A Phase II, Single-Arm Trial Assessing Local Control of Near Total Endoscopic Resection Followed by Concurrent Chemotherapy and Proton Radiation in the Treatment of Unresectable Sinonasal Tumors

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activites
Basking Ridge	All Protocol Activites
Monmouth	All Protocol Activites
Bergen	All Protocol Activites
Westchester	All Protocol Activities

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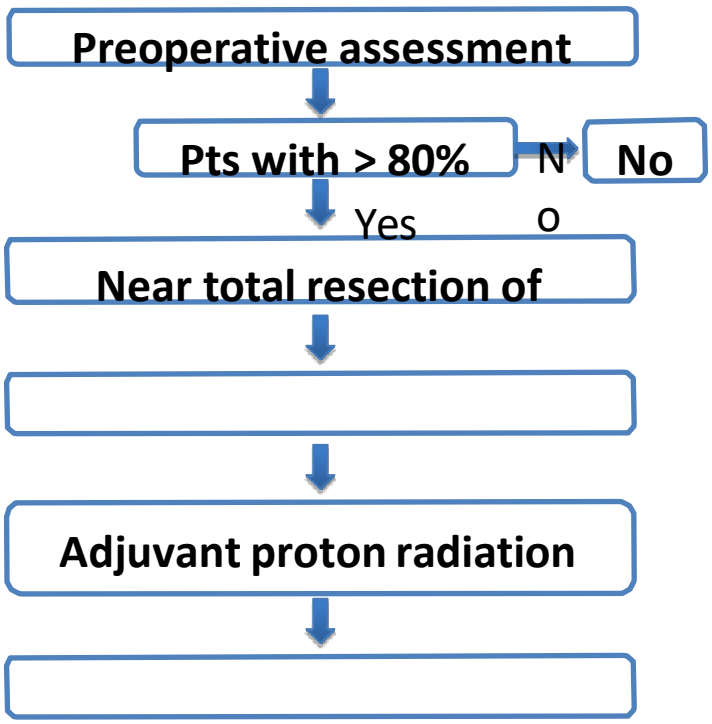
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Protocol Summary

This is a phase II, single-arm trial assessing local control (ie. no local failure) after near-total endoscopic resection (NTR) followed by concurrent chemotherapy with proton-beam radiation in unresectable tumors (which we define as expected inability to perform negative margin surgery) of the paranasal sinuses and nasal cavity. We will compare rate of local failure at 1 year after treatment in those undergoing NTR and adjuvant treatment with historical rates of failure in those undergoing non surgical management. As secondary and exploratory endpoints, we will assess other oncologic outcomes (overall survival, progression free survival, etc), physician reported complications of surgery and chemoradiation toxicity, and patient reported outcomes, and will store tissues obtained for IMPACT testing.

We plan to have 25 eligible patients, 15 of which will be Squamous Cell Carcinoma patients and the rest 10 shall be Adenoid Cystic Carcinoma, Esthesioneuroblastoma, or Adenocarcinoma patients.

Protocol Schema



2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

- To determine if near-total resection with minimally invasive endoscopic approach for unresectable paranasal sinus / nasal cavity tumors followed by concurrent chemotherapy and proton-beam radiation improves local control at 1 year after treatment compared to traditional approaches of nonsurgical management alone. Our historical data showed that the rate of local failure at 1 year with chemotherapy and IMRT alone is 50%. We hypothesize that adding NTR and proton radiation with chemotherapy will reduce the rate of local failure at 1-year to 25%. Local failure will be defined using a modification of RECIST 1.1.

Secondary Objectives

- To assess the complications of treatment related to minimally invasive endoscopic skull base surgery in patients with unresectable disease using Clavien-Dindo classification of surgical complications
- To assess toxicity of treatment based on CTCAE v4.03 scores in the acute setting (throughout treatment and up to the 3 month visit after end of treatment)
- To assess toxicity of treatment based on CTCAE v4.03 scores in the long-term setting (after the 3 month post treatment visit until the 24 month post treatment visit)
- To assess toxicity of treatment related to patient reported outcomes including EORTC (H&N43 and C30) and Skull Base Inventory (SBI)
- To determine the 1- and 2-year rates of regional/nodal, or distant-metastasis progression incidence, progression-free survival, disease specific mortality, and overall survival in our group of patients undergoing NTR / proton-beam radiation therapy (PBRT) and chemotherapy
- To obtain tissue of these rare tumor types for IMPACT assessement. Results of IMPACT testing will be banked for future investigation

3.1 BACKGROUND AND RATIONALE

3.2 Nasal Cavity / Paranasal Sinus Tumors

Locally advanced malignancies of the nasal cavity and paranasal sinuses that invade the skull base are rare with unclear management paradigms. Beginning in the 1950s, the "gold standard" for treatment of these malignancies, when resectable, has been a combined transfacial and transcranial approach followed by adjuvant radiation[1]. Memorial Sloan Kettering Cancer Center has been a global leader in the management of these patients and coordinated a large retrospective multi-institutional study that set the standard for rates of both oncologic control and treatment related morbidity for patients with resectable disease[2,3]. This work was first published in 2003. However, when tumors are deemed unresectable by the multidisciplinary consensus, often because of proximity to the carotid artery, brain parenchymal invasion, or involvement of the orbital apex, radiation (with or without chemotherapy) has been the primary treatment pursued. Outcomes for locally advanced paranasal sinus/nasal cavity tumors that receive radiation (with or without chemotherapy) are significantly worse than seen in patients who undergo surgery followed by radiation (+/- chemotherapy)[4].

In the past 15 years, advances in the pathologic understanding of these tumors, chemotherapeutic treatment options, and radiation technology, has led to significant variation of treatment of locally advanced nasal cavity and paranasal sinus cancers. The definition of "resectability" has been altered and tumors that were once considered nonsurgical (such as those with brain invasion) are now deemed resectable in many centers. Furthermore, single institution studies have demonstrated the technical and oncologic feasibility of endoscopic resection for select early and advanced paranasal sinus and skull base tumors, obviating the need for craniotomy and facial incisions, leading to decreased surgery-related treatment morbidity in certain patients[5,6].

Unresectable paranasal sinus and nasal cavity tumors treated with photon radiation (3D conformal or IMRT) +/- chemotherapy have poor outcomes, with MSKCC data revealing overall survival of 15% at 5 years, with a 0% local control rate for patients who receive less than 65 gray to the primary site [4]. In studies of salivary gland tumors, including adenoid cystic carcinoma, historic local control rates with radiaton +/- chemotherapy have been 0-43%[7-12]. This is in contrast to recent retrospective data that shows endoscopic or open surgery and proton radiation (+/- chemotherapy) in a variety of pathologies in locally advanced tumors, yields local control at 1 and 3 years of 92.4% and 82.7%[13]. Russo et al recently published 5-year local control rates after resection and proton radiation to be 77% for those patients who have undergone gross total resection (not synonymous with negative margin surgery—gross total resection includes patients with negative margins and microscopically positive margins)[14].

The suboptimal outcomes related to chemoradiation therapy alone coupled with the promise of trimodality therapy using minimally invasive surgery have introduced the idea of cytoreductive surgery for advanced disease prior to chemoradiotherapy. Although these cytoreductive interventions can often help with symptoms related to the tumor size, the oncologic validity of these approaches have yet to be determined[15]. Jansen et al have published the only study of the utility of subtotal resection in paranasal sinus cancers and they found improved local control and overall survival with debulking and conventional photon IMRT[16]. In a retrospective study by Kawashima et al that did not specifically examine cytoreductive surgery, the authors noted that degree of residual tumor burden after skull base surgery correlated with patient outcomes[17].

In addition to improved local control, cytoreductive surgery may allow for the reduction of radiation doses to normal structures, such as the optic nerves, chiasm, carotid arteries, and temporal lobes. This could reduce the probability of late cognitive, vascular, and visual toxicities. Historically, convention argued against subtotal surgical resection in these patients, as the only option was open surgery with craniotomy and facial incisions; such operations often required free flap reconstruction and led to prolonged hospital stays, with mortality rates of 5% at the most experienced centers, as well as an overall complication rate of 36%, a central nervous system complication rate of 16% (CSF leak, meningitis, pneumocephalus), and a wound complication rate of 20% (infection, dehiscence, flap necrosis)[3]. Prolonged recovery in these patients can also potentially lead to delays in adjuvant chemoradiotherapy. However, the use of minimally invasive surgical techniques have shortened hospital stays, as such procedures obviate the need for external incisions with free flap reconstruction and can decrease the risk of CSF leaks and infections. Such reductions in

the duration of hospitalization enable the initiation of adjuvant therapy sooner. Data on the national level have demonstrated that those undergoing endoscopic excision of paranasal sinus tumors start postoperative radiation (+/- chemotherapy) approximately 20 days earlier than those undergoing open craniofacial resection[18]. In addition, on the national level there is no significant difference in the time to starting radiation after diagnosis for those undergoing endoscopic surgery plus radiation compared to those not receiving surgery at all[18].

The feasibility and oncologic efficacy of near-total resection in unresectable paranasal sinus/nasal cavity tumors followed by PBRT and chemotherapy have yet to be studied in any prospective fashion. This is in contrast to clival chordomas, which occur in the same anatomic region and for which near-total resection coupled with adjuvant chemoradiotherapy has been shown to result in better outcomes than nonsurgical or less aggressive surgical treatment alone[19]. The extent of resection of chordoma has been directly correlated to outcomes in a meta-analysis[20]. In other brain and base of skull lesions, the degree of resection as a continuous variable is positively associated with survival[21,22]. Proton beam radiation, which is the preferred option for the treatment of skull base and pediatric tumors at many centers, can potentially minimize toxicity to adjacent structures to an even greater degree than was possible previously. The combination of near-total endoscopic resection, because of its reduction in gross disease requiring the highest dose of radiation, and proton radiation, because of its ability to spare normal tissue, may lead to significant reductions in treatment-related toxicity.

The prior studies including Jansen et al are retrospective assessments of outcome based on extent of surgical resection followed by adjuvant treatment, for patients that are presumably resectable. Our study is a prospective evaluation of the utility of addition of surgery in patients that otherwise may not have received it in order to assess the utility of endoscopic near total resection and proton radiation with chemotherapy. We want to rigorously study in a prospective fashion the ability to improve oncologic outcomes for patients with this rare tumor type.

3.3 Characteristics of endoscopic skull base resection

Endoscopic skull base surgery is a widely accepted modality for treatment of both benign and malignant lesions of the nasal cavity and the skull base. The goal, as with any oncologic surgery, is complete resection of the tumor with negative margins. The use of advanced technology has revolutionized surgical management in the paranasal sinuses. Relatively recently adopted use of high definition angled endoscopes enable magnified visualization which can assist in determining normal and abnormal anatomy. This enables the surgical team to ensure resection of all abnormal tissue. In addition, endoscopic resection relies on use of intraoperative image guidance, which similarly helps in ensuring safe resection of tumor surrounding critical structures. Resection can be tailored intraoperatively in real time based on PET, MRI, or CT scan findings. These technologies greatly assist in optimizing the goal of improved local control.

As noted previously, endoscopic excision also provides the potential advantages of obviating craniotomy or facial incisions and a more straightforward reconstruction in the presence of undisturbed tissue planes. Open surgical approaches may provide better access to certain

areas including soft tissues of the cheek, intraorbital contents, and significant intracranial extension, however, an endoscopic resection approach does provide adequate access for many patients without an extensive craniotomy and lateral rhinotomy (facial incision). In addition, the adoption of the regional vascularized nasoseptal flap provides a safe way to reconstruct large intranasal defects, preventing the need for free flap or other reconstruction. Because of the minimally invasive nature of the techniques, patients undergoing endoscopic skull base surgery leave the hospital significantly earlier than those undergoing open surgery and, consequently, the time to adjuvant treatment is decreased. In addition, for locally advanced lesions, a cytoreductive surgery can potentially decrease the tumor volume prior to adjuvant radiation in an anatomic area where a difference of a few millimeters in the radiation target area can be critical.

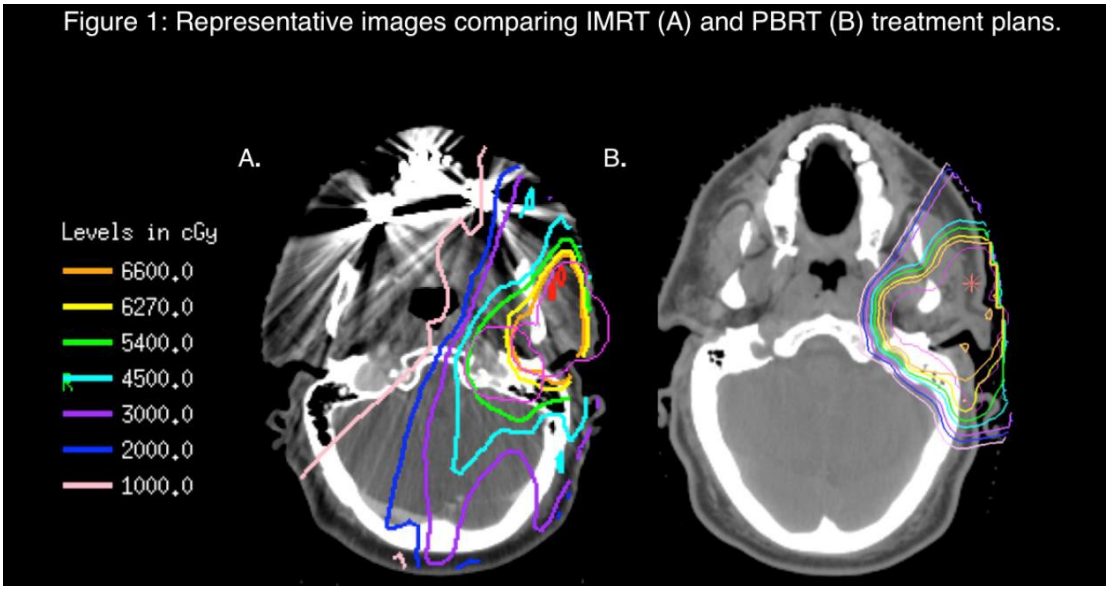
3.4 Characteristics of Proton Beam Radiation Therapy (PBRT)

Intensity modulated radiation therapy (IMRT), the most commonly used form of photon beam radiation therapy in the treatment of HNC, uses multiple x-ray beams to irradiate a tumor target, but deposits not insignificant exit dose delivered to normal tissues beyond the treatment target. PBRT utilizes multiple beams of directed protons to irradiate a tumor target. But in contrast to photons, protons deposit the bulk of their energy at the last few millimeters of their range without any significant exit dose[23]. Both radiotherapy modalities aim to maximize the dose of radiation to the tumor while sparing surrounding normal tissues like the oral cavity, salivary glands, larynx, muscles of the head and neck, spinal cord, and brainstem. However, given the physical characteristics of protons (i.e. minimal exit dose), PBRT may deliver radiation with less accompanying morbidity from damage to surrounding non-malignant tissue when compared with IMRT (Figure 1) [24-27]. This is especially critical in the skull base where damage to adjacent structures such as the brainstem, optic nerves, orbit, brain parenychema can have catastrophic consequences. Indeed, the need to limit dose to normal structures often results in some degree of underdosing to paranasal sinus and nasal cavity tumors. Because PBRT dramatically reduces the dose of radiation to normal structures, it may allow for a larger proportion of tumor to receive therapeutic radiation doses. Indeed, a recently published retrospective study presented evidence that such a benefit leads to improved local control compared to photon radiotherapy.[28]

However, despite these potential advantages to PBRT, it is uncertain as to whether the reduction in low and intermediate dose exposure to CNS tissue and consequent ability to provide tumoricidal doses to tumor results in a clinically meaningful decrease in toxicities and increase in local control. In addition, PBRT has greater intrinsic uncertainties than standard of care IMRT, such as the exact range of protons in tissue. Although these uncertainties have been mitigated in clinical practice for decades, there remain some unanswered questions, and prospective studies are needed to better characterize the impact of radiation dose alterations on clinical outcomes. PBRT could result in increased skin toxicity compared to

photon-based therapy.

Figure 1: Representative images comparing IMRT (A) and PBRT (B) treatment plans.



3.5 Patient Reported Outcome (PRO)

A patient reported outcome (PRO) is a measurement of a patient's health status that is obtained directly from the patient without interpretation of the patient's responses by a clinician or research associate. The Health and Medicine Division (formerly the Institute of Medicine) of the National Academies of Medicine and the Food and Drug Administration (FDA) have called for measuring PROs as primary or secondary endpoints of clinical trials[29,30]. Studies have shown that PROs can be more reflective of the patient experience and provide more complementary toxicity and symptom data than clinical or Common Terminology Criteria of Adverse Events (CTCAE) assessments alone[31,32]. In this trial, the secondary endpoints will be based on clinician-reported CTCAEs as well as patient reported outcomes.

Radiotherapy to the head and neck and, more specifically, to the skull base, is associated with marked acute and late adverse effects. Acute effects include paranasal sinus crusting and bleeding, mucositis, dysphagia, fatigue, dysgeusia, loss of voice, nausea, and fatigue. Late effects include xerostomia, dysphagia, trismus, permanent skin changes, neck fibrosis, and secondary malignancies. Careful assessment of treatment related morbidity is important, as patients who experience significant acute side effects of HNC radiation therapy are reported to have a decreased quality of life[33-38]. Significant deterioration is associated with those who report having trismus, xerostomia, dysgeusia, and dental problems. PBRT can deliver radiation with reduced dose to nearby normal tissues (e.g., oral cavity, major salivary glands, larynx, cochlea, spinal cord, brainstem, and brain), and potentially improve PRO. However, research on PRO after proton therapy is scarce.

3.5 IMPACT Testing

IMPACT testing will be done on all patients under IRB protocol #12-245. All patients will be consented to 12-245 and will have a piece of their specimen along with corresponding bloods taken perioperatively. All biospecimen collection and handling will follow the standard

procedure for 12-245 patients. This testing is important for this study, because of the extremely rare nature of the disease. As there are a small number of rare pathologies assessed in this study, specific questions for IMPACT assessment are challenging a priori. In the future, we will likely couple our IMPACT results with corresponding pathologic specimens.

3.6 Summary

The treatment of locally advanced paranasal sinus and skull base tumors is challenging. Patients deemed to have unresectable disease have significantly worse outcomes with these large-volume tumors, which are typically treated with chemotherapy and radiation; the associated toxicities can be significant. Endoscopic near-total resection, when compared with open surgery, offers the possibility of tumor debulking with minimal morbidity and shorter recovery. We hypothesize that multimodality treatment involving endoscopic near-total resection and adjuvant proton radiotherapy will both minimize toxicity and, most importantly, improve local control. A treatment paradigm involving the potential dosimetric advantages of postoperative proton treatment as well as minimal morbidity for endoscopic resection has the potential to change the treatment approach for patients with these lesions.

The primary endpoint of this study is to assess the local control for patients with unresectable disease, with secondary endpoints of distant metastasis development, disease free survival, overall survival, morbidity of treatment, and patient reported outcomes. Our study may also help to standardize treatment algorithms which, at this time, are widely divergent for patients with unresectable disease. If patients in this study demonstrate favorable outcomes, future studies could address the feasibility of cytoreductive surgical techniques with adjuvant chemotherapy and proton-beam radiation to improve outcomes in patients with “resectable” disease.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single center, phase II, single-arm trial assessing the efficacy of local control of near-total endoscopic resection followed by proton-beam radiation with concurrent chemotherapy in unresectable paranasal sinus/nasal cavity tumors. The primary endpoint is local control at 1 year from the end of treatment with failure defined as progression of disease by > 20% of the 12 month post treatment MRI (per RECIST) compared to the post- surgical MRI. If a patient dies during treatment, he/she will be counted as a failure. We will secondarily assess regional/nodal failure and distant metastases, overall survival, disease specific mortality, and progression free survival. Treatment toxicity will be assessed by the Clavien-Dindo Classification of Surgical Complications and CTCAE v4.03 as well as PRO measures including EORTC HN and SBI[39]. IMPACT testing will be performed for all patients undergoing treatment for this rare disease. Results of IMPACT testing will be banked for future investigation. We will include patients with a variety of histologic diagnoses including squamous cell carcinoma (SCC), esthesioneuroblastoma, adenoid cystic carcinoma, and adenocarcinoma.. Patients will be included if there is multidisciplinary consensus that the primary lesion is not resectable with negative margin surgery without significant morbidity. This could include lesions that (1) involve the carotid artery, (2) invade brain parenchyma, (3) involve the orbital apex, (4) invade the pterygoid musculature, (5) involve the cavernous

sinus, (6) involve the clivus, and/or (7) involve intraconal space. Patients will only be included if there is multidisciplinary consensus that at least 80% of the tumor bulk can be removed without significant risk of morbidity. There is no cut-off for residual disease. Although expected that we will resect >80% of patient's tumor as discussed pre-operatively, if less than this is resected, patient will still proceed with protocol. Patients will be stratified by the pathologic diagnosis.

As this study is going to include patients for which we will be unable to obtain negative margins (resections will take place for patients where we can anticipate removal of >80% but less than the entirety of the tumor). Our prospective study will be evaluating patients who we cannot obtain a negative margin. The inclusion criteria for our study exclude patients with resectable disease. R1 resections will be unlikely due to patient selection but will still be included if they met the initial inclusion criteria.

4.3 Intervention

Patients in this single-arm study will undergo near-total endoscopic resection of skull base tumors ($\geq$ 80%) followed by concurrent cisplatin-based chemotherapy with proton-beam radiation.

4.3.1 Descriptions of PRO Instruments

The PRO instruments and outcomes chosen for the proposed trials are well justified, hypothesis-driven, validated, reliable and meaningful to patients. Each instrument is described below. We estimate that patient response burden to complete these instruments will be approximately 35 minutes. The PRO instruments will be administered to patients preoperatively, at timepoints during the radiation and chemotherapy treatment period, and at post-treatment follow-up visits.

4.3.2 Standard of care PRO instruments currently implemented

Current standard of care PRO instruments will be used to prospectively collect data from all head and neck surgery and radiation therapy patients on this trial. We will use the EORTC HN measure and SBI measure.

4.3.3 Study Specific PRO Instruments

4.3.3.1 EORTC QLQ H&N 43 and C30

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module 43 (Appendix 1) is a validated 43-item site-specific assessment tool[40].The module uses 12 multi-item scales to measure problems with swallowing, salivating,senses, speech, social eating, pain, anxiety, body image, teeth, skin, shoulder and physical contact . In addition, 7 single-item scales are utilized in assessing problems with mouth opening, coughing, , neurology, weight loss,lymphedema and/or a wound,and, finally, social contact. All questions are based on a 4-point scale ranging from "not at all" to "very much."

The scoring procedure for the QLQ-H&N43 transforms all of the scale and single-item scores to range from 0 to 100. All QLQ-H&N43 scores are symptom scores, with higher scores

representing higher levels of symptomatology/problems. Internal consistency reliability for the multi-item scales was generally acceptable (Cronbach's alpha ≥ 0.70) in the validation.

The EORTC QLQ H&N 43 module was designed to be used together with the core questionnaire QLQ C30 (Appendix 2), which is an assessment of general well being.
The EORTC QLQ-C30 (Appendix 2) is a 30-item questionnaire designed to assess the quality of life of cancer patients[41]. The 30 items of the QLQ-C30 yield both multi-item scale scores and single-item scores, for a total of 15 distinct scores. These include one Global Health Status/QoL scale (2 items), five functional scales (Physical Functioning, 5 items; Role Functioning, 2 items; Emotional Functioning, 4 items; Cognitive Functioning, 2 items; and Social Functioning, 2 items), three symptom scales (Fatigue, 3 items; Nausea and Vomiting, 2 items; and Pain, 2 items), and six single item symptom scores (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties; all from single items). The questionnaire asks patients to indicate the extent to which they have experienced each of the problems "during the past week" on a 4-point Likert-type scale from "Not at all" to "Very much". The 2 exceptions are the 2 items of the Global Health Status/QoL scale, which patients are asked to rate on a 7-point scale from "Very poor" to "Excellent".
The scoring procedure for the QLQ-C30[42] transforms all of the scale and single-item scores to range from 0 to 100. High scores for the Global Health Status/QoL scale represents high QoL, high scores for the functional scales represent high/healthy levels of functioning, but high scores for the symptom scales/items represent high levels of symptomatology/problems. The instrument has been extensively validated and is widely used in clinical trials. The multi-item scales generally have good internal consistency reliability coefficients.

4.3.3.2 Skull Base Inventory

Skull Base Inventory (Appendix 3) is a 41-item site-specific assessment tool designed to assess quality of life in patients with anterior skull base pathology[43]. The SBI covers 11 disease-specific domains, including emotional, social, physical, cognitive, family, financial, spiritual, endocrine, nasal, neurologic, and visual. The 41 items are based on a 7-point scale ranging from" severe problem" to "no problem". Each domain is scored out of 100 with lower scores associated with poorer quality of life. Items within each domain for which a response was recorded were summed and averaged out of 100. A composite score assuming equivalent weighting of domains in overall quality of life was created by averaging domain scores. Recently, the SBI has been validated and shown to be reliable in assessing disease-specific quality of life for patients undergoing both endoscopic and open skull base surgery[44].

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Endoscopic Resection

As described previously, endoscopic resection follows the principles of open surgery, with emphasis on oncologic considerations. In brief, an endoscope is used and two surgeons perform the intervention in a binostril manner. Tumor is generally resected with an emphasis on identification of the attachments in the paranasal sinuses, nasal cavity, or skull base. In the region of attachment, negative margins are obtained by removing a tissue layer beyond the area where the tumor is present. If the tumor has invaded the skull base, the skull base is removed and, if necessary, dura is also removed. If the tumor has invaded the orbital wall, then the affected bone is removed and, if necessary, periorbital tissue is removed. Margins are obtained and mapping can be performed to assist in focusing the adjuvant radiation treatment. In cases in which one layer of tissue beyond the tumor is not resectable (e.g., if the extratumoral layer is the carotid artery, orbital apex, or other unresectable tissue), tumor is

removed only to that layer, if feasible. Use of recently integrated technology, mainly high definition straight and angled endoscopes, as well as intraoperative image guidance (CT/MRI/PET), have made this surgical technique significantly safer.

5.2 Adjuvant Proton Radiotherapy

Proton therapy treatment will follow the National Cancer Institute's "Guidelines for the Use of Proton Radiation Therapy in NCI-Sponsored Cooperative Group Trials" (https://rrp.cancer.gov/content/docs/proton.doc). Proton therapy techniques may include passively scattered or scanning or pencil beam technology.

5.3 Cisplatin Chemotherapy

Cisplatin should be administered on day 1 (+/- 3 days) of the start of radiotherapy and then every 3 weeks (unless there is a delay for safety concerns such as neutropenia) for a total of 3 cycles. Treatment can be given over 1 day or split over 2 days. The chemotherapy will be administered per MSKCC guidelines at 100 mg/m2 (dose reductions after the first cycle allowed for toxicity). Normal scheduled treatment can be +/- 72 hours from three weeks post the prior administration. Administration entails fluid and anti-emetics as per institution standard. Cisplatin should be infused over one hour. Cisplatin can be administered before or after radiation is given but is only started once the radiation program has been initiated. If cisplatin treatment in contraindicated after the first cycle of treatment due to toxicity (e.g., kidney failure), a change in chemotherapy is allowed after a discussion with the medical oncology co-PI.

5.4 Cisplatin with etoposide chemotherapy

If the final pathology shows SNUC, at the discretion of the treating medical oncologist, the patient will receive cisplatin on day 1(+/- 3 days) of the start of radiotherapy and then every 3 weeks (unless there is a delay for safety concerns) for a total of three cycles. In addition to cisplatin at 60 mg/m2 on day 1, the patient will receive etoposide chemotherapy at a dose of 120 mg/m2 on days 1-3. Normal scheduled treatment can be +/- 72 hours from three weeks post the prior administration. The chemotherapy will be administered per MSKCC guidelines (dose reductions after the first cycle allowed for toxicity). Administration entails fluid and anti-emetics as per institution standard. Cisplatin can be administered before or after radiation is given but is only started once the radiation program has been initiated. If cisplatin treatment in contraindicated after the first cycle of treatment due to toxicity (e.g., kidney failure), a change in chemotherapy is allowed after a discussion with the medical oncology co-PI.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Age greater than or equal to 18 years.
- Histopathologically confirmed diagnosis of one the following cancer types:
    - Squamous cell carcinoma
    - Esthesioneuroblastoma
    - Adenoid cystic carcinoma
    - Adenocarcinoma

- Paranasal sinus/nasal cavity malignancy is considered unresectable with negative margins surgery or resection would be considered excessively morbid. This could include lesions with:
    - Carotid involvement
    - Cavernous sinus invasion
    - Brain invasion
    - Orbital apex
    - Intraconal space
    - Pterygoid musculature involvement
    - Invasion of the clivus
- Resection of at least 80% of the volume of the tumor is feasible. Resectability will be determined by the surgeon and radiologist after discussion among the multidisciplinary team. For patients who have had surgery at an outside institution, the same parameters will be thoroughly screened to ensure the patient met the same inclusion criteria and resection standards.
- Patients must be a candidate for surgery (as per treating surgeon) and be able to tolerate proton radiation and chemotherapy (as per treating radiation oncologist and medical oncologist).
- Karnofsky performance status ≥70.
- The subject has organ and marrow function and laboratory values rendering safe administration of Cisplatin:
    - The ANC ≥ 1000/mm3 without colony stimulating factor support;
    - Platelets ≥ 100,000/mm3;
    - Hemoglobin ≥ 9 g/dL;
    - Bilirubin ≤ 1.5 □ the ULN. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL;
    - Serum albumin ≥ 2.8 g/dl;
    - Creatinine clearance (CrCl) ≥ 60 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:
        - Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72);
        - Female: Multiply above result by 0.85;
    - ALT and AST ≤ 3.0 □ ULN;
    - Serum phosphorus, calcium, magnesium and potassium ≥ LLN.
- No evidence of intercurrent infection.
- Negative pregnancy test for women of childbearing potential (<51 years of age) as per institutional policy.
- Patient must be able to read and write in English.
- Patients who intitially meet the histopathological inclusion criteria but surgical pathology report shows Sinonasal Undifferentiated Carcinoma.
-

6.3 Subject Exclusion Criteria

- Tumor is deemed to be resectable with negative margins by conventional surgical standards.
- Patients not able to receive standard-dose cisplatin based on the judgement of the

treating medical oncologist.

- Patients with chronic kidney disease (GFR <60), uncontrolled hypertension, congestive heart failure, pre-existing bone marrow dysfunction, or cytopenias.
    - Congestive heart failure (CHF): New York Heart Association (NYHA) Class II-IV at the time of screening;
- Concurrent uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment;If severe hearing impairment is measured or if significant neuropathy is reported at baseline the treating physician will discuss the risks for further permanent hearing loss and neuropathy with the patient.
- Patients not able to have a MRI (due to pacemaker, claustrophobia, etc.).
- Inability to return to MSKCC for frequent scheduled hydration sessions post-chemotherapy.
- Inability to comply with requirements for cisplatin administration anti-emetic regimens post-treatment.
- Patients not able or unwilling to travel for proton therapy.
- Patients with distant metastatic disease.
- Patients with prior radiation to the head and neck.

7.0 RECRUITMENT PLAN

7.1 General Recruitment Plan

Patients will be evaluated by an attending physician from the Department of Radiation Oncology, the Division of Head and Neck Surgery, Department of Surgery, the Department of Neurosurgery, or Department of Medical Oncology, and entered into the study if they are appropriate candidates. The attending physician will obtain informed consent from the eligible patients.

The protocol investigator, co-investigator(s), or a member of the treatment team can screen medical records of patients with whom they have a therapeutic relationship to identify potential research subjects eligible for this study. In addition, protocol investigator, co-investigator(s), and research study assistant(s) can screen medical records of patients with whom they do not have a therapeutic relationship for the limited purpose of identifying patients who would be eligible to enroll in the study, and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator, the research staff, and the patient, the patient may be asked to provide certain health information that is necessary for the recruitment and enrollment process. The investigator/research staff may also review portions of the patient's medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm whether the patient is eligible and to contact the patient regarding study enrollment. If the patient is deemed ineligible for the research study, the investigator and/or research study assistant will destroy all information collected during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, the investigator, or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened, and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects, and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

After initial contact with the patient, our research team will contact the PROCure or New York Proton Center (NYPC) team to initiate financial approval. The financial team at ProCure or NYPC will work closely with the patient and their insurance plan to determine his/her financial responsibility in regards to proton therapy. The patient will have all appropriate information prior to enrolling on the protocol.

7.2 Gender/race breakdowns

In selecting patients for this study and the projects proposed in this protocol, we have taken due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research populations. We expect that the study population will be representative of the range of paranasal sinus/nasal cavity patients seen at MSKCC. No specific outreach efforts are planned.

7.3 Target/planned enrollment

The anticipated accrual rate is 1-2 patients per month to meet the accrual goal of 25 patients (15 SCC and 10 ACC, esthesio, or Adenocarcinoma). Based on recent patient treatment patterns in the head and neck and radiation oncology services, we estimate that MSK treats approximately 20 patients each year who would be eligible for this trial. We do not anticipate any difficulties in meeting our accrual goal.

8.0 PRETREATMENT EVALUATION

All patients will receive the necessary scans and tests according to the standard of care for their paranasal/nasal cavity malignancy.

Table 2 contains all the tests that will be performed within 8 weeks of the start of surgery and then chemoradiation.

Table 2: PRE-TREATMENT ASSESSMENTS

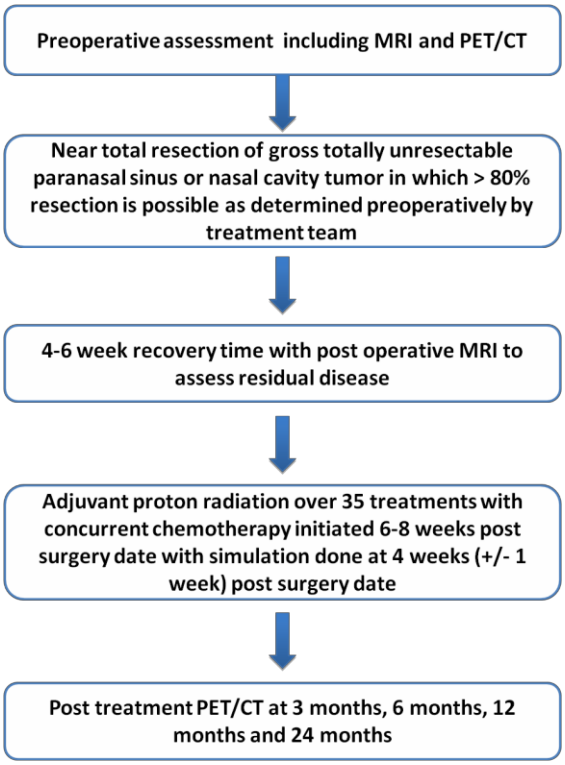
Assessments	Source	Prior to protocol calendar days
Consent form signed by patient	CRC	1-3 weeks[A]
History[B]	EMR	30 days

Physical	EMR	30 days
Audiogram	EMR	6 weeks
CBC, CMP, Hepatitis B Core and Surface antigen	EMR	6 weeks
Dental Evaluation	EMR	6 weeks
Pregnancy test[C]	EMR	14 days prior to surgery
Karnofsky performance status	EMR	6 weeks
PET-CT with CT Neck component to include IV contrast and MRI of the Nasal Cavity/Para-Nasal Sinuses with contrast[D]	EMR	4 weeks
SBI	PSA	6 weeks
EORTC QLQ C30 & H&N 43	PSA	6 weeks

A: Patients start treatment within 30 days from time of consent as per institution's standard
B: For cisplatin eligibility requirement, a medical history for neuropathy, history of kidney disease, diabetes, hypertension, and cardiac disease.
C: For women of childbearing potential: Pregnancy testing should be performed according to institutional standards.
D: Patients with contrast allergies should be pre-medicated; patients with specific contrast contraindications can have contrast administration deferred.
Abbreviations: CRC (Clinical Research Coordinator);PSA (Patient self-administered with or without CRCassistance); EMR (Electronic Medical Record)

9.1 TREATMENT/INTERVENTION PLAN

9.2 Therapy Schema:



9.1: Endoscopic Resection Treatment Technology

Endoscopic skull base surgery will be performed as per standard of care for any patient with tumors of the paranasal sinus and skull base treated at MSK, as described above. For patients who have had surgery elsewhere, they will be enrolled as long as standard of care parameters per MSKCC were met at the outside institution. Tissue used for IMPACT testing will be taken from the main specimen during the operation. For those who have had surgery elsewhere, tissue will be requested from the outside institution. The corresponding blood required for IMPACT testing will be drawn prior to the surgery.

9.2. Radiation Therapy

9.2.1 Immobilization and Simulation

9.2.1.1 Immobilization

Patients will undergo radiation simulation in the supine position using the standard thermoplastic mask for immobilization to ensure daily reproducibility of treatments.

9.2.1.2. Simulation Imaging

Standard simulation CT guidelines from the vertex of the scalp through the tracheal carina, encompassing the entire head and neck.

9.2.2 Definition of Target Volumes and Margins

GTV Gross Primary will include all existing gross disease at the primary site as seen on postoperative MRI and simulation CT scan. The CTV Primary Site will include the preoperative gross extent of primary tumor visible by imaging studies (CT, PET, and/or MRI), and/or clinical examination along with the postoperative surgical bed; for histologies with high risk of neutropic spread, a CTV Nerve will be created to encompass the affected nerve tracks. Fusion of preoperative and postoperative MRI to the simulation CT should be performed to aide in volume delineation. Irradiation of cervical and retropharyngeal nodal basins will be left up to the treating radiation oncologist. For patients in whom the cervical and retropharyngeal nodes will be treated, the CTV Node High Risk volume will include nodal basins wherein gross nodal was resected; CTV Node Low Risk will include nodal basins in which there was no gross nodal disease identified. If there are suspected grossly involved lymph nodes, a volume GTV Gross Node should be created. Skin bolus is acceptable and can be used for patients who are at high risk for skin involvement, at the discretion of the treating physician. Each CTV will be expanded by 3mm to a planning target volume (PTV), to account for intra-fractional patient motion, and inter-fractional setup error. The above are all standard radiation oncology treatment planning procedures.

9.2.3 Dose Prescription

PTV Gross Primary = 70 Gy (relative biological effectiveness [RBE])

PTV Primary = 60 Gy (RBE)

PTV Nerve (if applicable) = 54 Gy (RBE)

PTV Gross Node (if applicable) =70 Gy (RBE)

PTV Node High Risk = 54 Gy (RBE)

PTV Node Low Risk = 51 Gy (RBE).

9.2.4 Compliance Criteria and Dose-Volume Histogram (DVH) Analysis

Standard of care target coverage will be applied. Target coverage for PBRT should achieve a D95 ≥ prescription dose and the PTV D05 ≤ 110% of the prescription dose.

Organs at risk (OAR), including the parotid glands, submandibular glands, cochleas, oral cavity, larynx, esophagus, brachial plexus, brain stem, optic structures, and spinal cord, should be contoured according to standard guidelines for standard of care practice. A dose volume histogram will be constructed to evaluate target coverage and the doses to the surrounding OAR. The following standard of care radiation planning guidelines should be met:

1) Larynx:
    a. <70 Gy (RBE) maximum point dose
    b. <45 Gy (RBE) mean dose
2) Esophagus:
    a. <34 Gy (RBE) mean dose to the esophagus
3) Brachial plexus:
    a. <65 Gy (RBE) maximum point dose
4) Brainstem:
    a. <54 Gy (RBE) maximum point dose
5) Optic nerves:
    a. <54 Gy (RBE) maximum point dose
6) Optic chiasm
    a. <54 Gy (RBE) maximum point dose
7) Spinal cord:
    a. <45 Gy (RBE) maximum point dose to the spinal cord
8) Oral cavity:
    a. <40 Gy (RBE) mean dose to the oral cavity excluding overlapping PTV
9) Contralateral parotid
    a. <6 Gy (RBE) mean dose
10) Contralateral submandibular
    a. <6 Gy (RBE) mean dose

9.2.5 Treatment Planning Priorities and Instructions

Critical normal structure constraints, specifically, the brain stem, spinal cord, optic structures will take priority over coverage of the tumor. This is followed by adherence to brachial plexus, larynx, esophagus, oral cavity, contralateral parotid, and contralateral submandibular glands.

9.2.6 Planning

The initial phase of 30 fractions will include all gross (PTV expansions of GTV) and microscopic (PTV expansions of CTV) disease volumes. The final boost of 5 fractions will include only gross disease (PTV expansions of GTV). Normally, this course of radiation treatment will take 7 weeks to complete.
Proton therapy will be planned in CMS XIO (Elekta; Stockholm, Sweden) and RayStation(Raysearch labs,Stockholm Sweden), and delivered with uniform scanning or pencil beam scanning. Physical and biological uncertainties will be evaluated and taken into account, and worst- and best-case scenarios with the ranges of uncertainty (2.5% * range + 2mm) will be evaluated as per standard of care. We expect almost all patients to complete therapy.

9.2.7 Daily Treatment Localization

Setup accuracy will be confirmed with daily x-ray orthogonal verification of the isocenter based on bony anatomy. Verification CT scans will be obtained at Procure or NYPC a simulation CT scan. This is all part of the standard of care and will be performed at least once in the course of treatment to assess for changes in anatomy and reproducibility, most often in the first and/or fourth week of treatment.

9.3 Cisplatin Chemotherapy

Cisplatin should be administered on days 1-2, 21-22, and 42-43 of radiotherapy at a dose of 100mg/m2. The chemotherapy will be administered per MSKCC guidelines at 100 mg/m2 every three weeks. Normal scheduled treatment can be +/- 48 hours from three weeks post the prior administration. Administratoin entails pre-hydration with 1000 cc of Normal Saline (NS) and mannitol 25% before and after treatment. Fosaprepitant (150 mg), palanosetron (250 mcg), and decadron (12 mg) infusions are used for anti-emetic support before treatment. Cisplatin 100 mg/m2 is infused over one hour. Cisplatin can be administered before or after radiation is given but is only started once the radiation program has been initiated.

If the final surgical pathology report shows SNUC, at the discretion of the treating medical oncologist, the patient will receive an addition of etoposide chemotherapy to cisplatin chemotherapy. The dose of cisplatin will be decresed from 100 mg/m2 to 60 mg/m2. Cisplatin should be administered on days 1-2, 21-22 and 42-43 at a dose of 60 mg/m2 and Etoposide should be administered at days 1-3, 21-23, and 42-44 at a dose of 120 mg/m2. Infusion rate, anti-emetics, hydration will be administered as per institution's standard or physician's choice.

The post-chemotherapy administration protocol requires two days of intravenous hydration with 1000 cc NS following the day of cisplatin treatment in the chemotherapy suite. Dexamethasone 12 mg will be administered IV/PO on each of these days.

As needed anti-nausea medications will be prescribed for home and include Zofran 8 mg PO every 8 hours, Ativan 0.5 mg PO every 6 hours, and Compazine 10 mg every 6 hours. Patient will be advised to report any fever of 100.5 or greater or uncontrolled nausea or vomiting while at home.

9.4 Permitted Supportive/ Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol, and documented on each site's source documents as ancillary care or concomitant medication.

9.5 Prohibited Therapies

There are no explicitly prohibited therapies. Patients will be managed according to standard of care principles.

9.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections, or until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.

- Unacceptable adverse event(s).
- Patient decision to withdraw consent for participation in the study.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

All patients will be evaluated according to the standard of care for their nasal cavity, paranasal sinus, skull base tumor.

10.1 Evaluation during concurrent chemo-proton radiotherapy treatment (please see Table 3 for details):

- Standard weekly treatment evaluations
- Weekly CTCAEv4 toxicity (Appendix 4) and adverse event assessment
- Clavien-Dindo Classification of Surgical Complications (Appendix 5)
- Patient completion of required patient reported outcome assessments including:
    - Study specific PRO instruments:
        - EORTC QLQ C30 & H&N 43
        - SBI

Table 3. ASSESSMENTS DURING PROTOCOL TREATMENT

Assessments	Source	During Treatment
Toxicity and adverse events (CTCAEv4)	MD	Weekly throughout RT and at end of RT
Height and Weight	EMR	Postoperatively (pre RT), at week 4 of RT(+/- 7 days), and end of RT (+/- 7 days)
Postoperative MRI of the nasal cavity/paranasal sinuses	EMR	Should be completed 4 weeks post surgery (+/- 7 days)
History and Physical Exam	EMR	Safety evaluations during treatment with cisplatin involve weekly toxicity checks.
CBC and CMP	EMR	Safety evaluations during treatment with cisplatin involve weekly toxicity checks.
Clavien-Dindo Classification of Surgical Complication Assessmemt	MD	Postoperative but prior to radiation
EORTC QLQ C30 & H&N43	PSA	Postoperatively (pre RT), at week 4 of RT(+/- 7 days), and end of RT (+/- 7 days)
SBI	PSA	Postoperatively (pre RT), at week 4 of RT(+/- 7 days), and end of RT (+/- 7 days)

Abbreviations: MD (medical doctor); PSA (Patient self-administered with or without Research Study Assistant assistance); EMR (Electronic Medical Record)

10.2 Evaluation during follow up (please see Table 4):

- A focused history and physical exam
- Height and weight
- Dental evaluation
- Karnofsky performance status

- CTCAEv4 toxicity and adverse event assessment
- Study specific PRO instruments:
    - EORTC QLQ C30 & H&N43
    - SBI

Table 4. ASSESSMENTS IN PROTOCOL FOLLOW UP*					
		From End of Treatment			
Assessments	**Source**	**3 months (+/-2 weeks)**	**6 months(+/-4 weeks)**	**12 months (+/-4 weeks)**	**24 months (+/-4 weeks)**
History	EMR	X	X	X	X
Physical	EMR	X	X	X	X
Dental Evaluation	EMR		X	X	X
Karnofsky performance status	EMR	X	X	X	X
Toxicity and adverse events (CTCAEv4)	MD	X	X	X	X
MRI of nasal cavity/para-nasal sinuses AND PET/CT that includes diagnostic quality CT of neck.	EMR	X	x	X	X
EORTC QLQ C30/ H&N43	PSA	X	X	X	X
SBI	PSA	X	X	X	X

*Additional follow-ups are allowed per standard of care but are not protocol mandated. The patient will not need to fill out these QOL questionnaires at regular cancer follow-up visits after the 24-month follow-up visit.
Abbreviations: MD (medical doctor); PSA (Patient self-administered with or without Research Study Assistant assistance); EMR (Electronic Medical Record)

11.0 TOXICITIES/SIDE EFFECTS

11.1.1 Expected side effects of endoscopic skull base surgery

The expected side effects of endoscopic skull base surgery are managed in a routine fashion in the outpatient setting. These include nasal crusting requiring in-office debridements, temporary decrease in smell and taste, foul smell and taste, and nasal congestion. Possible complications of endoscopic skull base surgery (with the rates as per the largest series) include carotid artery injury (<0.5%), non-life-threatening epistaxis (2%), postoperative CSF leak requiring conservative or operative intervention (5%) [45-48]. Corresponding rates among the endoscopic skull base surgery team here at MSKCC are 0%, 1.6%, 3.2%. We will use the Clavien-Dindo classification of surgical complications, which grades from I-V the morbidity related to a specific postoperative complication [39].

11.1.2 Expected side effects of radiation therapy

A list of the adverse events and potential risks associated with radiotherapy of the head and neck appear below and will determine whether dose delays and modifications will be made, or whether the event requires expedited reporting in addition to routine reporting.

Radiation side effects are typically divided into those that occur acutely (during radiation and up to 3 months after radiation), and those that occur later (>3 months post-radiation).

11.1.3 Expected side effects of Cisplatin

The side effects of cisplatin include, but are not limited to, nausea, vomiting, decreased white blood count (more susceptible to infections), decreased red blood cells (or anemia, with a risk of needing a blood transfusion), decreased platelets (making it easier to bleed), fatigue, reversible hair loss, electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypomagnesemia), hearing loss, neuropathy, and kidney failure.

11.1.4 Expected side effects of Cisplatin and etoposide

The side effects of cisplatin plus etoposide include, but are not limited to nausea, vomiting, decreased white blood cell count (more susceptible to infections), decreased red blood cells (or anemia, with risk of needing blood transfusion), decreased platelets (making it easier to bleed), fatigue, hair loss, hearing loss, kidney failure, sores is mouth leading to dysphagia, electrolyte abnormalities, neuropathy, fevers, chills, allergic reaction, confusion, difficulty with imbalance, cardiovascular event including heart failure, skin rash, liver failure.

11.2 Expected Acute Side Effects of Radiation Therapy

Acute toxicity resulting from radiation therapy may include radioepithelitis of pharyngeal mucosa, xerostomia, thickened saliva, hypogeusia, dysphagia, hoarseness, nausea, emesis, skin irritation, erythema, epilation, weight loss, and fatigue.

11.3 Expected Late Side Effects of Radiation Therapy

Late toxicity resulting from radiation therapy may include permanent xerostomia, hypogeusia, dysphagia, trismus, nasal dryness, serous otitis media, dental decay, esophageal constriction, permanent skin changes including telangiectasias, hypothyroidism, ototoxicity (especially if concurrent cisplatin is administered), and increased risk for secondary malignancies. Osteoradionecrosis may occur in 5% or less of patients, but can be reduced by dental evaluation before radiation, as per the standard of care.

11.4 Toxicity Management

Toxicities will be managed by the treating investigators according to best standard of care to ensure optimal supportive care of study participants.

11.5 Dose Modifications/ Delays

At the discretion of the treating physician, any participant experiencing a grade 3 or higher toxicity may have a treatment break until resolution of the toxicity to grade 1 or less. If grade 3 toxicity persists, requiring a break of more than five consecutive treatments, the participant will be taken off protocol therapy per Section 13.0.

Cytopenias causing dose delays are not common with every three week dosing schedule and growth factors are not used in chemoradiotherapy protocols. Neutropenia of less than and ANC of 1000 and platelts of <100 would trigger a dose delay and re-assessment at 1 week. In the case of dose delays, the final dose of cisplatin may be given up to two weeks after completion of radiation therapy. Elevations in creatinine or BUN will be treated with extra sessions of intravenous hydration until the values normalize. Should the creatinine remain elevated between 1.4-1.6 mg/dl at the time of a subsequent dose, than cisplatin will either be dose reduced to 75 mg/m2 or discontinued. The risks of permanent kidney damage with additional cisplatin will be discussed with the patient prior to further administration. For creatinine levels >1.6 further cisplatin will not be administered. Interruption of treatment may occur due to holidays, weather closing or machines are down.

11.6 Adverse Event Reporting

This study will use the Common Terminology Criteria for Adverse Events (CTCAE) version v4.03 for adverse event (AE) reporting. After the Informed Consent Document (ICD) is signed, study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease. During the study, site personnel will record any change in the pre-existing condition(s), and the occurrence and nature of any new adverse events.

Expected events during radiation therapy are:

- Fatigue/malaise
- Weakness
- Nausea
- Mild anorexia
- Oral mucositis
- Radiation dermatitis
- Xerostomia
- Dysphagia
- Tinnitus
- Dysgeusia

General Therapy Related Events:

- Catheter related events (thrombosis, bleeding, infection)
- Hospitalization for the management of any of the above expected events

Reporting Results:

- All AEs related to protocol procedures are reported. All AEs occurring after the patient receives the first dose of radiation therapy must be reported in regard to their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, and/or radiation modality via CRF. If a patient's radiation treatment is discontinued as a result of an AE, personnel must clearly report the circumstances and data leading to any such dosage reduction or discontinuation of treatment.
- Events leading to the clinical outcome of death due to disease progression will be included as part of the safety and efficacy analyses for this study.
- If a death is considered related to treatment, the death should be reported as a Serious Adverse Event and appropriate guidelines followed for SAE reporting. Any clinically significant findings from labs, vital sign measurements, and other procedures should be reported as well.

11.7 Definitions of Adverse Events

11.7.1 Adverse Event (AE)

Defined as any harm or untoward medical occurrence in a research participant who is administered a medical product, medical treatment or procedure, even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment, or procedure, whether or not considered to be related. Resources containing information on AEs include monthly transcripts, assessment forms obtained after each clinic visit, and hospital progress and discharge notes. Grade ≥3 adverse events other than hematologic toxicities will be recorded, graded, and reported appropriately.

11.7.2 Related or Possibly Related AE

An AE is "related or possibly related to the research procedures" if, in the opinion of the principal investigator, it is more likely than not caused by the research procedures. AEs that are solely caused by an underlying disease, disorder, or condition of the subject, or by other circumstances unrelated to the research are not "related or possibly related". If there is any question whether or not an AE is related or possibly related, Grade 3 or higher AE should be reported to the PI and IRB.

11.7.3 Unexpected AE

An AE is "unexpected" when its nature (specificity), severity, or frequency are not consistent with (a) the foreseeable risk of adverse events associated with the research procedures described in protocol-related documents, such as the IRB-approved research protocol, informed consent document, product labeling and package inserts, and; (b) the characteristics of the subject population being studied, including the expected natural progression of any underlying disease, disorder or condition or any predisposing risk factor profile for the adverse event. AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol.

11.7.4 Attribution to Therapy

For reporting purposes, attribution is the assessment of the likelihood that an adverse event is caused by the research agent, or protocol intervention. The attribution is assigned by the principal investigator after considering the clinical information, the medical history of the subject, and the past experience with the research agent/intervention.

This is recorded using one of the following four categories:

- Related
- Possibly Related
- Not Related
- Unknown

"Related" events are those which are most certainly caused by the procedures involved in the research.

"Possibly related" events are those which may have been caused by the procedures involved in the research.

"Not related" events are those which are due to an underlying disease, disorder, or condition

of the subject, or due to other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

"Unknown" events are those which have an unclear relationship to the procedures involved in the research, either because more information is needed, and will be provided in follow-up, or because there is no way to make a determination.

11.8 Follow-up of Adverse Events

All adverse events will be followed up according to Good Clinical Practice.

During Treatment: Throughout the duration of the study, site personnel will track any change in the condition(s), the occurrence, and the nature of any AEs, and record the highest grade of the adverse event per cycle on the CRF. CTCAE grading will be assigned before each visit for any adverse events experienced during the previous visit period.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Local Failure

The main cancer outcome of interest is local failure defined as recurrence of the primary paranasal sinus or nasal cavity cancer within the primary disease site at one year from end of treatment. Local responses to therapy will be recorded using RECIST 1.1 criteria with the baseline comparator MRI being the postoperative/pre-chemoradiotherapy MRI. Progressive disease (PD) per RECIST 1.1 will be defined as a local failure.

12.2 Locoregional Failure

The cumulative incidence of locoregional failure will be recorded from the end of treatment. This will be defined as any progressive disease at the local site or regional/nodal (cervical/retropharyngeal) failure. If gross nodes are treated with radiotherapy, a regional/nodal failure will be defined using RECIST 1.1 as any progressive disease in a treated node. This will be assessed as per standard of care.

12.3 Distant Metastasis

Distant metastasis is defined as any distant (below the clavicles) recurrence from the end of treatment.

12.4 Progression

Progression is defined from the end of treatment to first local,regional/nodal or distant recurrence event, or death.

12.5 Disease Specific Mortality

Disease specific mortality is defined from the end of treatment to death from disease. Deaths due to other causes will be regarded as competing risks.

12.6 Overall Survival

Overall survival is defined from the end of treatment to death from any cause.

13.1 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops locally progressive disease, s/he will be taken off study and referred for alternative therapy. If at any time the patient develops unacceptable toxicity, s/he will be removed from the study. If at any time the patient dies while on study, s/he will be removed from the study. If grade 3 toxicity persists, requiring a break of more than five consecutive treatments, the participant will be taken off protocol therapy. We will, however, continue to follow them for the protocol.

The primary endpoint of which the power calculation is based on number of patients needed to observe a difference in local control following surgery then chemoradiation compared to historic rates of chemoradiation alone. Patients who are taken off study due to unacceptable toxicities will not be replaced as they will be counted as failures towards the primary endpoint. Patients who are lost to follow-up do not need to be replaced as they will be counted towards failures towards the primary endpoint. The chance of patients lost to follow-up (3 months from end of chemoradiation) is extremely low as all patients in our experience will return to see us for their first post-treatment follow-up visit. If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e. a change in diagnosis), the patient will be reviewed and determined whether to keep on study or not at the discretion of the treating physician.

A patient has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician, or at the institution. Should a patient (or a patient's legally authorized representative) decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation should be made at the time of the patient's withdrawal. Patients will be removed from one or more parts of the study, at the Investigator's discretion, if one or more of the following events occur:

- Significant noncompliance on the part of the patient
- Refusal of the patient to continue treatment or observations
- Decision by the Investigator that termination is in the patient's best medical interest
- Patient is lost to follow-up 6 months post registration

14.0 BIOSTATISTICS

A one-stage design will be used for this trial. Of the 25 patients to be enrolled, 15 will be SCC patients and the remaining 10 will be ACC, Esthesio, or Adenocarcinoma. Based on historical data, current standard non-surgical treatment has a 1-year local failure rate of 40% for SCC patients and 65% for ACC, Esthesio or Adenocarcinoma patients. Therefore, a mixed cohort of 15 SCC and 10 ACC/Esthesio/Adenocarcinoma patients should have 1-year local failure rate of 50% under standard non-surgical treatment[4]. We expect to decrease such a rate to 25% using the proposed new treatment. This design depends on a one-arm, one-sided binomial test and has a decision rule as follows: If, among the total 25 patients enrolled, we have at least 17 patients who are alive, followed and local failure free (or equivalently, at most 8 patients who are dead, lost to follow up or withdrew from the study, or have local failure) one year from the end of the treatment, then we shall declare the proposed treatment strategy

worthy of further investigation. Any patient who is taken off study due to unacceptable toxicities or lost to follow up, dies or withdraws within one year from the end of treatment will be regarded as a local failure. Patients who die during treatment will also be counted as failures, though such a probability will be small. This design has a type 1 error rate of 0.05 and type 2 error rate of 0.15 for testing the hypothesis p>=50% vs p<25%, where p represents the 1-year local failure rate.

To assess the complications of minimally invasive endoscopic skull base surgery in patients with unresectable disease, we will use Clavien-Dindo classification of surgical complications and summarize the grades (I-V) and types. This will be done after surgery but before radiation.

To assess acute and long-term toxicity of radiotherapy, we will summarize the CTCAE v4.03 scores and present descrptive statistics. This will be done weekly throughout RT, at the end of RT, and then 3 months after the end of RT for acute toxicities. Long-term toxicities will be assessed at 6, 12 and 24 months after the end of RT.

Patient reported outcomes of toxicity due to radiatherapy, EORTC(H&N43 and QLQ C30) and SBI, will be summarized and reported at the following time points: After surgery (pre RT), week 4 of RT(+/- 7 days),1 week within end of RT, and then at 3, 6, 12 and 24 months after the end of RT.

Specifically, the following subscales for the QLQ will be summarized at each time point.

For EORTC C30, we will look at 15 distinct groupings. These scales are: Global Health Status/QoL scale 2 items (29,30); Physical Functioning, 5 items (1-5); Role Functioning, 2 items (6,7); Emotional Functioning, 4 items (21-24); Cognitive Functioning, 2 items (20,25); Social Functioning, 2 items (26,27); Fatigue, 3 items (10,12,18); Nausea and Vomiting, 2 items (14,15); Pain, 2 items (9,19); 6-single item symptom scores (Dyspnea (8); Insomnia (11); Appetite Loss (13); Constipation (16); Diarrhea (17); and Financial Difficulties (28); all from single items).

For EORTC H&N43, we will look at 19 distinct groupings. Swallowing, 4 items (35, 36,37,38); Salivating, 2 items (42,43); Senses, 2 items (44,45); Speech, 5items (47, 55, 56, 57, 58); Social eating, 4 items (51, 52, 53, 54); Pain, 4 items (31, 32, 33, 34); Anxiety, 2 items (69, 70); Body image, 3 items (48,49, 50);Teeth, 3 items (39,40, 73); Skin, 3 items (65,66, 67); Shoulder problems, 2 items (62, 63); Physical contact, 2 items (60, 61); 7-Single item symptom scores (Mouth opening (41), coughing (46), neurology (72), social contact (59), weight low (68), lymphadema (64), problems with wound healing(71)).

For SBI, we have 11 disease-specific domains/scales: Emotional, 4 items (35,36,37,38); Social, 4 items (23,28,29,32); Other Physical, 6 items (8,11,15,18,19,24); Cognitive, 4 items (12,13,21,22); Family, 3 items (31,34,40); Financial, 2 items (30,39); Spiritual, 2 items (33,41); Endocrine, 4 items (7,25,26,27); Nasal, 4 items (2,3,14,16); Neurologic, 4 items (1,9,10,20); Visual, 4 items (4,5,6,17). A composite score assuming equivalent weighting of domains in overall quality of life will also be created by averaging domain scores and summarized.

Overall survival and progression free survival will be evaluated by Kaplan-Meier method. Regional/nodal progression, distant metastasis progression and disease specific death will be evaluated by cumulative incidence function where death without event or not due to disease will be classified as a competing risk. We will also report, if feasible, all 1- and 2-year rates.

For the correlative studies, we will collect tissue samples from patients and bank them for future investigations. No statistical analyses are planned.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

This study is not randomized.

16.1 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator/CRCwill be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into our secure clinical research database (CRDB). Source documentation will be available to support the computerized patient record. All research material from this study will be handled with the same confidentiality as patients' other medical data.

16.2 Quality Assurance

Eligibility of patients will be verified with the principal investigator. Only the designated investigators can obtain informed consent.

There are several different mechanisms by which clinical trials are monitored for data safety and quality. There are institutional processes in place for quality assurance (e.g. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA), and departmental procedures for quality control. In addition, there are two institutional committees that are responsible for monitoring the activities of our clinical trials program. These include: *Data and Safety Monitoring Committee (DSMC)* for Phase I

and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, both of which report to the Center's Research Council and Institutional Review Board (see section 16.2).

During the protocol development and review process, each protocol will be assessed for the level of risk and the degree of required monitoring. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) is reviewed, and monitoring procedures are established at the time of protocol activation.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://cancertrials.nci.nih.gov/researchers/dsm/index.html*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found at the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.html*

17.1 PROTECTION OF HUMAN SUBJECTS

There are no foreseen additional risks to the patients from this study.

Risks of Study Participation: Patients in this study will be receiving the current standard of care for their specific disease site.

Financial Costs to Patients: All diagnostic and therapeutic interventions are accepted as routine care of patients/ subjects eligible for this study.

Patient Confidentiality: Patient/subject privacy and confidentiality will be maintained according to MSKCC guidelines, and all data derived from this study will be kept in a secure database. All data and results will be anonymously reported with regard to individual subjects.

Voluntary Nature of Study: Subjects will be made aware of the voluntary nature of the study as part of the informed consent process. They will be allowed to withdraw participation at any time without the risk of alteration in the quality of their medical care.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated

in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

• Death

• A life-threatening adverse event

• An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

• A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

• A congenital anomaly/birth defect

• Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

• The date the adverse event occurred

• The adverse event

• The grade of the event

• Relationship of the adverse event to the treatment(s)

• If the AE was expected

• Detailed text that includes the following

o An explanation of how the AE was handled

o A description of the participant's condition

o Indication if the participant remains on the study

• If an amendment will need to be made to the protocol and/or consent form

• If the SAE is an Unanticipated Problem

For IND/IDE protocols:

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1: EORTC QLQ H&N43
Appendix 2: EORTC QLQ C30
Appendix 3: Skull Base Inventory
Appendix 4: CTCAE v4.0
Appendix 5: Clavien-Dindo Classification