Surgical resection of nonmelanoma skin cancer (NMSC) may be performed via Mohs micrographic surgery (MMS) or standard surgical excision with complete margin analysis. Whereas MMS may necessitate delayed reconstruction surgery, intraoperative frozen section analysis (IFSA) may be used to ensure clear surgical margins before proceeding with reconstruction. To achieve curative resection while optimizing aesthetic outcomes, surgeons may use surgical excision guided by IFSA to forego extensive or delayed reconstruction. Patients undergoing wide local excision for NMSC using IFSA from October 2008 to November 2016 were evaluated. Analysis included IFSA versus permanent section outcomes, the number of required excisions, and the recurrence rate. Our analysis contained 145 patients involving 162 lesions. IFSA demonstrated that 73.4 per cent of margins were negative after one excision and 26.5 per cent were re-excised until achieving negative margins. Analysis revealed one false-positive case (0.62%) and four false-negative cases (2.47%). Nine patients had local recurrence (5.56%). Frozen section sensitivity was 88.99 per cent and specificity 99.20 per cent. The positive predictive value was 96.97 per cent, and negative predictive value was 96.90 per cent. Mean follow-up time was 39 months. Both resection and recurrence data of excised NMSC lesions at our institution suggest that surgical excision using IFSA is a safe and effective alternative to MMS.

Nonmelanoma skin cancer (NMSC) is the most commonly occurring malignancy in the United States, with an estimated 1.5–2 million cases occurring each year.1 Of these, 70–80 per cent are basal cell carcinoma (BCC) and approximately 20 per cent are squamous cell carcinoma (SCC).1 Multiple treatment modalities presently exist; however, a meta-analysis comparing available treatment methods demonstrated that surgical excision provides superior outcomes in lesion response, NMSC clearance, and has a lower rate of recurrence than other treatments options such as cryotherapy, radiotherapy, pharmacotherapy (5-flurouracil and imiquimod), or photodynamic therapy.2

Although surgical excision remains the standard of care, the method of excision is still under debate. Notably, excisions involving wide margins may result in a poor cosmetic outcome, whereas conservative resections may lead to incomplete tumor removal, resulting in local recurrence. To achieve an appropriate balance, the use of intraoperative frozen section analysis (IFSA) may help achieve tumor-free margins, thereby circumventing the need for extensive or delayed reconstruction. The use of IFSA has recently been called into question with some arguing that the false-negative rate (discrepancy of negative IFSA and positive final pathology) is too high. The debate formed as a result of specific studies demonstrating IFSA false-negative rates as high as 19.5 per cent3 and 28.7 per cent4 because of incomplete excision. This finding has subsequently led to the avoidance of IFSA utilization in certain practices.

Presently, wide local excision of NMSC, typically 4 mm for BCC and 4 to 6 mm for SCC, is recommended as per the National Comprehensive Cancer Network (NCCN) guidelines, followed by postoperative vertical sectioning for final pathology. Using this method, not all margins of the specimen undergo pathological evaluation, resulting in a cure rate of 90–95 per cent.5 By contrast, Mohs micrographic surgery (MMS) involves excision with narrower margins, typically 1–2 mm. In addition, MMS uses a horizontal sectioning
technique for pathologic testing, allowing comprehensive examination of the entire tissue margin. This difference has made MMS the most effective method of treatment for NMSC, with a five-year cure rate of 98.9 per cent. A randomized controlled trial comparing standard surgical excision versus MMS showed no difference in recurrence of primary facial BCC between the two treatment modalities. However, there was a significant reduction in secondary recurrence of facial BCC after Mohs surgery than after standard excision. As per the NCCN guidelines, resection with complete circumferential margin assessment using IFSA is an alternative to MMS.

Variations in the geographical availability of MMS, patient waiting times, and costs continue to affect patient preference between these two surgical modalities. Furthermore, MMS commonly requires a delayed reconstruction leading to additional surgeries, increasing the patient’s risk of an adverse outcome. To achieve curative resection and provide favorable cosmetic outcomes, plastic surgeons may use IFSA-guided excision to forego a delayed reconstruction. Our center offers excision of such lesions by complete margin IFSA, with most patients undergoing reconstruction on the same day.

The purpose of this study was to examine the outcomes of IFSA-guided excision of NMSC with regard to local recurrence. The IFSA results were compared with final permanent pathology reports to determine the false-negative rate and whether IFSA is an effective method to reduce recurrence of NMSC.

Methods

All initial and recurrent NMSCs excised by the plastic surgery department of Altru Health System in Grand Forks, ND, with complete margin IFSA from October 2008 to November 2016 were retrospectively reviewed. All patients who underwent IFSA-guided NMSC excision were included in the study. All patients provided written consent for surgery before NMSC excision. Institutional Review Board approval was obtained from the University of North Dakota and Altru Health System. Data collected included patient demographics, site of excision, size of excision, cancer subtype, number of resections performed to achieve clear margins on intraoperative histopathology, complete excision rates, final histopathological diagnosis, and recurrences to date. All resections were performed by one of three plastic surgeons, with local anesthetic infiltration of the site before surgery, and analyzed by one of eight attending pathologists. The primary excision margin around the NMSC lesion was consistent with the NCCN guidelines with resection with complete circumferential margin assessment to obtain negative margins with curative intent. Using IFSA, initial resection margins were approximately 2 to 3 mm. If frozen section analysis revealed a positive margin, an additional 1 to 2 mm resection was completed, as per the operating surgeon’s discretion. The operating surgeon frequently delivered each specimen to the attending pathologist immediately after excision. All margins of concern and relevant procedure details were directly discussed between the surgeon and the pathologist to ensure clear communication.

Histopathological Technique

The submitted specimens were given a gross description and measured. If orientation was provided by the surgeon, the specimen was differentially inked. First, the ellipses were serially sectioned in a bread loaf fashion. Then, the slices were completely submitted in one or more sections for margin assessment. Microscopic determination of the lesion subtype (BCC or SCC) was determined as the margin status was assessed. Either face-to-face or direct intercom communication to the surgeon was immediately completed. Based on the results, the surgeon either chose to submit additional tissue for examination or proceeded to closure. The next day after processing, frozen section results were compared with permanent sections to confirm correlation.

Results

A total of 145 patients with a mean age of 72 years (median, 73; range, 38–95 years) and a total of 162 lesions were treated using the aforementioned techniques. The breakdown of subtypes was 61.73 per cent BCC and 38.27 per cent SCC (Table 1). Of the analyzed lesions, 83.94 per cent involved excisions of the head or neck. Table 1 outlines the anatomical location of each NMSC lesion included in the study.

| Table 1. Cancer Subtype and Location |
|-------------------------------------|
| **Subtype** | % |
| BCC | 61.73 |
| SCC | 38.27 |
| **Location** | % |
| Nose/ala | 24.07 |
| Ear | 13.58 |
| Cheek | 10.49 |
| Upper extremity | 10.49 |
| Temple | 9.26 |
| Scalp | 7.41 |
| Upper/lower lip | 6.17 |
| Forehead | 4.32 |
| Eyelid/canthus | 4.32 |
| Neck | 4.32 |
| Lower extremity | 4.32 |
| Chest/breast | 1.23 |
Operative reports demonstrated that 73.5 per cent of margins were clear after one excision. The remaining 26.5 per cent of cases with residual positive margins after primary excision were identified using IFSA and were re-excised until negative margins were achieved. A total of 16 per cent required a second excision, and the remaining 10.5 per cent required three or more excisions to attain clear margins (Table 2).

Patients had a mean follow-up of 39 months (median, 37; range, 1–108), with 29 patients lost to follow-up (all deceased). The follow-up period was based on the time of excision to the most previously documented visit to a plastic surgeon, dermatologist, or primary care physician. Six patients with a follow-up period of less than one year were called, and a phone survey was completed. One additional recurrence was reported after completing the phone surveys, and one patient was unreachable.

Nine patients had local recurrence: a recurrence rate of 5.56 per cent. Three recurrences occurred following negative results on both IFSA and final permanent histopathology reports, whereas four recurrences arose following positive results on both reports. Finally, two recurrences occurred for patients with negative IFSA results but were positive on permanent section analysis (Fig. 1). Frozen sections with positive margins identified by IFSA were re-excised until negative margins were achieved. Once re-excision was complete, negative margins identified by IFSA were compared with final pathology, giving rise to a false-negative rate of 2.47 per cent. All other frozen sections demonstrating positive margins by IFSA were re-excised until clear.

Retrospective analysis revealed one false-positive case, resulting in a false-positive rate of 0.62 per cent. Four false-negative results were identified: a false-negative rate of 2.47 per cent. The sensitivity of IFSA was 88.89 per cent, and the specificity was 99.20 per cent. This sensitivity is the detection of a true-positive margin on IFSA as compared with the permanent section on final pathology. The positive predictive value of IFSA was 96.97 per cent with a negative predictive value of 96.90 per cent (Fig. 1).

Discussion

Conventional surgical excision remains the most widely available surgical treatment for NMSC, with reported cure rates for low-risk lesions reaching or exceeding 95 per cent. Unfortunately, standard pathologic processing using vertical sections only allows approximately 44 per cent of the margin to be examined. This may contribute to a higher recurrence rate after standard pathologic analysis than MMS, which involves histologic examination of up to 100 per cent of the surgical margin, resulting in a cure rate of 98–99 per cent.

As the accessibility of MMS increases, evaluating the safety and efficacy of NMSC excision using IFSA versus MMS is important in providing patients with appropriate treatment to optimize outcomes and reduce complications. In rural and underserved territories, the greater presence of surgeons capable of standard surgical excision than fewer Mohs-trained physicians and histotechnicians must be considered. Presently, limited geographical availability of MMS, prolonged patient waiting times, and costs continue to play a role in patient preference.

Operative treatment of NMSC is difficult, especially when performed on challenging areas of the head and neck. Notably, surgical excision necessitates complete tumor resection while considering the physiologic and cosmetic consequences of operating on an area highly associated with an individual’s identity. Aggressive excisions involving wide margins may result in larger defects with poor cosmetic outcomes, whereas conservative resections with tighter margins may lead to higher rates of recurrence. Striking a delicate balance between each end of the spectrum is critical in avoiding significant damage to the patient’s physical, mental, and emotional well-being.

Given the aesthetic appreciation of an individual’s head and neck regions, plastic surgeons may be consulted to attempt delayed reconstruction after MMS. The reconstruction can be quite complex, occasionally

### Table 2. Number of Excisions Required to Achieve Negative Margins on IFSA, Mean Excisions, and Recurrence Data

| Excisions required to achieve clear margins on IFSA (%) | 1 | 73.45 (re-excised: 26.5) |
| Mean age (years) | 72 (range, 28–95) |
| Mean follow-up (months) | 39 (range, 1–108) |
| Mean number of excisions | 1.40 (range, 1–4) |
| Patients with recurrence to date (%) | 5.56 |

**Permanent Final Pathology**

| Intraoperative Frozen Section | Positive | Negative |
|-----------------------------|---------|---------|
| Positive | 32 (Recur: 4) | 1 (Recur: 0) |
| Sensitivity = 32/(32+1) = 88.89% |
| Specificity = 125/(125+1) = 99.20% |
| PPV = 32/(32+1) = 96.97% |
| NPV = 125/(125+4) = 96.90% |
| Negative | 4 (Recur: 2) | 125 (Recur: 3) |

**Fig. 1.** Intraoperative frozen section vs permanent frozen section results including calculations.
requiring advanced local tissue rearrangement or flap reconstruction. Having to undergo two separate procedures, the patient may be subjected to unnecessary risk by returning home with an open wound, only to inconveniently return for a reconstructive surgery at a later date. Conversely, primary NMSC resection performed by a reconstructive surgeon may be advantageous in achieving negative margins while minimizing resection defects. In addition, the effective use of IFSA enhances the surgeon’s ability to receive immediate intraoperative feedback to ensure tumor-free margins. Given this readily retrievable information, the surgeon is able to attain finer margins of uninvolved skin surrounding the lesion. This aids in producing a cosmetically acceptable outcome for the patient while providing curative resection in one comprehensive procedure.

When comparing IFSA to final pathology, there is always a possibility of discovering a false-negative result. As Moncrieff et al. first reported, each false negative may be due to one of three different stages in the tissue sampling process. The possibility of obtaining a false negative may be due to a sampling error by the surgeon taking the biopsy, a section sampling error by the pathologist, and/or misinterpretation of the frozen section biopsy. However, because the surgeons communicated directly with the pathologist immediately after excision, and sometimes even hand-delivered the specimen, we believe our study minimizes the probability of these errors occurring. We believe IFSA provides helpful and acceptably accurate data to guide NMSC excisions, with only a 2.47 per cent false-negative rate and 96.97 per cent positive predictive value based on our institutional analysis.

This review has demonstrated that Altru Health System’s plastic surgeons have attained similar NMSC recurrence rates when compared with national averages using surgical excision guided by IFSA. Although there continues to be room for improvement, in both recurrence rates and in pathologic analysis, the data are supportive in showing that our health system’s plastic surgeons are aligned with the rest of the nation in terms of NMSC resection outcomes. Because MMS is time-consuming and not widely available in North Dakota and other rural communities, the results demonstrate that surgical excision guided by IFSA is a safe and effective alternative to MMS.

For further study, it would be beneficial to include a comparison of recurrence rates with false-positive and false-negative results in this sample set to data from local MMS surgeons to evaluate differences between the two approaches and how that may affect patient safety. In addition, further evaluation of the lesion’s anatomic location may show differences in high-risk versus low-risk NMSC rates of recurrence.

The first limitation of our study is because of its size with a relatively small sample set consisting of 145 patients and 162 excisions. Second, follow-up for recurrence was calculated based on last recorded visit to a plastic surgeon, primary care physician, or dermatologist; however, not all visits within these categories included documentation of a thorough skin examination, giving rise to the possibility that some patients had recurrences that went undocumented in the electronic medical record. Third, we acknowledge that this is a retrospective study which may introduce a period and patient selection bias by involved clinicians; however, we believe our findings to be valid and unbiased. Originally, we planned to collect all data for a period of 11 years spanning from 2007 to 2017, but we were unable to access the information of 32 patients because of EMR chart unavailability. These patients were excluded based on unavailable EMR chart access. The physical paper charts were also deemed unavailable after specific request. Fourth, the resections were performed by one of three different plastic surgeons and assessed by one of eight pathologists. The influence of 11 total physicians on the study results presents the possibility of variable interpretation, analysis, and lack of continuity. Last, by completing a phone survey for all patients with a follow-up period of less than one year, we were able to detect one additional recurrence. By expanding the number of patients completing a phone survey, we may have been able to detect additional recurrences. However, phone surveys possess their own limitations including, but not limited to, misinterpretation, assumptive behavior, and high dependence on the patient’s health care literacy.

**Conclusion**

IFSA–guided excision outcomes and recurrence rates of nonmelanoma skin cancers excised at our institution are comparable with national trends using standard surgical excision. Our findings demonstrate that resection using IFSA is consistent with high sensitivity and specificity, and that it is a safe and effective alternative to MMS. The use of IFSA may assist surgeons in achieving tumor-free margins, thereby circumventing the need for extensive or delayed reconstruction. Clinicians must understand both the benefits and the potential pitfalls of IFSA when surgically removing a NMSC lesion. Before undergoing surgery, patients should still be fully informed and educated on the possibility of false-positive or false-negative reports.

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