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ORIGINAL PAPER

Malignant eyelid tumors: Are intra-operative rapid frozen section and permanent section diagnoses of surgical margins concordant?

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Abstract

Purpose To study the concordance between intra-operative rapid frozen section and permanent section diagnoses of surgical margins following wide surgical excisional biopsy of malignant eyelid tumors.

Methods This is a retrospective study of 120 cases and 429 frozen section slides.

Results Of 120 cases, 75 (63%) had sebaceous gland carcinoma, 34 (28%) had basal cell carcinoma, and 11 (9%) had squamous cell carcinoma. All cases with these malignant eyelid tumors underwent wide surgical excisional biopsy under frozen section control of surgical margins. A total of 429 frozen section slides were reviewed for rapid frozen section diagnosis. Eyelid reconstruction was performed in all cases after clearance was obtained by rapid frozen section diagnosis of surgical margins as negative for tumor infiltration. Permanent section diagnosis of surgical margins was positive for tumor infiltration in 5 (1%) slides, which were reported as negative on rapid frozen section diagnosis of surgical margins, and was negative for tumor infiltration in 3 (< 1%), which were reported as positive on initial rapid frozen section diagnosis of surgical margins. The sensitivity, specificity, and accuracy of intra-operative rapid frozen section diagnosis of surgical margins for malignant eyelid tumors were 89%, 99%, and 98%, respectively.

Conclusion The concordance between the intra-operative rapid frozen section and permanent section diagnoses of surgical margins following wide surgical excisional biopsy of malignant eyelid tumors is excellent at 98%.

Keywords Eye · Eyelid · Tumor · Frozen section · Permanent section · Histopathology · Sebaceous gland carcinoma · Basal cell carcinoma · Squamous cell carcinoma

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Introduction

Rapid diagnosis by intra-operative Mohs micrographic surgery or frozen section control of surgical margins is valuable in ensuring the complete resection of tumor and maximizing the conservation of normal tissues [1–5]. In ophthalmic pathology, frozen section diagnosis is useful for margin control in eyelid and orbital tumors [6]. Errors in frozen section diagnosis can occur due to misrepresentation of the margins or tissue sampling error, or due to technical issues such as crush artifacts, uneven staining, or folds in the tissue

section resulting in false positive or false negative frozen section diagnosis [7, 8]. The accuracy of frozen section diagnosis plays an important role in the patient management. The rate of concordance between conventional rapid intra-operative frozen section and permanent section diagnoses for malignant eyelid tumors has not yet been studied. In this report, we study the accuracy of intra-operative frozen section diagnosis and study the degree of concordance between frozen section and permanent section diagnoses for malignant eyelid tumors.

Methods

This is a retrospective review of clinical records and histopathological slides of all patients who underwent wide excisional biopsy of malignant eyelid tumors under intra-operative frozen section control of surgical margins. Institutional review board approval was obtained for the study. The study period was between the years 2012 and 2017. All cases that underwent wide excisional biopsy of malignant eyelid tumors under frozen section control of surgical margins and with known frozen section and permanent section diagnoses were included in this study. Only the three common eyelid malignancies (sebaceous gland carcinoma, basal cell carcinoma, and squamous cell carcinoma) were included in this study. Those who underwent wide excisional biopsy due to suspicion of malignant eyelid tumor but with a final histopathology diagnosis of a benign eyelid tumor or uncommon malignant eyelid tumor were excluded from the study.

The following details were included from the clinical records: age, gender, history of previous surgical intervention of eyelid tumor, tumor location, tumor size, and clinical diagnosis. All cases underwent wide excisional biopsy of the tumor with 4-mm clear margins from the clinical extent of the malignant eyelid tumor. The true surgical margins in the excised specimen were inked with a permanent marker pen and 1-mm full-thickness tissue was obtained from each surgical margin by the operating surgeon in the operating room, and the labeled surgical margins were sent for rapid frozen section diagnosis for margin clearance by conventional frozen section technique or the entire excised specimen was sent to the pathology laboratory. When the entire excised specimen was sent to the pathology laboratory, the true surgical margins were inked with Indian ink all around and the pathologist obtained 1-mm full-thickness tissue from each surgical margin. The 1-mm surgical margin was then placed flat with the inked true surgical margin facing-up, and 5 microns sections are cut serially. The sections are cut parallel to the true surgical margin, thus ensuring that the section includes full thickness of the surgical margin. These sections were then studied under the microscope for the presence of tumor cells. If the margins were tumor-free, the eyelid defect was reconstructed appropriately. Those cases with suspicion of tumor infiltration of surgical margins on initial intra-operative rapid frozen section diagnosis underwent repeat excision of margins and repeat intra-operative rapid frozen section analysis until clearance was obtained. The details from surgical notes included: dimensions of margins excised beyond the clinical extent of tumor, number of surgical margins sent for frozen section clearance, and number of repeat excision of margins required to obtain clearance by rapid frozen section diagnosis. The information recorded from histopathology reports included: final diagnosis of the tumor and surgical margins. The rate of concordance between rapid frozen section and permanent section diagnoses for the surgical margins was recorded. The details of tumor recurrence during the follow-up period were recorded.

Results

Of 124 patients who underwent wide excisional biopsy of malignant eyelid tumor under frozen section control of margins during the study period, 120 (97%) were included in this study. Four cases including eyelid malignant melanoma ($n = 3$) and eyelid adenoid cystic carcinoma ($n = 1$) were excluded from this study owing to small number of patients. Of the 120 cases included in this study, the diagnosis included sebaceous gland carcinoma ($n = 75$, 63%), basal cell carcinoma ($n = 34$, 28%), and squamous cell carcinoma ($n = 11$, 9%).

Overall, the mean age at presentation was 58 years (median, 58 years; range, 21–92 years). There were 39 (33%) males and 81 (67%) females with malignant eyelid tumor. History of prior surgical intervention was present in 40 (33%) patients, and the surgical procedures included fine-needle aspiration biopsy ($n = 1$), incisional biopsy ($n = 9$), and excisional

biopsy (n = 30). The tumor epicenter was located in the upper eyelid (n = 65, 54%), lower eyelid (n = 52, 43%), or medial canthus (n = 3, 3%). The mean tumor diameter was 12 mm (median, 10 mm; range, 2–30 mm). All cases underwent wide excisional biopsy of the tumor with 4-mm clear margins from the clinical extent of the malignant eyelid tumor, and the surgical margins were analyzed by frozen section for rapid diagnosis. A total of 429 frozen section slides were reviewed for rapid frozen section diagnosis. Suspicion of tumor infiltration of the surgical margin was noted in 42 (9%) surgical margins. These 42 margins were re-excised including at least 2 mm from the previous surgical margin, and the margins were sent for re-analysis by frozen section. None of the cases required more than 1 revision of the surgical margin to obtain clearance from frozen section for negative tumor infiltration of the margin. Rapid diagnosis of the surgical margin was obtained within 1 h of surgical excision. Appropriate eyelid reconstruction was performed in all cases the same day, after the margin clearance. Permanent section diagnosis of the tumor and the surgical margins was available within 10 days in all cases. Five surgical margins (1%) of 4 cases including basal cell carcinoma (n = 2 cases; 3 margins) and sebaceous gland carcinoma (n = 2) reported to be free of tumor by rapid frozen section diagnosis were noted to have tumor infiltration by permanent section diagnosis; and three (< 1%) surgical margins of 3 cases including sebaceous gland carcinoma (n = 2) and basal cell carcinoma (n = 1), reported to have tumor infiltration of the surgical margin by rapid frozen section diagnosis, were noted to be free of tumor on permanent section diagnosis. All 5 margins of the 4 cases with tumor infiltration by permanent section diagnosis underwent double freeze-thaw cryotherapy of the margins. None of them underwent repeat excision of surgical margins. Comparing the rapid frozen section and permanent section diagnoses, the sensitivity, specificity, and accuracy of intra-operative rapid frozen section diagnosis of surgical margins for malignant eyelid tumors were 89% (95% CI 75.44–96.21%), 99% (95% CI 97.74–99.84%), and 98% (95% CI 96.36–99.19%), respectively. The positive predictive value and negative predictive value were 93% (95% CI 80.73–97.58%) and 99% (95% CI 97.10–99.43%). The details of individual tumors are listed in Table 1.

During the mean follow-up period of 7 months (median, 4 months; range, < 1 to 54 months), 2 (2%) patients with sebaceous gland carcinoma (n = 1) and basal cell carcinoma (n = 1) developed tumor recurrence and both recurrences occurred at the junction of the residual and reconstructed eyelid. Of these, the patient with basal cell carcinoma had tumor infiltration of medial and superior margins based on permanent section diagnosis. Tumor recurrence was noted 24 months postsurgical excision, in spite of double freeze-thaw cryotherapy to the surgical margins based on the permanent section diagnosis of margin involvement by the tumor (Fig. 1). The patient with sebaceous gland carcinoma had no tumor infiltration based on rapid frozen section or permanent section diagnosis of surgical margins. Fifteen site map biopsy performed at the time of primary excisional biopsy of the tumor was also negative. In this patient, tumor recurrence was noted 36 months after surgical excision (Fig. 2).

Discussion

Eyelid tumor excision under intra-operative frozen section for surgical margin control is critical to maximize the normal residual tissue and minimize the tumor residue. However, the sensitivity and specificity of conventional frozen section are not 100%. In a study of 24,880 cases (97,914 frozen section slides) of general surgical pathology including various lesions, the accuracy of frozen section diagnosis was 98% [7]. According to published literature, the median rate of discordance between frozen section and permanent section diagnoses is 2.9% (range, 1.4–12.9%), with 75% of studies showing a discordance rate of less than 5% [8]. In our study of 120 malignant eyelid tumors with 429 frozen section slides, the accuracy of frozen section diagnosis was 98% with false positive rate of < 1% and false negative rate of 1%. False negative results on frozen section were noted in basal cell carcinoma (n = 2) and sebaceous gland carcinoma (n = 2). False positive result on frozen section was noted in sebaceous gland carcinoma (n = 2) and basal cell carcinoma (n = 1).

Malignant eyelid lesions excised without intra-operative Mohs micrographic surgery or conventional frozen section control have 5–64% chances of positive margins on permanent sections, and the rate of tumor recurrence in these cases is reported at 4–23% [9–12].

Table 1 Details of eyelid malignant tumors

Feature	Sebaceous gland carcinoma $n = 75$	Basal cell carcinoma $n = 34$	Squamous cell carcinoma $n = 11$
Age at presentation (years)	58 (60, 21–92)	58 (57, 29–86)	54 (52, 28–80)
Mean (median, range)			
Gender			
Male	26 (35)	6 (18)	7 (64)
Female	49 (65)	28 (82)	4 (36)
History of prior intervention	30 (40)	6 (18)	4 (36)
Incisional biopsy	7 (9)	2 (6)	0 (0)
Excisional biopsy	22 (29)	4 (12)	4 (36)
FNAC	1 (1)	0 (0)	0 (0)
Tumor epicenter			
Upper eyelid	53 (71)	6 (18)	6 (55)
Lower eyelid	21 (28)	26 (76)	5 (45)
Medial canthus	1 (1)	2 (6)	0 (0)
Maximum tumor basal diameter (mm)	11 (10, 2–30)	13 (13, 3–30)	18 (15, 5–30)
Number of margins submitted for frozen section analysis	269	117	43
Correlation between permanent section diagnosis and frozen section diagnosis of surgical margins ($n = 429$)			
True negative	241 (90)	101 (86)	43 (100)
False negative	2 (< 1)	3 (3)	0 (0)
True positive	24 (9)	12 (10)	0 (0)
False positive	2 (< 1)	1 (< 1)	0 (0)
Sensitivity in % (95% CI)	92 (74.87–99.05)	80 (51.91–95.67)	–
Specificity in % (95% CI)	99 (97.06–99.90)	99 (94.66–99.98)	100 (91.78–100)
Accuracy in % (95% CI)	99 (96.24–99.59)	97 (91.48–99.06)	100 (91.78–100)
Positive predictive value in % (95% CI)	92 (75.03–97.96)	92 (62.67 to 98.85)	–
Negative predictive value in % (95% CI)	99 (96.95–99.78)	97 (92.44–98.93)	100
Tumor recurrence	1 (1)	1 (3)	0 (0)
Follow-up duration (months)			
Mean (median, range)	7 (4, < 1 to 50)	7 (4, < 1 to 54)	4 (4, 2 to 7)

FNAC = fine-needle aspiration biopsy; CI = confidence interval

Adequate margin control by intra-operative Mohs micrographic surgery or conventional frozen section aids in minimizing the tumor recurrence. Various other studies have shown that the rate of tumor recurrence of periocular malignancies is 0–7%, when the surgery is performed under Mohs micrographic surgery control [13–18].

The rates of tumor recurrence of eyelid malignancies following Mohs micrographic surgery and conventional frozen section are comparable. In a study of 90 patients with periocular basal cell carcinoma who underwent excisional biopsy under conventional frozen section control, the tumor recurrence rate was 2.2% at 5-year follow-up [11]. Various other studies have shown that the rate of recurrence of periocular basal cell carcinoma is 0–2.2%, when the surgery is performed under conventional frozen section control [9, 19–21]. In our study including 34 cases of basal cell carcinoma, recurrence was noted in one case (3%) with false negative margins on frozen section and positive margins on permanent section.

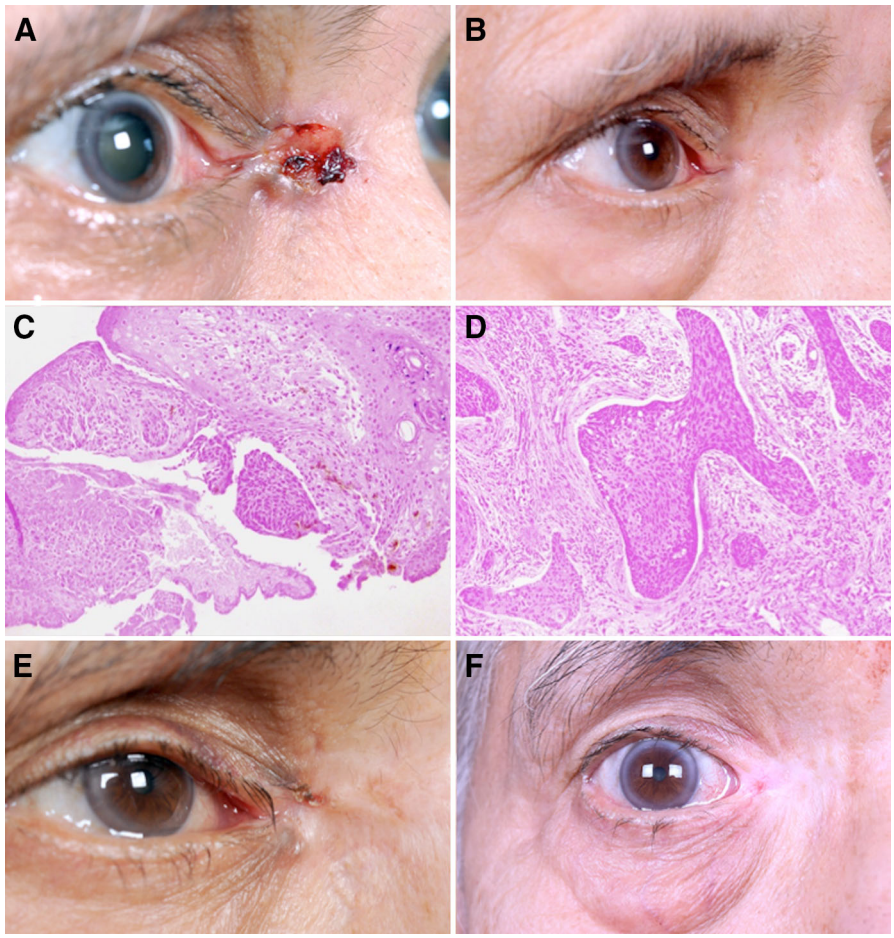

Fig. 1 Tumor recurrence in a patient with basal cell carcinoma. **a** A 75-year-old female presented with basal cell carcinoma in the right medial canthal area. Wide excision biopsy was performed under frozen section control. After obtaining margin clearance by frozen section diagnosis, eyelid reconstruction by glabellar flap was completed. **b** The patient was doing well at 3-month follow-up. **c** The permanent section diagnosis revealed residual tumor at nasal (hematoxylin & eosin stain, × 10 magnification) and **d** superior margins (hematoxylin & eosin stain, × 10 magnification). **e** The patient developed tumor recurrence at the junction of residual and reconstructed eyelid 2 years post-surgery, and **f** the patient did well after treatment of tumor recurrence with intensity-modulated radiotherapy

The recurrence rate of sebaceous gland carcinoma is high at 32% when the excisional biopsy is done without intra-operative margin clearance [22, 23]. The use of intra-operative diagnosis by Mohs micrographic surgery or conventional frozen section control for eyelid sebaceous gland carcinoma can be challenging due to inaccuracy of detecting intra-epithelial pagetoid spread on frozen sections. However, the recurrence rates are low compared to when done without intra-operative margin clearance. The recurrence rate of sebaceous gland carcinoma treated by Mohs micrographic surgery is reported at 0–12% [24, 25]. The recurrence rate of sebaceous gland carcinoma treated by conventional frozen section margin control is reported at 22% [26]. In our study including 75 sebaceous gland carcinomas, the recurrence rate was 1%. However, the follow-up duration in this subset was relatively short. One patient had tumor recurrence in spite of margin clearance by frozen and permanent sections. In this case, map biopsy also did not reveal any skip lesions nor the patient had any clinical evidence of residual lesion or pagetoid conjunctival involvement.

The recurrence rate of squamous cell carcinoma following tumor excision under frozen section control is 0.9–6% [27–29]. In our study including 11 cases of squamous cell carcinoma, recurrence was not seen in any case during the follow-up period. However, the follow-up duration in this subset was relatively short.

The drawbacks of the study include retrospective nature of the study and the short follow-up duration. The recurrence rates of eyelid tumors are relatively low in our study, which could be related to short follow-up duration. Longer follow-up duration is recommended to assess the recurrence rates accurately for these malignant eyelid tumors. The rare possibility of false negative interpretation of frozen section and

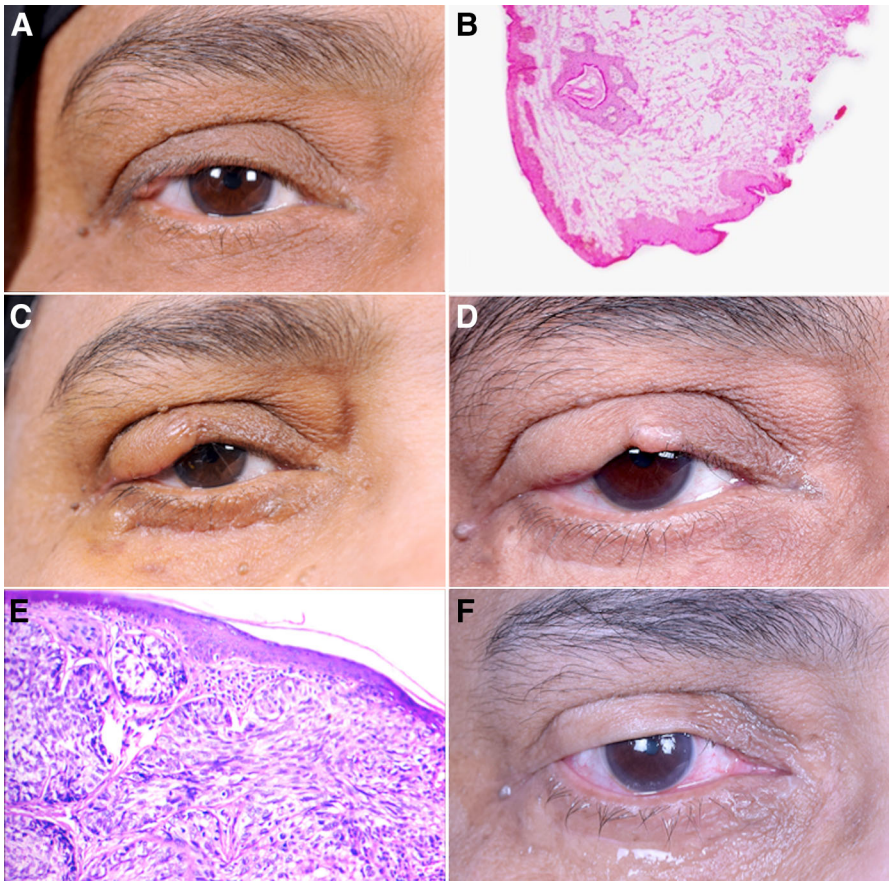

Fig. 2 Tumor recurrence in a patient with sebaceous gland carcinoma. **a** A 56-year-old female with sebaceous gland carcinoma of the lateral one-third of the right upper eyelid. Wide excision biopsy was performed under frozen section control. **b** Frozen section diagnosis and permanent section of the medial surgical margin (hematoxylin & eosin stain, × 4 magnification) did not show any residual tumor. Fifteen site map biopsy from the residual conjunctiva was also negative for tumor. **c** Two months post-surgery, there was lymphedema in the reconstructed eyelid with no evidence of tumor recurrence. **d** The patient developed tumor recurrence at the junction of medial residual and lateral reconstructed eyelid 3 years post-surgery. **e** The recurrent tumor was confirmed on histopathology (hematoxylin & eosin stain, × 10 magnification), and **f** the patient did well after excisional biopsy of recurrent tumor under frozen section control

permanent section diagnoses in these cases cannot be ruled out.

In conclusion, there is excellent concordance between the intra-operative rapid frozen section and permanent section diagnoses of surgical margins following wide surgical excisional biopsy of malignant eyelid tumors with an accuracy of 98%. The rate of tumor recurrence in our series was low at 2%. Meticulous surgery and careful interpretation of frozen sections of the surgical margins of the malignant eyelid tumors by an experienced surgical pathologist play an important role in influencing the overall outcome of the surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Jacyna LS (1988) The laboratory and the clinic: the impact of pathology on surgical diagnosis in the Glasgow Western Infirmary, 1875–1910. Bull Hist Med 62:384–406
2. Wright JR Jr (1985) The development of the frozen section technique, the evolution of surgical biopsy, and the origins of surgical pathology. Bull Hist Med 59:295–326
3. Fechner RE (1977) The birth and evolution of American surgical pathology. In: Rosai J (ed) Guiding the surgeon's hand. American Registry of Pathology, Armed Forces Institute of Pathology, Washington DC
4. Gal AA (2005) The centennial anniversary of the frozen section technique at the Mayo Clinic. Arch Pathol Lab Med 129:1532–1535
5. Lechago J (2005) The frozen section: pathology in the trenches. Arch Pathol Lab Med 129:1529–1531
6. Chévez-Barrios P (2005) Frozen section diagnosis and indications in ophthalmic pathology. Arch Pathol Lab Med 129:1626–1634
7. Ferreiro JA, Myers JL, Bostwick DG (1995) Accuracy of frozen section diagnosis in surgical pathology: review of a 1-year experience with 24,880 cases at Mayo Clinic Rochester. Mayo Clin Proc 70:1137–1141
8. Mahe E, Ara S, Bishara M et al (2013) Intraoperative pathology consultation: error, cause and impact. Can J Surg 56:E13–E18
9. Older JJ, Quickert MH, Beard C (1975) Surgical removal of basal cell carcinoma of the eyelids utilizing frozen section control. Trans Am Acad Ophthalmol Otolaryngol 79:658–663
10. Downes RN, Walker NPJ, Collin JRO (1990) Micrographic (Mohs') surgery in the management of periocular basal cell epitheliomas. Eye 4:160–168
11. Wong VA, Marshall JA, Whitehead KJ et al (2002) Management of periocular basal cell carcinoma with modified en face frozen section controlled excision. Ophthal Plast Reconstr Surg 18:430–435
12. Hamada S, Kersey T, Thaller VT (2005) Eyelid basal cell carcinoma: non-Mohs excision, repair, and outcome. Br J Ophthalmol 89:992–994
13. Mohs FE (1986) Micrographic surgery for the microscopically controlled excision of eyelid cancer: history and development. Adv Ophthal Plast Reconstr Surg 5:381–408
14. Mohs FE (1986) Micrographic surgery for the microscopically controlled excision of eyelid cancers. Arch Ophthalmol 104:901–909
15. Robins P, Rodriguez-Sains R, Rabinovitz H et al (1985) Mohs surgery for periocular basal cell carcinomas. J Dermatol Surg Oncol 11:1203–1207
16. Monheit GD, Callahan MA, Callahan A (1989) Mohs micrographic surgery for periorbital skin cancer. Dermatol Clin 7:677–697
17. Pieh S, Kuchar A, Novak P et al (1999) Long term results after surgical basal cell carcinoma excision in the eyelid region. Br J Ophthalmol 83:85–88
18. Leib ML, Johanson DA, Eliezri YD (1992) Mohs histographic surgery and ophthalmic plastic reconstruction. Ophthal Plast Reconstr Surg 8:262–270
19. Glatt HJ, Olson JJ, Putterman AM (1992) Conventional frozen sections in periocular basal-cell carcinoma: a review of 236 cases. Ophthalmic Surg 23:6–8
20. Frank HJ (1989) Frozen section control of excision of eyelid basal cell carcinomas: 81/2 years' experience. Br J Ophthalmol 73:328–332
21. Chalfin J, Putterman AM (1979) Frozen section control in the surgery of basal cell carcinoma of the eyelid. Am J Ophthalmol 87:802–809
22. Ratz JL, Luu-Duong S, Kulwin DR (1986) Sebaceous carcinoma of the eyelid treated with Mohs' surgery. J Am Acad Dermatol 14:668–673
23. Spencer JM, Nossa R, Tse DT, Sequeira M (2001) Sebaceous carcinoma of the eyelid treated with Mohs micrographic surgery. J Am Acad Dermatol 44:1004–1009
24. Snow SN, Larson PO, Lucarelli MJ et al (2002) Sebaceous carcinoma of the eyelids treated by mohs micrographic surgery: report of nine cases with review of the literature. Dermatol Surg 28:623–631
25. Brady KL, Hurst EA (2017) Sebaceous carcinoma treated with Mohs micrographic surgery. Dermatol Surg 43:281–286
26. Callahan EF, Appert DL, Roenigk RK, Bartley GB (2004) Sebaceous carcinoma of the eyelid: a review of 14 cases. Dermatol Surg 30:1164–1168
27. Nemet AY, Deckel Y, Martin PA et al (2006) Management of periocular basal and squamous cell carcinoma: a series of 45 cases. Am J Ophthalmol 142:293–297
28. Gayre GS, Hybarger CP, Mannor G et al (2009) Outcomes of excision of 1750 eyelid and periocular skin basal cell and squamous cell carcinomas by modified en face frozen section margin-controlled technique. Int Ophthalmol Clin 49:97–110
29. Donaldson MJ, Sullivan TJ, Whitehead KJ et al (2002) Squamous cell carcinoma of the eyelids. Br J Ophthalmol 86:1161–1165