

Is HPV a Factor in Outcomes of Aggressive Open/ Endoscopic Resection of Sinonasal Undifferentiated Carcinoma (SNUC)

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ABSTRACT

Objectives: SNUC is an uncommon/highly aggressive tumor with poor prognosis. This paper reviews outcomes and assesses HPV tumor presence, which is well known to impact on prognosis of oropharyngeal squamous cell carcinoma(SCC).

Methods: Since 2003 we have treated nine patients. Seven(7) had aggressive surgical resection combined with chemotherapy/radiation, one surgical resection and postoperative radiation alone, and one had combined chemotherapy and radiation alone. Patients were treated by open techniques utilizing endoscopic instruments to assure complete resection at the skull base tumor bed. HPV tumor status was determined using a real time, multiplex PCR assay that detects and quantifies 15 known high risk HPV types and targets HPV oncogene E6 as well as a beta globulin control and P16 confirmation.

Results: Seven (of 9) underwent multimodality treatment. One patient's disease was too extensive for surgical resection and was treated with chemotherapy/radiation alone, and survived 3 months. Four patients of seven (57%) having aggressive resections combined with chemotherapy/radiation are still alive/NED an average of 8.7 years from the time of treatment. Those with combined treatment who succumbed to disease(3) still had an average survival time of 18 months from diagnosis. All tumors were negative for HPV.

Conclusion:

A combination of aggressive open surgical intervention utilizing endoscopic techniques with closely applied chemotherapy and radiation has resulted in a 57% long-term survival and prolonged disease free intervals in these very aggressive tumors. We recently demonstrated a much better survival in our HPV positive nasal SCC's. There is no evidence of HPV virus in these tumors, however.

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INTRODUCTION

Sinonasal undifferentiated carcinoma (SNUC) is an uncommon, highly aggressive carcinoma of uncertain etiology that was first described by Frierson et al in 1986.¹ The median age at presentation is in the fifth decade and patients are more likely to be men by a 2:1 ratio. Initial symptoms of bloody rhinorrhea, nasal obstruction, headaches, and visual changes are often ignored or attributed to a more benign etiology initially, delaying diagnosis (Figure 1).² As such, it is usually locally advanced upon presentation, and very commonly involves the orbit and skull base, with frequent intra-cranial extension (Figure 2). Prognosis of this disease is very poor, with studies describing survival rates ranging from 20% to 63%.²

Given the aggressive nature of this malignancy, a multimodality approach is uniformly advocated, but no consensus has been reached on the optimal order of treatment which can include combinations of surgical debulking, radiation, and chemotherapy. Given the rarity of this malignancy, significant prognostic factors have been difficult to determine. High-risk human papillomavirus (HPV) has a well-established association with head and neck carcinoma in the oropharynx. Recently, several series have demonstrated the presence of HPV in lesions of the sinonasal tract.

The objective of this paper was to review outcomes for patients with SNUC and assess HPV presence in tumor samples of these patients.

METHODS AND MATERIALS

After approval from the Institutional Review Board at the University of Kansas, nine patients diagnosed with SNUC from 2003 to 2016 were identified retrospectively. Surgically patients were treated by open techniques utilizing endoscopic instruments to assure complete resection at the skull base tumor bed and subsequently underwent a combination of chemotherapy and/or radiation depending on the patients condition at diagnosis (Figure 3).

HPV tumor status was determined using a real time, multiplex PCR assay that detects and quantifies 15 known high risk HPV types and targets HPV oncogene E6 as well as a beta globulin control and p16 confirmation. Tissue samples were evaluated by a single head and neck pathologist.



Figure 1: Endoscopic picture of a SNUC filling the nasal cavity

RESULTS

Seven out of nine patients underwent multimodality treatment. One patient's disease was too extensive for surgical resection and was treated with chemotherapy/radiation alone, and survived 3 months. One patient had surgical resection and postoperative radiation without chemotherapy as he was too sick to complete chemotherapy and succumbed to disease within 33 months. Four patients out of those seven patients (57%) who had aggressive resections combined with chemotherapy and radiation are still alive without disease an average of 8.7 years from the time of treatment. The three patients who did undergo multimodality treatment yet succumbed to disease still had an average survival time of 18 months from diagnosis. On HPV testing, all SNUC tumor specimens were negative for HPV in our cohort of patients.

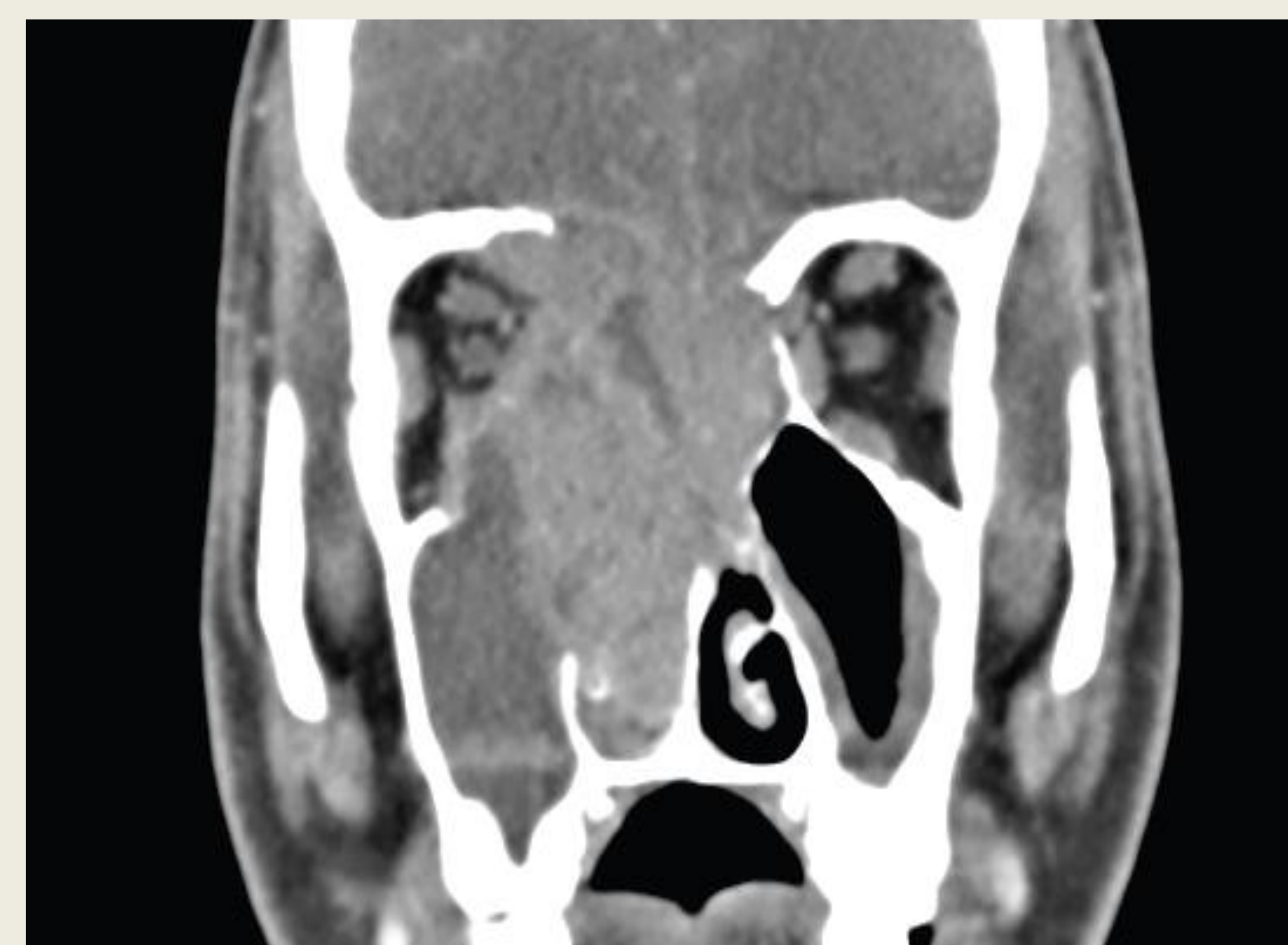


Figure 2: Coronal, contrasted CT through mid-orbit showing central and orbital extension (R>L)

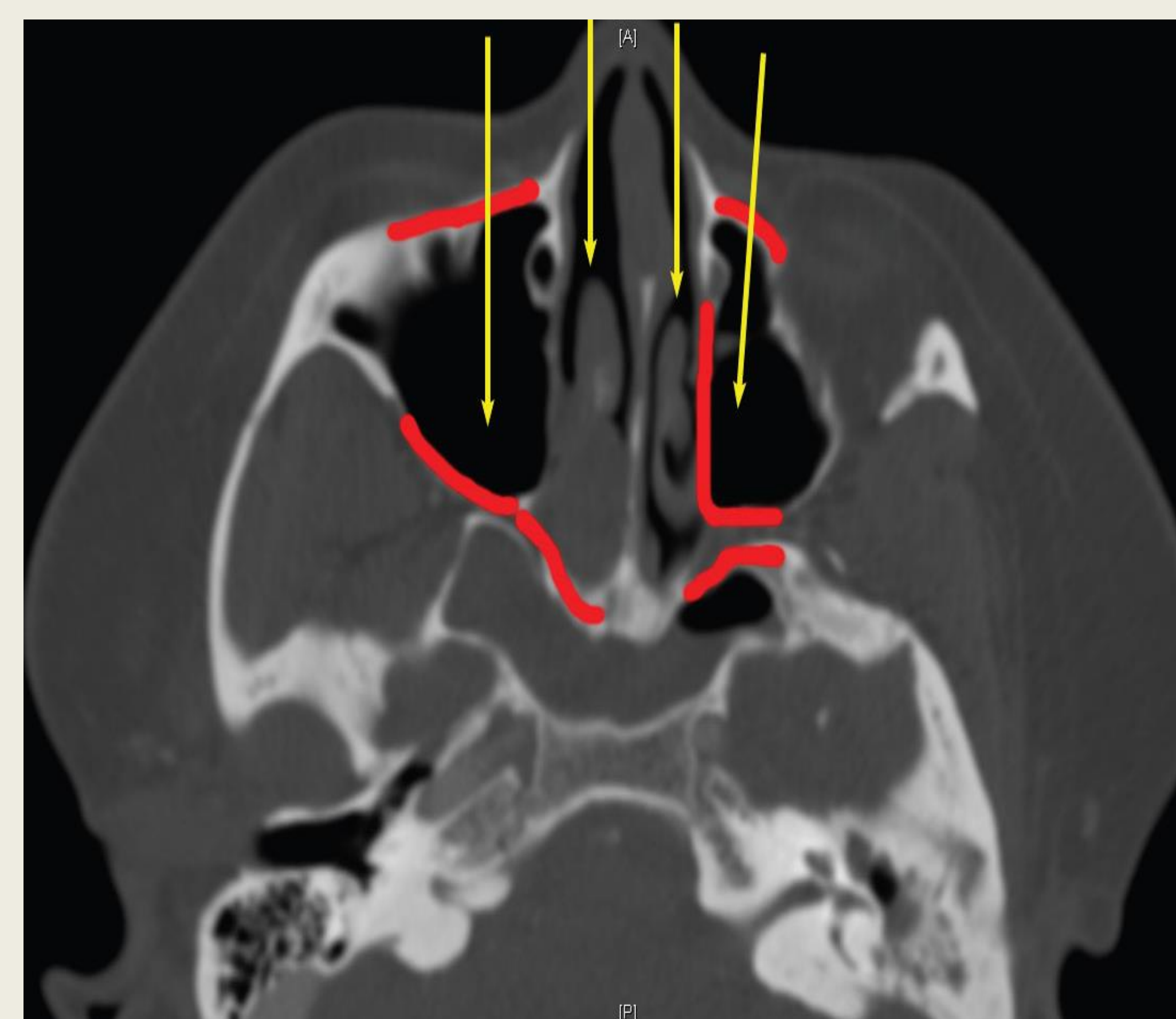


Figure 3: Red = bone removal, yellow = approach. Transnasal and sublabial transmaxillary approaches with endoscopic assistance.

DISCUSSION

In our cohort of nine patients, we were unable to detect the presence of HPV in our SNUC tumor specimens, even though recently we demonstrated a much better survival in our HPV positive nasal squamous cell carcinomas.³ A retrospective review conducted by Gray et al. in 2015 demonstrated that SNUC specimens from 11 out of 19 patients in their cohort were p16-positive and 9 of these were also HPV-positive. Furthermore, Kaplan Meier analysis demonstrated improved survival.⁴ Contrary to the previous study, a retrospective review conducted by Wadsworth et al. in 2011 demonstrated strong diffuse positivity for p16 in all five SNUC cases, but HPV DNA was not detected in these SNUC specimens. However, this may represent residual p16 staining, which is normally present in the sinonasal tract.⁵ Given the contradictory findings and minimal understanding of SNUC risks factors and its immunohistochemistry, further cases of SNUC will need to be evaluated to confirm the absence or presence of HPV DNA.

Our study is limited by its retrospective nature, and sampling of old tissue which may affect the ability to detect HPV. As such, further cases of SNUC samples would benefit from being tested for HPV on a real-time prospective basis, especially given the significant impact of HPV status on clinical outcomes.

CONCLUSIONS

A combination of aggressive open surgical intervention utilizing endoscopic techniques with closely applied chemotherapy and radiation has resulted in a 57% long-term survival and prolonged disease free intervals in these very aggressive SNUC tumors. We recently demonstrated a much better survival in our HPV positive nasal squamous cell carcinomas. However, there is no evidence of HPV virus in our SNUC tumor samples.

REFERENCES

1. Frierson HF, Jr., Mills SE, Fechner RE, Taxy JB, Levine PA. Sinonasal undifferentiated carcinoma. An aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. *The American journal of surgical pathology.* 1986;10(11):771-9.
2. Reiersen DA, Pahilan ME, Devaiah AK. Meta-analysis of treatment outcomes for sinonasal undifferentiated carcinoma. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2012;147(1):7-14.
3. Chowdhury N, Manna P, Tawfik OS, Girod DA, Beahm DD, Kerley SW, Hoover L. Prevalence, Distribution, and Levels of High-Risk HPV in Squamous Cell Carcinoma of the Nasal Cavity. Presented at Combined Sections Meeting 2015.
4. Gray ST, Herr MW, Sethi RK, Diercks G, Lee L, Curry W, et al. Treatment outcomes and prognostic factors, including human papillomavirus, for sinonasal undifferentiated carcinoma: a retrospective review. *Head & neck.* 2015;37(3):366-74.
5. Wadsworth B, Bumpous JM, Martin AW, Nowacki MR, Jenson AB, Farghaly H. Expression of p16 in sinonasal undifferentiated carcinoma (SNUC) without associated human papillomavirus (HPV). *Head and neck pathology.* 2011;5(4):349-54.