Implications of Malignancy, Radiation, and Timing of Major Nasal Reconstruction

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KEYWORDS

• Nasal reconstruction • Skin cancer • Mohs • Timing

KEY POINTS

- Complex Nasal Anatomy: The central face's intricate, multilayered nasal anatomy presents a significant challenge for reconstructive surgeons during major nasal reconstruction.
- Surgeon's Responsibility: Reconstructive surgeons must be well-versed in common cutaneous malignancies and excisional techniques, as these can result in complex nasal defects.
- Discussion on Malignancies: This article aims to discuss various cutaneous malignancies commonly encountered, shedding light on their characteristics and implications for nasal reconstruction.
- Excisional Techniques: The article also delves into excisional techniques used in addressing these malignancies, providing insights for reconstructive surgeons in managing complex cases.
- Radiation's Impact: In addition, the article explores how radiation therapy affects tissues, offering valuable knowledge for surgeons dealing with postradiation reconstructive challenges.

BACKGROUND

The incidence of cutaneous melanoma (CM) and nonmelanoma skin cancer (NMSC) is increasing both within the United States and on a global scale. Within the United States, this is represented by one in five Americans being diagnosed with skin cancer by age 70 years.[1] For NMSC, up to 95% are diagnosed in the head and neck (H&N) region due to ultraviolet light exposure.[2] Furthermore, more than 50% of individuals will develop a second primary NMSC within 5 years.[2] The incidence of CM has increased by 51.1% over 20 years in pediatric and young adult populations, with approximately 20% of CM occurring in the H&N.[3] Skin cancer places a substantial health and economic burden on health care systems. The overall treatment cost of skin cancers within the United States is estimated to be more than $8.1 billion annually.[4]

Treatment and reconstruction of these increasingly prevalent H&N cutaneous malignancies poses a challenging feat. The difficulty arises from the prominently visible location of the nose and its role in essential functions including smell and breathing. Therefore, optimizing reconstruction following a complete oncologic resection of these malignancies carries a heightened importance. As the nose acts as the center piece of the face, with nuanced three-dimensional contours and variability in skin composition, it is a particularly difficult area for reconstruction. This is corroborated by previous reports demonstrating skin cancer repair on the nose as an independent

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predictive factor in patient's postoperative psychosocial distress.[5] Furthermore, the multilayered skin, cartilage and mucosal reconstruction of full thickness defects, requires a more complex reconstruction. Among the many considerations to optimize a nasal repair, the decision of timing of reconstruction is an area of contention. Herein, the authors discuss the variables implicated in determining the best timing for nasal reconstruction following skin cancer resection.

RESECTION MODALITIES

The eradication of malignancy before reconstruction is of paramount importance to the reconstructive surgeon. The current clinical consensus on recommended surgical resection techniques for skin cancers predominantly consists of wide local excision (WLE), Mohs micrographic surgery (MMS), and staged excision.[6]

Wide Local Excision

Within WLE, the surgical specimen is assessed via vertical bread-loaf sectioning, which examines only about 1% of the surgical margin (**Fig. 1**). Therefore, making a determination on margin clearance is considered a calculated decision rather than a true clearance.[6,7] When intraoperative frozen section analysis is performed, inaccuracies of margin status may arise from gross sampling errors by the surgeon, misinterpretation of the frozen section biopsy by the pathologist, or sampling error due to the technique of only analyzing a portion of the specimen.[8] Facial plastic and reconstructive surgeons should be aware of the risk of false-negative results for frozen section analysis of high-risk basal cell carcinoma (BCC) and SCC of the H&N, as one large retrospective analysis of these cases demonstrated frozen section false-negative rates of 28.7% and 27.5%, respectively.[8] When WLE is performed with postoperative margin assessment, healing by secondary intention, linear repair, or skin grafting are acceptable options. Local flaps, extensive undermining, or tissue rearrangement should only be performed once clear margins are identified.

Mohs Micrographic Surgery

MMS is generally considered a favorable technique for NMSC, as peripheral and deep tissue is prepared and examined by the Mohs surgeon from the flattened tissue for complete margin analysis (**Fig. 2**).[6] Because 100% of the margin face can be examined, margin control is more reliable than standard WLE for NMSC. The primary advantage of the Mohs technique is that facial plastic and reconstructive surgeons can perform local tissue rearrangement and reconstruction immediately rather than in a delayed fashion.

A prospective randomized trial compared MMS with WLE for primary and recurrent BCC. MMS versus WLE showed 10-year recurrence rates for primary BCC of 2.5 vs. 4.1% ($P = .397$) and recurrent BCC of 2.4 versus 12.1% ($P = .15$).[9] These findings occurred with an initial 3 mm resection margin for both treatment arms, which resulted in complete resection within two stages for 78% of MMS cases.[9] In addition, MMS offers the advantage of tissue sparing compared with WLE. A study of 30 patients with subcentimetric facial BCC treated with WLE and MMS incorporating 4 and 2 mm margins, respectively, yielded resultant median area of surgical defects of 116.6 mm^2 and 187.7 mm^2, respectively.[10] Likewise, a prospective study of 256 primary facial and scalp BCCs compared suspected defect surface area incorporating 5 mm surgical margins for WLE versus actual surface area following MMS. With a median tumor size of 71 mm^2, the median defect size following MMS versus expected WLE defect dimensions was 154 mm^2 and 298 mm^2, respectively, resulting in a 46.4% tissue sparing effect.[11] However, MMS remains a controversial

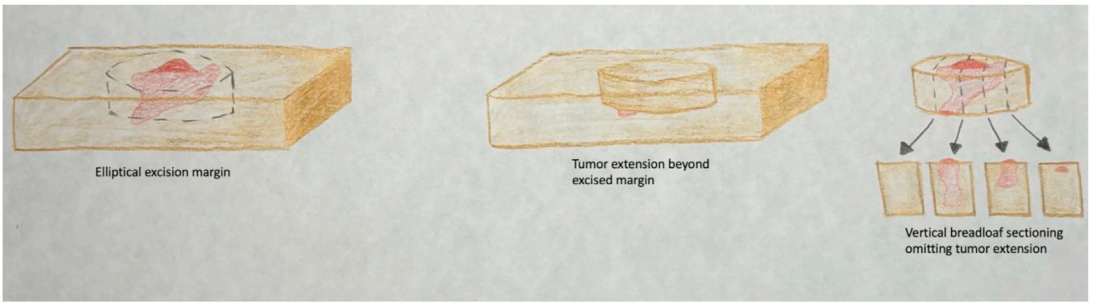

Fig. 1. Histology section obtained through conventional wide local excision. (Artwork performed by Emily Z. Stucken, MD.)

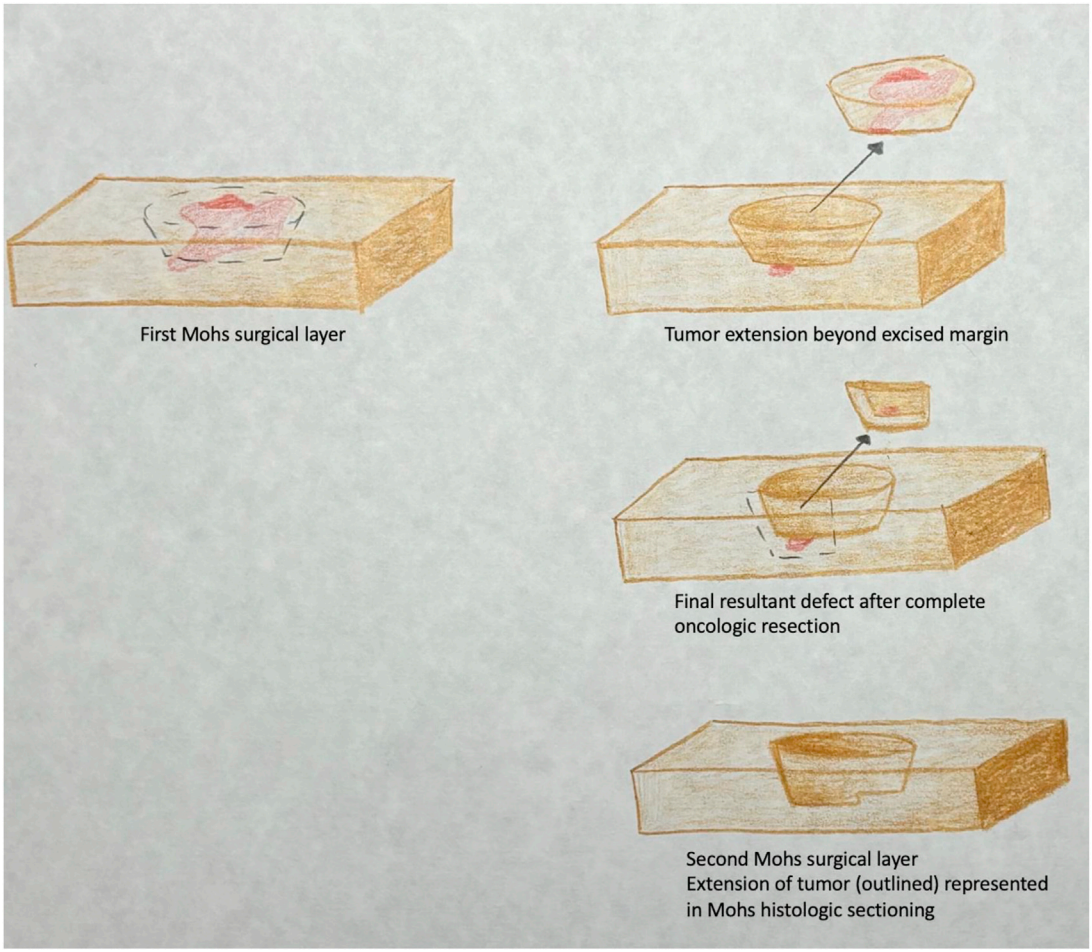

Fig. 2. Histology section obtained through Mohs micrographic surgery. (Artwork performed by Emily Z. Stucken, MD.)

option for CM, and permanent section analysis remains the gold standard.[12]

Yet, as MMS is not without shortcomings it should not be applied indiscriminately. MMS may also be seen as a labor intensive feat, as patients often require anywhere from 1 to 6 rounds of resection for histologic clearance.[13] Other considerations include potentially requiring coordination between two surgeons, which can result in delays in executing treatment plans. Furthermore, as MMS is generally performed under local anesthesia, it becomes a nonviable option for larger tumors that require general anesthesia for more extensive surgical resection.

Staged Excision

Last, staged excision entails resection of CM or NMSC followed by permanent section histologic assessment. Using formalin-fixed tissue has the disadvantage of a 24 to 48 hour delay in histologic result but yields better quality sections, which can be processed using the automated systems of a histopathology laboratory. However, patients may require several procedures to obtain clear margins. Complex reconstruction should be deferred until clearance of permanent section margins, thereby requiring another surgical intervention and potentially appropriate wound care in the interim.

The standard treatment of invasive melanoma is with WLE (with or without sentinel lymph node biopsy depending on T stage) with delayed reconstruction. Delaying reconstruction can be seen as an inconvenience. However, it allows for definitive clearance of malignancy and allows the reconstructive surgeon time to develop a reconstructive plan and counsel patients.

One potential modality for obtaining permanent section analysis with melanoma in situ (MIS) is incorporation of the square procedure. MIS poses a particular challenge due to the propensity for

subclinical extension beyond visible pigmented borders, potentially resulting in incomplete excision when adhering to National Comprehensive Cancer Network (NCCN) guidelines predicated on clear specimen borders.[14] In addition, the difficulty of differentiating the atypical melanocytic hyperplasia from chronically damaged skin exacerbates this problem. The staged square procedure entails excising a peripheral 2-mm wide strip of tissue corresponding to 100% of the peripheral margin for permanent vertical section margin analysis.[14] The resulting peripheral defect can then be sutured to surrounding wound edges, mitigating challenges with wound fibrosis or granulation bed bleeding during subsequent formal reconstruction.[14] A square procedure case of MIS in which there is significant subclinical extension of disease is illustrated in **Fig. 3**A–C.

Regardless of the resection modality chosen, mitigating the likelihood of positive margins and local recurrence is imperative to permit a subsequent safe reconstruction. The ability of the surgeon to produce a cosmetically and functionally adequate reconstruction would therefore be compromised if the primary reconstructive option was abandoned or irradiated due to the risk of residual disease. **Fig. 4**A, B shows the clinical challenge of managing a patient that was formally reconstructed before obtaining negative margins, thereby voiding a reconstructive option and clouding the ability to discern positive margin sites. This patient was ultimately referred to the senior author's practice (CLS) for treatment after she developed recurrent BCCs along the bilateral edges of the forehead flap.

SKIN CANCERS

The reconstructive surgeon should possess a solid background knowledge of common cutaneous malignancies as disease treatment and risk of recurrence impacts reconstructive surgery.

Melanoma

CM is the third most commonly diagnosed skin cancer in the United States.[6] Compared with NMSC, melanoma resections have higher local recurrence risk, greater degree of subclinical spread, and greater likelihood of requiring tissue rearranging reconstructive surgery.[15] Moreover, compared with trunk and proximal extremity CMs, those in the H&N subsites are two to three-fold more likely to have microscopic extension beyond the clinically visible tumor and are fivefold more likely to have positive margins after conventional excision.[15]

Owing to the aforementioned limitations of frozen section analysis, most CM has been treated with WLE. Margin recommendations for WLE are listed in **Table 1**.[16]

The risk of positive margins are higher in patients with advanced age, diagnosis via shave biopsy, lentigo maligna, or demosplastic subtypes, increasing tumor thickness, and presence of ulceration.[15] However, although NCCN guidelines acknowledge

Fig. 3. (*A*) Patient with nasal melanoma in situ that had specimen and margin edges marked out using the square procedure. (*B*) After three-staged square procedures demonstrating the subclinical extension of melanoma in situ. (*C*) Followed by excision of diseased central island of tissue and skin graft reconstruction once negative margin status confirmed on permanent section analysis.

Fig. 4. (*A, B*) Patient with a nasal BCC that underwent excision and immediate forehead flap reconstruction at another institution with negative frozen section margins but positive permanent section margins later presented with recurrent malignancy along the edges of the flap.

peripheral resection margins may be modified to accommodate specific anatomic considerations, there is no prospective randomized assessment of this adaptation and narrower than recommended margins may increase the risk of persistent and recurrent disease. Furthermore, the NCCN maintains a strong preference to delay complex reconstruction until histologic margin assessment is complete due to the morbidity and difficulty of deconstructing complex reconstructions for further margin analysis. To date, there has not been a randomized trial directly comparing MMS with standard WLE or different forms of staged excision with permanent section analysis. MMS is not recommended as the primary treatment for invasive CM when standard clinical margins can be obtained.[12] The NCCN endorses permanent section analysis of CM as the current gold standard.

Table 1
Recommended excision margins for melanoma based on tumor thickness

Tumor Thickness	Recommended Margin
Melanoma in situ	0.5–1.0 cm
≤ 1.0 mm	1 cm
1–2 mm	1–2 cm
≥ 2 mm	2 cm

Basal Cell Carcinoma

BCC is the most common type of skin cancer and the single leading cause of cancer among Caucasian individuals. The primary risk factors include increasing age, sun exposure, radiation exposure, fair skin, red or blond hair, light eye color, mutations of the *PTCH1* gene on chromosome 9q, and genetic syndromes including albinism, xeroderma pigmentosum, and nevoid BCC syndrome.

As BCC often possesses a highly favorable prognosis, minimizing morbidity becomes imperative with these skin cancers. Management for these relatively innocuous lesions can include cryosurgery, curettage, electrodesiccation, radiotherapy, and photodynamic therapy. However, these would not be considered primary interventions due to a lack of histologic confirmation of clearance. With respect to surgical margins, NCCN guidelines for low-risk BCC are 4-mm clinical margins. All BCC that occur on the nose are by definition high risk for local recurrence.[17]

An exception to standard WLE for BCC may be based on perioperative case-specific factors. Some higher risk features for poor prognosis within BCC include close or positive margins, tumor size ≥ 2 cm, poor tumor differentiation, perineural invasion (PNI), depth of invasion, and immunosuppression.[18] This has led to suggestions that with patients who possess high-risk features, there is a greater role of ensuring adequate resection via staged excision or MMS before reconstruction. Studies evaluating MMS versus WLE techniques for BCC have

demonstrated more favorable results with MMS, with local recurrence rates estimated at 3.1% and 14%, respectively.[19] In addition, systematic reviews have suggested lower recurrence rates in both primary and recurrent BCC cases following MMS.[20]

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the second most common skin cancer, with more than 700,000 new cases diagnosed each year in the United States.[21] Prognosis remains excellent for the majority of cases, with a 95% cure rate with surgical excision.[22] Yet the discordance between frozen section and permanent margin analysis has been reported to be as high as 19.5%, with greater false-negative rates on frozen sections associated with poorly differentiated carcinoma, lymphovascular invasion, and PNI at 14%, 36% and 26%, respectively.[22]

As aforementioned, studies evaluating resection modalities within NMSC have demonstrated lower recurrence rates with MMS than those of WLE.[23] Specifically, studies have suggested cutaneous SCC managed with MMS yield a three times lower risk of recurrence relative to standard WLE after adjusting for tumor size and depth of invasion.[21] Moreover, MMS has been shown to yield smaller defects after resection in cutaneous SCC,[21] which in the nasal subunits may be the deciding variable between a local versus a more involved interpolated flap reconstruction.

Recent investigations of the NCCN stratification of cutaneous SCC into low, high, and very high-risk groups have reaffirmed the oncologic importance of surgical resection modality. Location on the nose is a high risk factor independent of tumor size. High and very high-risk cohorts demonstrate worse prognoses and therefore yield significantly improved outcomes of local recurrence, distant metastasis, and disease-specific death rates when MMS is the selected resection technique.[7] Similarly, nationwide prospective cohort studies have shown favorable incidence rates of recurrence at 1.3 and 4.5 per 100 person-years for BCC and SCC, respectively, following MMS.[24] Hence, the evidence to date favors MMS when managing high-risk cutaneous SCC.

RADIATION

Previous exposure to radiation or future plans to radiate skin may impact reconstructive plans. Skin is particularly radiosensitive, with more than 95% of patients receiving radiotherapy developing moderate to severe skin reactions. In the acute phase, the skin typically becomes erythematous and may desquamate or ulcerate.[25] Acute damage usually resolves after therapy is completed, but chronic damage can develop months or years later and is collectively known as late radiation tissue injury. On the molecular scale, cytokine cascades and fibroinflammatory pathways are up-regulated due to radiation which can progress for many years leading to substantial fibrosis, the hallmark of chronic RT damage.[25] Late clinical manifestations include soft tissue fibrosis, skin atrophy, epithelial ulceration, skin necrosis, fistula formation, major vessel rupture, and impaired wound healing.[26] **Fig. 5**A, B shows late radiation changes to the nose including fibrosis, telangiectasias, nasal valve stenosis, and thinning of the epithelium.

For melanoma, adjuvant radiotherapy to the primary site of malignancy yields improved local control in high recurrence risk cases after surgery. Patients may have a combination of risk factors including H&N subsite, extensive neurotropism, pure desomoplastic histology, and close margins where re-resection is not feasible.[16] In the context of stage III melanoma, specifically as postoperative treatments after lymph node dissection, radiotherapy to the nodal basin may be indicated in select high-risk patients.[16]

For NMSC, similar high-risk features including deep invasion, lymphovascular invasion, size over 2 cm, poor differentiation, and PNI have been cited as indications for adjuvant radiotherapy.[27] In patients with extensive perineural or large nerve involvement, adjuvant radiotherapy may be effective in preventing local recurrence in the setting of surgery with negative margins.[28]

The contemporary literature evaluating the effect of adjuvant radiotherapy before or following nasal reconstruction on final functional and esthetic outcomes is scarce. From a practical point of view, the timing of immediate versus delayed reconstruction would be contingent on the possibility of clear oncologic resection, the characteristics of the final defect, and the complexity of the reconstruction. The American College of Surgeons and Commission on Cancer recently released the first quality metric for H&N oncology, wherein time to initiation of postoperative radiotherapy in surgically managed H&N SCC patients must be within 6 weeks.[29] As this is reflective of the robust evidence demonstrating worse oncologic outcomes with delayed initiation of postoperative radiotherapy, adherence to these recommendations is imperative. Thus, if a nasal defect requires a complex multilayered and multistaged reconstruction for definitive repair and it cannot be completed within the interval treatment window, a simple single-stage reconstruction can

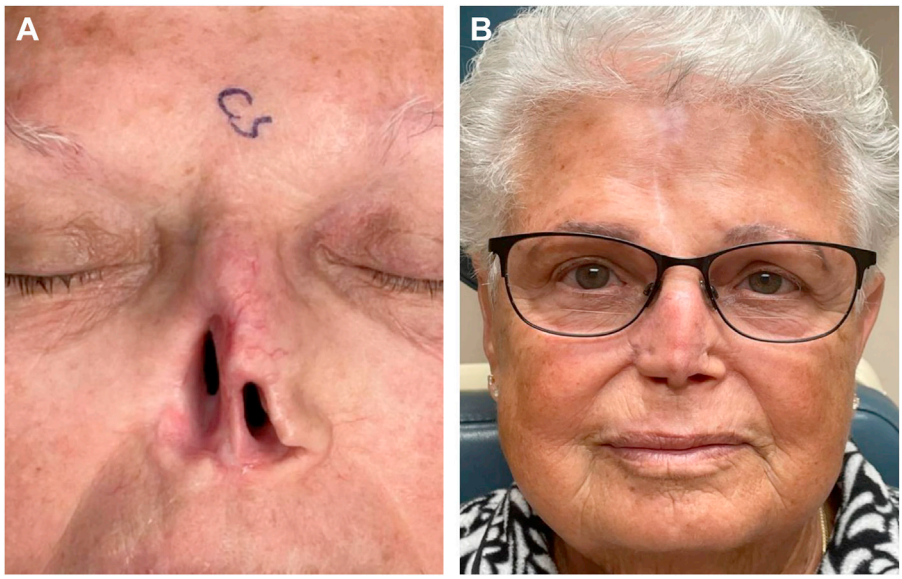

Fig. 5. (*A*) Patient with a nasal SCC who underwent partial rhinectomy and adjuvant radiation therapy. (*B*) Reconstructive outcome using a multistaged prelaminated forehead flap that was performed after the completion of adjuvant radiation.

be implemented with a formal reconstruction deferred until completion of adjuvant radiotherapy.

PATIENT OUTCOMES

Patient self-reported questionnaires following facial skin cancer surgery have shown younger age, female sex, history of anxiety and/or depression, and nasal subsites as independently predictive of psychosocial distress.[5,30] Heightened anxiety about meeting new people is the persistent quality of life metric that does not seem to normalize by 3 months, illustrating the long-term social impact of facial reconstruction.[30] In evaluation of H&N melanomas, worse visual analog scale scores occurred with skin grafting compared with locoregional reconstruction.[31] In addition, patient-reported satisfaction scales have demonstrated decreased scores with lower nasal subunit defects and with primary closure as opposed to local flap reconstruction.[32] Hence, nasal tip defects warrant reconstruction by a surgeon with significant experience in this type of repair, even if it requires a brief treatment delay for referral.

DELAYED RECONSTRUCTION

Historically, there was concern that delayed reconstruction may result in greater risk of infection as the wound is left open, requiring local wound care. However, literature to date has not suggested an increased risk of infection in circumstances where reconstruction is delayed by a variable range from a few days to few weeks.[1,33] Studies estimate that delayed and immediate reconstructions yield comparable rates of minor infections which can vary on average from 4% to 9.3%.[1,33,34] Likewise, previous assumptions that delaying reconstruction in patients with comorbidities requiring anticoagulation or with diabetes mellitus causing greater rates of complication have not been demonstrated.[33] Similarly, there is no significant increased rate of perioperative bleeding or hematoma in patients with ongoing use of oral anticoagulants.[1] Delayed reconstruction may permit more time for patient counseling, shared decision-making for surgical plans, and preoperative consultations if these undertakings were not completed before resection.

From a physiologic perspective, delayed reconstruction has been demonstrated to improve full-thickness skin graft (FTSG) as well as composite graft viability, with those undergoing delayed reconstruction by a week or greater having lower likelihood of postoperative complications including graft failure.[35,36] Delaying graft placement allows the development of granulation tissue within the wound bed to enhance the optics of composite and skin graft survival beyond relying solely on plasma imbibition.[37,38] Other potential benefits of delayed grafting include better contour restoration from proliferation of granulation tissue, as well as smaller final defect size due to wound contraction and partial healing by secondary

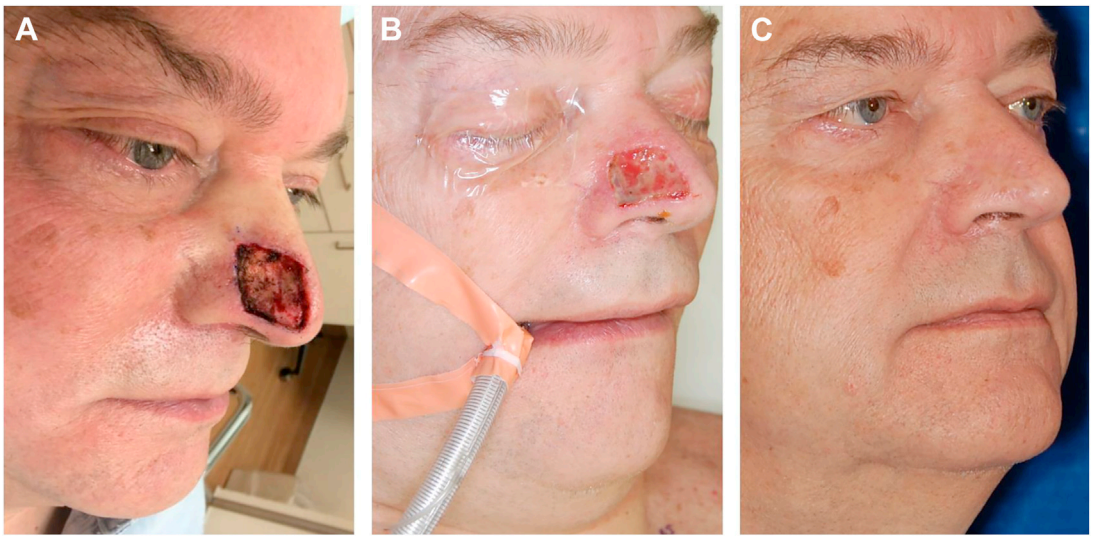

Fig. 6. (*A*) Nasal defect after excision of melanoma in situ, confirmed with permanent sections. (*B*) Two weeks of granulation. (*C*) After cartilage graft and full-thickness skin graft.

intention.[33] This physiologic postulation has been validated in previous studies comparing immediate versus delayed FTSG in nasal skin cancer following MMS, to demonstrate lower rates of partial graft loss in delayed grafting.[39] Likewise, delayed FTSG has demonstrated lower rates of nasal valve impairment and graft depression.[39] **Fig. 6**A–C demonstrates some of the aforementioned advantages of delaying reconstruction when cartilage or FTSG is planned.

Ultimately, if a more complicated repair or use of a composite graft is anticipated, or among active smokers, a delayed reconstruction for a period of 1 or 2 weeks may afford a greater likelihood of graft uptake due to the healthy granulation tissue bed.[35] Yet, reconstruction must still be performed with consideration of the overall timing to avoid sequelae once scar remodeling has begun. As wound contracture will plateau and scar will fill the remainder of the defect, the implications of specific nasal consequences such as alar notching must be considered.

One must be mindful of the fact that nasal defects tend to require the longest reconstruction time among the facial subunits, possess among the highest rates of complication, and more than 50% of incidences of facial reconstruction often require additional smaller modification procedures.[40] When comparing FTSG versus local flap reconstruction in NMSC, studies have demonstrated higher rates of hematoma and partial necrosis in patients undergoing skin graft reconstruction, with male sex and tumors above 15 mm size at a significantly higher risk of complication.[41] With respect to more intricate reconstructions, literature to date corroborates full thickness or larger defects occupying multiple facial subunits, and those requiring composite grating or interpolated flaps carry a significantly higher risk of complication.[33,34] This is pertinent in nasal reconstruction as forehead flap reconstruction and auricular cartilage grafting is considered the workhorse of larger nasal tip defects.

SUMMARY

Ultimately, literature to date does not clearly demonstrate the optimal time frame between resection and reconstruction. Inevitably, it falls on the clinician to consider the cutaneous malignancy at hand to select the appropriate timing of reconstruction. Subsequently, the patient-specific factors and reconstructive techniques used are cardinal variables in selecting the appropriate timing of repair.

CLINICS CARE POINTS

- Complex reconstructive techniques after resection of cutaneous malignancy should ideally be used once negative margins are confirmed. If adjuvant radiotherapy is indicated, then reconstruction should not delay the initiation of radiation, which must start within 6 weeks of surgical resection.
- Delayed nasal reconstruction following skin cancer is not associated with higher risk of complication and may be a favorable decision when planning for full-thickness skin grafting, composite grafts, or interpolated flaps.

DISCLOSURE

The authors have nothing to disclose.

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