Sinonasal and Skull Base Cancer Progress, Challenges, and Future Directions

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Context
- Advances in Diagnosis
  - Office endoscopy
  - High Resolution Imaging
  - Better Histopathologic Classification
- Advances in Treatment
  - Surgery
    - Craniofacial and skull base surgery
    - Endoscopic and Robotic surgery
  - Conformal Radiation: IMRT and Proton
  - Active chemotherapeutic agents and treatment intensification

ETIOLOGY
- Occupational
  - Furniture and hardwood
  - Nickel refining
  - Leather and boot
  - Radio-active paint
- Previous irradiation
- Chronic infection
- Tobacco and alcohol

Sinonasal Cancer MDACC Experience
- Department Database
  - 2698 patients with sinonasal cancer
  - 1944-April 2007
Site Distribution of Sinonasal Malignancies in Patients Seen at MDACC

Histologies of Sinonasal Malignancies in Patients Seen at MDACC

SPREAD
- Local
- Direct extension
- Perineural
- Fissures and foramina
- Regional
  - Lymphatic
- Distant
  - Hematogenous

AJCC Stages of Sinonasal Malignancies Seen at MDACC

Histologies of Sinonasal Malignancies in Patients Seen at MDACC

- Squamous Carcinoma 45%
- Unclassified Carcinoma 9%
- Other Neoplasms 5%
- Neuroblastoma 4%
- Other Carcinoma 7%
- Adenoid Cystic Carcinoma 8%
- Adenocarcinoma 6%
- Malignant Melanoma 6%
- Sarcoma 10%
- Other 5%

Site Distribution of Sinonasal Malignancies in Patients Seen at MDACC

- Paranasal Sinus, NOS 6.3%
- Anterior (Maxillary Sinus) 4.9%
- Nasal Cavity 34.3%
- Ethmoid Sinus 11.3%
- Sphenoid Sinus 2.0%
- Frontal Sinus 1.3%

N=2698 patients
Patient Evaluation

Objectives
- Establishing the diagnosis
- Determining the extent of tumor
- Planning a treatment strategy

Symptoms and Signs of Early Disease
Office Endoscopy

Signs and Symptoms
Advanced Disease
- Of extension beyond the sinonasal tract
  - Orbital
  - Facial
  - Oral
  - Neurologic

Nasal
Facial
Orbital
Neurologic
Oral
Imaging

- Indications
  - Suspicion of a neoplastic process
  - Evaluation of site and extent of disease

- Type of imaging study
  - Most commonly used: (CT/MRI/PET)
  - Selectively used: (Angiography)
  - Specific information for treatment planning

Benign vs. Malignant

CT vs. MRI

MRI T1 vs. T2
**Biopsy**

**Histopathologic Examination**

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**Neuroendocrine Tumors – Overall Survival**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>5y-OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENB</td>
<td>93.1%</td>
</tr>
<tr>
<td>NEC</td>
<td>64.2%</td>
</tr>
<tr>
<td>SNUC</td>
<td>62.5%</td>
</tr>
<tr>
<td>SmCC</td>
<td>28.6%</td>
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</tbody>
</table>


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**Differential Diagnosis**

- **Neuroendocrine Tumors**
  - **Overall Survival**
  - **Time (months)**
  - **5y-OS**: ENB 93.1%, NEC 64.2%, SNUC 62.5%, SmCC 28.6%

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**Markers**

- **PanMec/S100**
- **CD99**
- **Desmin**
- **Myogenin**
- **Pankeratin**

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**Images**

- Olfactory Neuroblastoma
- Neuroendocrine Carcinoma
- Sinonasal Undifferentiated Carcinoma

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**References**

Surgical Treatment

- **Surgical Approach**
  - Endoscopic
  - Transfacial
    - Lateral rhinotomy
    - Weber- Ferguson
  - Transoral - Transpalatal
  - Sublabial “Facial Degloving”
  - Transcranial

- **Extent of Resection**
  - Ethmoidectomy
  - Partial maxillectomy
  - Total maxillectomy
  - Orbital exentration
  - Anterior cranial base resection
  - Pterygopalatine fossa
  - Infratemporal fossa dissection

External Ethmoidectomy Approach

- **Indications**
  - Limited tumors of the ethmoid sinus or medial orbit
  - No significant extension into the maxillary sinus or cribriform plate

External Ethmoidectomy: Soft Tissue Approach

External Ethmoidectomy: Bone Resection
**External Ethmoidectomy:**

- **Postoperative Appearance**

**Medial Maxillectomy**

- **Indications**
  - Tumors of the lateral nasal wall
  - No significant extension into the maxillary sinus

**Lateral Rhinotomy**
Medial Maxillectomy: Medial Maxillectomy:

- Soft Tissue Approach
- Management of the Lacrimal Sac
- Exposure of the nasal cavity
- Osteotomies
Medial Maxillectomy: Closure

Postoperative Appearance

Inferior Maxillectomy

Indications
- Upper alveolar ridge tumors
- No significant extension into the maxillary sinus

Inferior Maxillectomy

Technique
- Soft tissue approach
  - Sublabial
  - Facial degloving
- Osteotomies
Facial Degloving Approach

- Indications
  - Bilateral medial or inferior maxillary resection
  - No significant superior/posterior extension

- Advantage
- Disadvantage
- Technique

Inferior Maxillotomy

Total Maxillectomy

- Indications
  - Tumors originating from the maxillary sinus
  - Tumors with significant extension into the maxillary sinus

Total Maxillectomy
Soft tissue approach
**Total Maxillectomy**

**Osteotomies**

**Reconstruction**

**Palate and Dentition**

**Indications**
- Tumors originating from the olfactory groove
- Tumors extending to or invading the cribriform plate

**Craniofacial Resection**

**SURGICAL PRINCIPLES**
- Adequate oncologic resection
- Minimal brain retraction
- Protection of critical neurovascular structures
- Meticulous reconstruction of the anterior skull base
- Optimal esthetic outcome

**Cranial Base Resection for Malignancy**
Extracranial Approach

A. Transfacial
B. Sublabial
C. Endoscopic

Transfacial Approach

Frontal Craniotomy
Osteotomies

Reconstruction of the Cranial Base
Pericranial Flap

Tumor Resection

Closure
Postoperative Appearance

Management of the orbit in sinonasal malignancy
- Exenteration
- Preservation
- Role of Radiation
- Reconstruction

Orbital Exenteration and Orbitectomy
Orbital Defect Reconstruction

Orbital Exenteration

- Almost routine in 1950s-1960s
- Rationale
  - Oncologic safety
    - (Harrison 1976, 1985, 1989)
  - Emotional impact

Orbital Preservation

- The orbit is preserved unless there is invasion of the orbital
  - fat, muscles
  - apex, posterior ethmoids, infraorbital n.
  - periorbita?
Orbital Exentration

Orbital Reconstruction

Function of the preserved orbit

- Radiation induced problems
  - Keratopathy, cataract, optic atrophy
- Surgery induced problems
  - Ectropion, hypoglobus, diplopia
- Poor functional and esthetic outcome of the preserved eye (Jiang 1991, Stern 1993)

Radiation factors
- dose, field, shielding
- 3-D Conformal Therapy
- IMRT

Surgical factors
- Orbital reconstruction
  - Bone grafts (Calvarial, rib, etc.)
  - Alloplastic implants (Medpor, Marlex, Titanium, Vitallium, etc.)

Extent of Orbital Resection and Bony Orbital Reconstruction

Improving Function of the Preserved Orbit
Secondary Orbital Reconstruction:
Calvarial Bone Graft

Outcome
Are we making progress?

Overall Survival over Five Years of Patients with Sinonasal Malignancies
Seen at MDACC from 1944 - April 2007

Died
Last Contact

0 12 24 36 48 60

Cumulative Proportion Surviving

2698 patients

1944 - 1953 vs. 1964 - 1973 & All Later Periods:  p < 0.05
1954 - 1963 vs. 1974 - 1983 & Later:  p < 0.05
1964 - 1973 vs. 1974 - 1983 & Later:  p < 0.05
1974 - 1983 vs. 1994 - 2003:  p < 0.05
Overall Five-Year Survival of Sinonasal Malignancy Patients by Histology (Simpler)

Died

Last Contact

0 12 24 36 48 60 Months from Presentation at MDACC

Cumulative Proportion Surviving

SQUAMOUS CARCINOMA

UNCLASSIFIED CARC.

ADENOCARCINOMA

OTHER NEOPLASMS

OTHER CARCINOMA

SARCOMA

MALIGNANT MELANOMA

ADENOID CYSTIC CARC.

NEUROBLASTOMA

Overall Ten-Year Survival of Sinonasal Malignancy Patients by Histology (Simpler)

Died

Last Contact

0 24 48 72 96 120 Months from Presentation at MDACC

Cumulative Proportion Surviving

SQUAMOUS CARCINOMA

UNCLASSIFIED CARC.

ADENOCARCINOMA

OTHER NEOPLASMS

OTHER CARCINOMA

SARCOMA

MALIGNANT MELANOMA

ADENOID CYSTIC CARC.

NEUROBLASTOMA

Craniofacial Resections MD Anderson Experience

Other Skull Base Tumors

CPR for Skull Base Tumors

CPR for Other Skull Base Tumors

266 patients

Disease-Specific Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections

Died of Disease

Last Contact

0 24 48 72 96 120 Months from Presentation at MDACC

Cumulative Proportion Surviving

266 patients
Overall Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections by Tumor Stage

- T1 or 2 or 3, N = 37
- T4, N = 131

Cumulative Proportion Surviving

Overall Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections by Disease Status at Presentation

- Initial disease - No Previous treatment, n = 170
- Recurrent disease - after treatment elsewhere, n = 66
- Persistent disease - after treatment elsewhere, n = 27

Cumulative Proportion Surviving, Initial vs. Recurrent Disease: p = 0.001

Overall Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections by Finding of Perineural Invasion

- No Perineural Invasion, N = 217
- Perineural Invasion Found, N = 49

Cumulative Proportion Surviving, Perineural Invasion: p = 0.003

Overall Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections by Finding of Angioinvasion

- No Angioinvasion, N = 253
- Angioinvasion Found, N = 13

Cumulative Proportion Surviving, Angioinvasion: p = 0.0001
Progression-Free Survival

- **Subdural spread**
  - Mean PFS 68.7 months
- **Brain invasion**
  - Mean PFS 22.3 months
  - *p*=0.005

Overall Survival – Surgical Margins

- **Negative margins**
  - Mean 102.9 months
- **Positive margins**
  - Mean 49.3 months
  - *p*=0.049

Overall Survival – Resection method

- **En bloc resection**
  - Mean 71.4 months
- **Piecemeal resection**
  - Mean 67.3 months
  - NS (*p*=0.951)

Improvements/Limitations/Future Directions

- Craniofacial skull base surgery
- Endoscopic and Robotic Approaches
- Conformal Radiation
- Active chemotherapeutic agents
- Treatment intensification
Endoscopic Resection
Advantages

- Direct access to the anterior and central skull base with no brain retraction
- Avoiding craniofacial incisions and extensive bone removal commonly used in open surgical approaches.
- Wider angle of vision and angled lenses
  - increases the range of the endoscopic visual surgical field
  - “seeing around corners” compared to the “line of sight” visual field gained by surgical loups or microscopes.

MORBIDITY AND MORTALITY OF ANTERIOR CRANIOFACIAL RESECTION

<table>
<thead>
<tr>
<th>Study</th>
<th># of Patients</th>
<th>Mortality</th>
<th>Morbidity</th>
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<tr>
<td>Catalano et al 1994</td>
<td>73</td>
<td>2.7%</td>
<td>63%</td>
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<tr>
<td>Shah et al 1997</td>
<td>115</td>
<td>3.5%</td>
<td>35%</td>
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<tr>
<td>Dias et al 1999</td>
<td>104</td>
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<td>48.6%</td>
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<tr>
<td>Solero et al 2000</td>
<td>168</td>
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<td>30%</td>
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Morbidity of ACFR

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<th></th>
<th>Intracranial</th>
<th>Extracranial</th>
<th>Systemic</th>
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<tr>
<td></td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
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<tr>
<td>Transient MS changes 15%</td>
<td></td>
<td></td>
<td>Diplopia 19%</td>
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<tr>
<td>CSF Leak 6%</td>
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<td>Enophthalmus 4%</td>
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<tr>
<td>Seizure 4%</td>
<td>2%</td>
<td></td>
<td>Pneumonia 2%</td>
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<tr>
<td>Meningitis 2%</td>
<td></td>
<td></td>
<td>Lagophthalmos 2%</td>
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<tr>
<td>Paracocciphal 2%</td>
<td></td>
<td></td>
<td>Epiphora 2%</td>
</tr>
<tr>
<td>CVA 2%</td>
<td></td>
<td></td>
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<tr>
<td>Extradural fluid</td>
<td></td>
<td></td>
<td>Wound dehiscence 2%</td>
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Hanna et al: AHNS 2006

Skull Base Surgery
MDACC

Total Number of Skull Base Procedures by Fiscal Year
During the last decade, there has been increasing adoption of endoscopic approaches for surgical resection of sinonasal malignancy.

Despite this growing enthusiasm, the oncologic outcomes for endoscopic resection of sinonasal cancers have not been adequately reported.

So What Are The Oncologic Outcomes of Endoscopic Resection of Sinonasal Cancer?

Findings

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of patients</th>
<th>Total</th>
<th>EE AA</th>
<th>CE A</th>
<th>All patients</th>
<th>EE AA</th>
<th>CE A</th>
<th>All patients</th>
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<tbody>
<tr>
<td>Preop</td>
<td>100</td>
<td>194</td>
<td>93 (77.5%)</td>
<td>134 (73%)</td>
<td>27 (22.5%)</td>
<td>50 (27%)</td>
<td>6% 28%</td>
<td>6% 28%</td>
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<tr>
<td>Postop</td>
<td>170</td>
<td></td>
<td>96 (56.5%)</td>
<td>140 (82%)</td>
<td>34 (19.4%)</td>
<td>64 (37.6%)</td>
<td>6% 28%</td>
<td>3% 12%</td>
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<td>Mean follow up</td>
<td>37 months</td>
<td>34 months</td>
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<td>Prior treatment</td>
<td>59% 28%</td>
<td>59% 28%</td>
<td>59% 28%</td>
<td>59% 28%</td>
<td>59% 28%</td>
<td>59% 28%</td>
<td>59% 28%</td>
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<tr>
<td>Stage</td>
<td>EE AA</td>
<td>CE A</td>
<td>All patients</td>
<td>EE AA</td>
<td>CE A</td>
<td>All patients</td>
<td>EE AA</td>
<td>CE A</td>
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<tr>
<td>T1</td>
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<td>3% 2%</td>
<td>3% 2%</td>
<td>3% 2%</td>
<td>3% 2%</td>
<td>3% 2%</td>
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<td>T2</td>
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<tr>
<td>T3</td>
<td>15% 15%</td>
<td>15% 15%</td>
<td>15% 15%</td>
<td>15% 15%</td>
<td>15% 15%</td>
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<tr>
<td>T4</td>
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<td>15% 15%</td>
<td>15% 15%</td>
<td>15% 15%</td>
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<tr>
<td>Histopathology</td>
<td>Adenocarcinoma</td>
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<td>14% 27%</td>
<td>14% 27%</td>
<td>14% 27%</td>
<td>14% 27%</td>
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<tr>
<td></td>
<td>Esthesioneuroblastoma</td>
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<td>7% 12%</td>
<td>7% 12%</td>
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<tr>
<td></td>
<td>Melanoma</td>
<td>14% 9%</td>
<td>14% 9%</td>
<td>14% 9%</td>
<td>14% 9%</td>
<td>14% 9%</td>
<td>14% 9%</td>
<td>14% 9%</td>
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<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>14% 8%</td>
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<td>14% 8%</td>
<td>14% 8%</td>
<td>14% 8%</td>
<td>14% 8%</td>
<td>14% 8%</td>
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<td></td>
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<td>7% 12%</td>
<td>7% 12%</td>
<td>7% 12%</td>
<td>7% 12%</td>
<td>7% 12%</td>
<td>7% 12%</td>
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<tr>
<td></td>
<td>Neuroendocrine Carcinoma</td>
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<td>4% 7%</td>
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<tr>
<td></td>
<td>SMJC</td>
<td>3% 9%</td>
<td>3% 9%</td>
<td>3% 9%</td>
<td>3% 9%</td>
<td>3% 9%</td>
<td>3% 9%</td>
<td>3% 9%</td>
</tr>
<tr>
<td></td>
<td>Sarcomas</td>
<td>1% 2%</td>
<td>1% 2%</td>
<td>1% 2%</td>
<td>1% 2%</td>
<td>1% 2%</td>
<td>1% 2%</td>
<td>1% 2%</td>
</tr>
</tbody>
</table>
Finding Hanna et al 2009 MD Anderson Nicolai et al 2008 Italy

Adjuvant Therapy
None (surgery only) 50% 47%
Radiation 37% 39%
Chemoradiation 13% 3%
Chemotherapy 6% 4%

Recurrence
Local 15% 15%
Regional 6% 1%
Distant 5% 7%

5-year Disease-specific survival
Overall 87% 82%
EEA 86% 91%
CEA 92% 59%

Survival in Patients Who Had Endoscopic Surgery for Sinonasal Cancers

Training and Expertise
Overall Survival in Patients Who Had Endoscopic Surgery for Sinonasal Cancers by Status at Presentation at MDACC

- Died
- Last Contact

Cumulative Proportion Surviving

<table>
<thead>
<tr>
<th>Months from Presentation at MDACC</th>
<th>0.0</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
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<th>0.9</th>
<th>1.0</th>
<th>1.1</th>
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<tbody>
<tr>
<td>Initial Disease, N = 49</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Recurrent Disease, N = 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Persistent Disease, N = 55</td>
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</tbody>
</table>

Initial vs. Persistent Disease: \( p = 0.002 \)
Initial vs. Recurrent Disease: \( p = 0.215 \)
Persistent vs. Recurrent Disease: \( p = 0.286 \)

Limitations of Endoscopic Approaches
Dural Reconstruction and CSF leaks

While endoscopic resection of sinonasal and skull base tumors is gaining popularity, valid concerns exist regarding the adequacy and reliability of endonasal reconstruction of major skull base and dural defects.

Dural Defect Repair?

A layered reconstruction of the dura with inlay and onlay fascial grafts has been described as an effective technique for repair of large dural defects.

The CSF leak rate with these techniques is significantly higher than rates reported with standard craniofacial resection.

In a recent study reporting the combined experience of the U. Miami and U. Pittsburgh with endoscopic endonasal resection of ENB, 4 of 23 patients (17%) had postoperative CSF leak.


CSF Leak

- A layered reconstruction of the dura with inlay and onlay fascial grafts has been described as an effective technique for repair of large dural defects.
- The CSF leak rate with these techniques is significantly higher than rates reported with standard craniofacial resection.
- In a recent study reporting the combined experience of the U. Miami and U. Pittsburgh with endoscopic endonasal resection of ENB, 4 of 23 patients (17%) had postoperative CSF leak.
Reconstruction of Large Dural Defects

- Our current policy is to perform CEA in patients who require large dural resections, and because of the high likelihood of delivering postoperative high-dose radiation therapy in these patients, our preference is to use vascularized flaps for reconstruction of the skull base.
- In addition to allowing wider dural resection, CEA in our hands allows us a more reliable reconstruction using water-tight suture duraplasty reinforced with a well vascularized pericranial flap.

CSF leak

- Following these principles, the postoperative CSF leak was rare (3%) in the current study and compares favorably with results obtained in standard open craniofacial resections.

The right approach?

- Complete Resection
- Adequate Reconstruction

Limits of endoscopic approach
- Facial Soft Tissue
- Deep Orbital Invasion
- Lateral supraorbital extension
- Anterior wall of frontal sinus
- Brain parenchymal invasion

Improvement/Limitations/Future Directions

- Craniofacial skull base surgery
- Endoscopic and Robotic Approaches
- Conformal Radiation
- Active chemotherapeutic agents
- Treatment intensification
Does conformal radiation improve outcomes or reduce toxicity?

Local control by era/technique

Ahamad et al, AHNS 2007

Table 6: Crude complications observed for all patients in group 1 and group 2.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Ocular</th>
<th>Auditory</th>
<th>Bone</th>
<th>Brain</th>
<th>Subcut Tissue</th>
<th>Skin</th>
<th>Endocrine</th>
<th>Infection</th>
<th>Total</th>
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Complication Free Rate

Complications between the Two Groups

Proton Therapy
33 yo female
Adenoid cystic carcinoma

Nasopharynx- ACC
70 CGE + CDDP

33 yo female
Adenoid cystic carcinoma

At presentation
One year follow up
Should the N0 neck be treated with elective nodal radiation?

Nodal Disease by Histology (%)

Presenting N+ Recurrent N+

SCC and Undiff (N = 100) Other (N = 47)

P = 0.007 P = 0.025

Nodal Control Rate in Patients with SCC or Undifferentiated Histology ± ENI

Percent Nodal Control

Elective Neck Irradiation
No Elective Neck Irradiation

P = 0.0004

Craniofacial skull base surgery
Endoscopic and Robotic Approaches
Conformal Radiation
Active chemotherapeutic agents
Treatment intensification
When do we use it?

- Significant brain parenchymal invasion
- Orbital invasion requiring exentration
- Facial soft tissue and skin invasion
- Nodal metastasis
- Gross cavernous sinus invasion

Before induction chemotherapy

One year after treatment

Post-Treatment Survival Time of Patients with Sinonasal SCC by Response to Induction Chemotherapy

- Partial Response or Stable Disease
  - N = 27
- Progressive Disease
  - N = 13

50 patients with T3/T4 SCC

p = 0.009
Disease-Free Survival in Patients with SNUC Who Underwent Induction Chemotherapy

Had Recurrence or Died ▲ Last Contact

Partial or Complete Response
N = 17

Stable or Progressive Disease
N = 10

p = 0.0003

Integrated Multidisciplinary Approach

As Presentation  Induction Chemotherapy  Concurrent Chemoradiation  Craniofacial Resection  2 yr. F/U

Summary

- Diagnostic imaging
- Craniofacial skull base surgery
- Endoscopic and Robotic Approaches
- Conformal Radiation
- Active chemotherapeutic agents
- Treatment intensification
SAVE THE DATE

24th Annual NASBS Meeting:
February 14-16, 2014
in SAN DIEGO, CA

Pre meeting Courses
February 12-13, 2014

Thank you