which would necessitate immunohistochemical (IHC) staining as well as lesions with diagnostic uncertainty even after the use of FNAB. They also concluded additional advantages such as safety, efficiency, and cost-effectiveness.[20] Obtaining a good and representative sample is highly dependent on using the proper technique. In 2014, the technique for CT-CNB was emphasized aiming at obtaining a successful and representative sample by Jeng Tyng *et al*. in their detailed report of two cases of primary orbital tumors diagnosed by CT-guided percutaneous biopsy. The procedure was done under conscious sedation with the use of local anesthesia. The biopsy was performed using the coaxial method with entry of a 17-gauge needle along the lateral transpalpebral route, between the eyeball and the greater wing of the sphenoid in a path parallel to the optic nerve (case 1) and along the inferior transpalpebral route, between the eyeball and the zygoma, in a path inferior to the lateral rectus muscle (case

2). After positioning the coaxial needles, 18-gauge cutting needles are introduced, and 3–5 fragments were collected with a 1.5 cm shot, respectively, in both cases uneventfully.[18]

Incisional biopsy

Incisional biopsy is a surgical biopsy that obtains only part of the tumor for histopathological examination and is mostly done under general anesthesia. One of the advantages of incisional biopsy is that it allows fixation of the extracted specimen, and thus, a cytopathologist is not required to be present in the operating theater. It also provides large tissue sample rather than cells. Surgeons should aim at obtaining the most representative adequate sample from the lesion itself to avoid inadequate or insufficient sampling resulting in inconclusive pathology reporting or obtaining the sample from adjacent normal orbital tissue, which becomes nondiagnostic and requires repeated incisional biopsy with additional burden on the patient and possible delayed diagnosis.[21,22] It is particularly useful in certain orbital cases, such as idiopathic orbital inflammation, immunoglobulin G4-related disease, lymphoproliferative lesions, autoimmune disease-related changes, and sarcoidosis. In addition, incisional biopsy would be the method of choice for primary malignant and metastatic tumors of the orbit, where the lesion is either large for undergoing excisional biopsy, needs subtyping of a diagnosed malignancy, or does not require therapeutic total excision.[23]

Excisional biopsy

Excisional biopsy is when all the masses are surgically removed for histopathological examination rather than part of it and it is the common technique of obtaining a good specimen from an orbital lesion. It has the advantage of removing the whole mass, thus providing adequate specimen for histopathological diagnosis. Therefore, it can be used when other methods, like FNAB, cannot provide enough tissue. It is also used as a therapeutic excision, in cases such as cavernous venous malformations, lacrimal gland pleomorphic adenoma, cystic lesions, and other circumscribed solid benign or malignant lesions. Sometimes, the therapeutic excision is done after the diagnosis has been already confirmed by FNAB, to avoid unnecessary tissue removal. If so, the tissue can be analyzed further after the excision to predict prognosis and plan follow-up treatment. Associated morbidity and expenses are the drawbacks of this method.[22] The description of the surgical approaches for excisional biopsy of orbital lesions depends on the location and the size of the lesion and it is beyond the scope of this review.

Comparison between the different modalities above is summarized in Table 1.

Special handling and precautions

Generally, all pathology specimens should be handled carefully with and guidelines that are usually available in pathology laboratories.[24] The recommendations emphasize avoiding crushing or thermally injuring the specimen by avoiding/limiting the use of surgical instruments, including the heat-driven ones, when possible, as this may affect the diagnosis. Following specimen collection, it should be placed in a fixative immediately, and if a fixative is not available, it should be put in a sterile basin with sterile saline and transported to the laboratory to be refrigerated at the earliest possible, until a fixative is available. The containers used for the specimen are supposed to be unbreakable, impermeable, rigid, and nonreactive to the fixative used.[25]

As for orbital biopsies, similar precautions should be followed, as careful handling of the specimen would affect the diagnostic outcome, especially in small-volume specimens. During dissection and removal of the orbital specimen, it should not get torn, cauterized, or crushed. Drying out of the specimen before fixation may interfere with the histopathology result, and thus should be avoided. Furthermore, avoiding excessive hemorrhage is advised. To reduce trauma risk to the eye and the specimen, a dermatological biopsy punch that is disposable should be the tool used when the anterior part of the extraocular muscle is being biopsied. Extra care should be also taken in certain tumors, such as lymphomas and soft mesenchymal tumors, as they are extra fragile and more likely to be crushed, thus gentle handling with the forceps is advised.[24,25]

Intraoperative biopsy

A need for intraoperative diagnosis, obtained through methods of frozen section and cytologic diagnosis, has been well-defined in the literature, albeit scarcely studied in orbital surgery. Particular benefit may be obtained when there is no preoperative diagnosis or when an intraoperative

Table 1: Comparative summary of various biopsy techniques

Technique	Comments
FNAB	Advantages: Less invasive, accurate, fast
	Disadvantages: Possibility of insufficient tissue, limited cellularity, unavailability of representative histological sample, difficulty in interpretation, not suitable for benign encapsulated orbital tumors, fear of globe and/or optic nerve traumatic injury
CNB and imaging-guided CNB	Advantages: Sufficient tissue, less complications with the image-guided CNB
	Disadvantages: Possibility of nonrepresentative sampling, need for learning experience, and readily available radiology facility
Incisional biopsy	Advantages: Better fixation of the extracted specimen, usually large tissue sample compared to FNAB and CNB
	Disadvantages: More invasive than FNAB and CNB, relatively lengthier process until interpretation, possibility of nonrepresentative or inadequate sampling
Excisional biopsy	Advantages: Combined diagnostic and therapeutic purposes, enough tissue sampling for ophthalmic pathologists
	Disadvantages: Possible unnecessary tissue removal, associated morbidity and expenses, technical difficulty with unexperienced surgeons depending on tumor type, location, and accessibility

FNAB=Fine-needle aspiration biopsy; CNB=Core-needle biopsy

diagnosis may alter final surgical management. Frozen section examination is also useful for assessment of surgical margins in cases of adnexal malignancy.[25,26] Intraoperative diagnosis of ocular pathology can be rapidly achieved through squash and imprint cytologic techniques. A study conducted by Vemuganti *et al*. has assessed the accuracy of the aforementioned technique by comparing intraoperative cytologic diagnosis with the final histopathological diagnosis.[26] Biopsies were obtained from eyelids, conjunctiva, intraocular tissue, and orbit, and the results showed that a working diagnosis may be established within an interval of 5–8 min of sample receival, and a favorable outcome in terms of accuracy.[26] For example, the histologic-cytologic comparison by some reporters had shown complete concordance in 91% of the cases, partial concordance in 3 cases, and an inconclusive result in 1 case.[27] Challenges included the demand of a proficient cytologist and an ophthalmic pathologist who pays attention to fine details and conducts thorough ophthalmic pathology examination to avoid any possibility of misdiagnosis.[21,27] Similarly, frozen section diagnosis has not been extensively studied in orbital and oculoplastic surgery. The correlation between diagnostic concordance of intraoperative rapid frozen section versus permanent section was explored by Karcioglu and Caldwell in a retrospective study of malignant eyelid tumors.[28] Out of 429 cases, 5 (1%) and 3 (<1%) of slides which were reported by permanent section as positive and negative for tumor infiltration, respectively, had subsequently shown incompatible results on frozen section. Thus, a favorable concordance of 98% was concluded.[28] Chévez-Barrios has reviewed the indications for frozen sections and the most common was for control of surgical margins of eyelid lesions in about half of the cases followed by orbital lesions in 38.3%.[25] However, the use of frozen section in eyelid malignant tumors was not popular in managing sebaceous gland carcinoma (SGC) because of the surgeons' preference in that institution to have permanent evaluation of the margins of SGC, especially when the conjunctiva is involved by pagetoid spread.[25] Alam *et al*. evaluated the value of frozen section in diagnosing orbital and adnexal malignancies.[29] Frozen section was found to be 100% specific and sensitive in cases of basal cell carcinoma with equal specificity (100%) but less sensitivity to SGC (83.3%). They stressed on the fact that it should not be used as a complete alternative for permanent sections.[29]

Conclusions

There is a growing body of literature, which emphasizes the value of orbital biopsy as a diagnostic tool, particularly in cases of orbital malignancy but also in inflammatory orbital disease and for research purposes. However, the available modalities have not been equally practiced among different eye centers across the world because of variable experience, learning curve, and available facilities from one area to the other. The details of techniques for periocular and orbital lesions need to be studied and discussed further in the literature, with a great demand for comparative studies. Building knowledge and practical training by oculoplastic surgeons – if needed – is of paramount importance to master various techniques and to be selective in making the proper choice of the desired and most suitable method for diagnostic and/or therapeutic purpose.

We have tried in this review to provide thorough explanation of the different techniques and challenges of obtaining an orbital biopsy for better understanding. Major modalities readily available for oculoplastic and orbital surgeons as well as other pathology-related issues from an ophthalmic pathologist point of view have been highlighted.

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Conflicts of interest

There are no conflicts of interest.

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