Sinonasal Cancers: Contemporary Standards of Management and Outcomes

Ehab Hanna
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
Are we making progress?
Sinonasal Cancer
MDACC Experience

• Department Database
  – 3564 patients with sinonasal cancer
  – 1944-May 2015
Overall Survival at 5 Years of Patients with Sinonasal Malignancies
Seen at MDACC from 1944 - May, 2015

Died Last Contact

Cumulative Proportion Surviving

N = 3564

47% Surviving at 5 Years
Overall Survival at 5 Years of Patients with Sinonasal Malignancies
By Year of Presentation at MDACC

Died  Last Contact

0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8  0.9  1.0
Cumulative Proportion Surviving

1944 - 1953, n = 68
1954 - 1963, n = 242
1964 - 1973, n = 344
1974 - 1983, n = 438
1984 - 1993, n = 540
1994 - 2003, n = 759
2004 - 2013, n = 1026
2014 - May 2015, n = 147

N=3564 patients
Overall Survival at Three and Five Years of Patients with Sinonasal Malignancies Seen at MDACC Over Time

Survival at 3 Years
Survival at 5 Years

N=3564 patients
N=3564 patients

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<thead>
<tr>
<th>Site</th>
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<td>ANTRUM (MAXILLARY SINUS)</td>
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<td>NASAL CAVITY</td>
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<td>FRONTAL SINUS</td>
<td>43</td>
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</table>
Site Distribution of Sinonasal Malignancies Seen at MDACC over Time

N=3564 patients
T Stages of Sinonasal Tumors Seen at MDACC

N=3564 patients
Neck Stages of Sinonasal Malignancies Seen at MDACC

N0: 81%
N1: 7%
N2: 9%
N3: 2%
NX: 1%

N=3564 patients
M Stages of Patients with Sinonasal Malignancies Seen at MDACC

N=3564 patients

M0 95%
M1 3%
MX 2%
AJCC Stages of Sinonasal Malignancies Seen at MDACC

- Stage I: 11% (11% of 3564 patients)
- Stage II: 11% (11% of 3564 patients)
- Stage III: 20 (20% of 3564 patients)
- Stage IV: 58 (58% of 3564 patients)

N=3564 patients
Treatment Modalities of Patients with Sinonasal Malignancies before Presentation at MDACC

- None: 47%
- Surgery: 24%
- Srg+XRT: 11%
- Srg+Chemo: 2%
- XRT: 4%
- Chemo: 2%
- XRT+Chemo: 3%
- Srg+X RT+: 3%

N=3564 patients
Treatment Modalities of Patients with Sinonasal Malignancies at MDACC

- Surgery: 22%
- XRT: 16%
- Chemo: 12%
- XRT + Chemo: 12%
- Srg + XRT: 25%
- Srg + XRT + Chemo: 5%
- Other: 4%

N=3564 patients
Treatment Modalities for Patients with Sinonasal Malignancies at MDACC over Time

- Surgery
- Srg+XRT
- Srg+Chemo
- XRT
- Chemo
- XRT+Chemo

N=3564 patients
Cranial Base Resection for Malignancy

SURGICAL PRINCIPLES

• Adequate oncologic resection
• Minimal brain retraction
• Protection of critical neurovascular structures
• Meticulous reconstruction of the anterior skull base
• Optimal esthetic outcome
Surgical Approach

A. Transfacial
B. Sublabial
C. Endoscopic
Transfacial Approach
Frontal Craniotomy
Osteotomies
Tumor Resection
Reconstruction of the Cranial Base
Pericranial Flap
Closure
Postoperative Appearance
Before surgery

7 yr FU
Craniofacial Resections
MD Anderson Experience

- Other Skull Base Resections: 357
- CFR for Sinonasal Tumors: 266
- CFR for Other Skull Base Tumors: 91

Total: 783

Feb. 14, 2007
Disease-Specific Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections

Died of Disease  Last Contact

Cumulative Proportion Surviving

Months from Presentation at MDACC

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

- Died
- Last Contact

T1 or 2 or 3
N = 37

T4
N = 131

p = 0.003

Cumulative Proportion Surviving

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

Died  Last Contact

Initial vs. Recurrent Disease : $p = 0.001$

- Initial disease - No Previous treatment, $n = 170$
- Recurrent disease - after treatment elsewhere, $n = 66$
- Persistent disease - after treatment elsewhere, $n = 27$
Overall Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections by Finding of Perineural Invasion

Died

Last Contact

Cumulative Proportion Surviving

No Perineural Invasion

$N = 217$

Perineural Invasion Found

$N = 49$

$p = 0.004$
Overall Survival of Sinonasal Cancer Patients Who Had Craniofacial Resections by Finding of Angioinvasion

Died  Last Contact

Cumulative Proportion Surviving

No Angioinvasion
N = 253

Angioinvasion Found
N = 13

p = 0.0001
Progression-Free Survival subdural vs brain

- **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
Skull Base Surgery
Open and Endoscopic
MDACC

Number by FY and Type

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<td>2015</td>
<td>581</td>
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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 loupes or microscopes.
Endoscopic Resection Technical Steps

- Debulking the tumor
- Mapping out the epicenter
- Vascular control
- Bony dissection
- Dural exposure/resection
- Intracranial exposure/resection
- Margin Control
- Reconstruction
Endoscopic Resection of Sinonasal Tumors

Classification Based on Extent of Resection
Proposed Classification

- **Type I**
  - Extracranial (Sinonasal)
    - N,E,M,F,S,NP
- **Type II**
  - Skull Base Bone
    - CP,FE
- **Type III**
  - Dural Resection
- **Type IV**
  - Brain Resection

- **Unilateral or Bilateral**
- **Lateral Extension**
  a. Pterygopalatine Fossa
  b. Pterygoid Plates
  c. Infratemporal fossa
- **Orbital Extension**
  O1: Lamina Papyracea
  O2: Peri-orbita
  O3: Orbital Contents

Examples: Unilateral Type I, NE, a, O1
Bilateral Type III, O2
Type I Extracranial (Sino-nasal) Resection
Type II
Skull Base Bone Resection
Type III
Dural Resection
Type IV
Brain Resection
Lateral Extension
PTF
O1: Lamina Paprycea

O2: Periorbita

O3: Orbital contents
Hemangiopericytoma
Endoscopic Resection
Low Grade Chondrosarcoma

Preop

7 yr. Postop.

2017
Lateral Nasal Wall
High Grade Sarcoma
Lateral Nasal Wall
High Grade Sarcoma
Endoscopic-assisted Medial Maxillectomy
Lateral Nasal Wall
High Grade Sarcoma
Open Vs. Endoscopic Approaches?

- Is it the right question?
Endoscopic Resection
Intracranial
Endoscopic Resection
Intracranial Reconstruction

Fascia Lata
Endoscopic Craniectomy Reconstruction
Postoperative Endoscopy
Postoperative Imaging
Endoscopic Assisted Anterior Craniofacial Resection
Endoscopic Assisted Anterior Craniofacial Resection
Endoscopic Assisted CFR Pericranial Flap
Postop. Pneumocephalus
Vascularized Turbinate Flap
Skull Base Reconstruction
Turbinate Flap
Endoscopic Resection

- Oncologic Outcomes
Endoscopic Resection of Sinonasal Tumors

Updated Database
391 patients
Epicenters of Sinonasal Malignancies Treated with Endoscopic Surgery

- Nasal Cavity: 63%
- Maxillary Sinus: 15%
- Ethmoid Sinus: 15%
- Sphenoid Sinus: 3%
- Nasopharynx: 2%
- Frontal Sinus: 1%

N = 391 patients
Clinical T Stages of Sinonasal Malignancies Treated with Endoscopic Surgery

- T4: 56%
- T3: 13%
- T2: 17%
- T1: 13%
- TX: 1%

N=391 patients
Clinical N Stages of Sinonasal Malignancies Treated with Endoscopic Surgery

- N0: 91%
- N1: 2%
- N2b: 3%
- N2c: 3%
- NX: 1%

N=391 patients
Clinical M Stages of Sinonasal Malignancies Treated with Endoscopic Surgery

- M0: 98%
- M1: 1%
- MX: 1%

N=391 patients
Clinical AJCC Disease Stages of Sinonasal Malignancies Treated with Endoscopic Surgery

N = 391 patients
Skull Base Involvement

Histogram: TcExtendSkullBase
- No: 191 (55%)
- Yes: 154 (45%)

Histogram: TcInvadeSkullBase
- No: 237 (68%)
- Yes: 109 (32%)
Histologies of Sinonasal Malignancies Treated with Endoscopic Surgery

- Squamous Cell Carcinoma: 23%
- Adenoid Cystic Carcinoma: 9%
- Adenocarcinoma: 7%
- Sinonasal Undifferentiated Carcinoma: 11%
- Neuroendocrine Carcinoma: 15%
- Esthesioneuroblastoma: 13%
- Melanoma: 13%
- Sarcoma: 7%
- Other: 11%

N=391 patients
Overall Treatment for Original Disease of Sinonasal Malignancies Treated with Endoscopic Surgery

- Surgery: 51%
- Surgery + XRT: 25%
- Surgery + XRT + Chemo: 20%
- Surgery + Chemo: 4%

N=391 patients
5-Year Disease-Specific Survival of Sinonasal/Skull Base Cancer Patients Who Had Endoscopic Surgery

- Died of Disease
- Last Contact

- 89.1% Not Dead of Disease at 3 Years
- 87.5% Not Dead of Disease at 5 Years
10-Year Disease-Specific Survival of Sinonasal/Skull Base Cancer Patients Who Had Endoscopic Surgery

- Died of Disease
- Last Contact

N = 391

- 89.1% Not Dead of Disease at 3 Years
- 87.5% Not Dead of Disease at 5 Years
- 81.0% Not Dead of Disease at 10 Years
Overall Survival of Patients with Sinonasal Malignancies Treated with Endoscopic Surgery for Original Disease by Status of Disease at Presentation

- Died
- Last Contact

<table>
<thead>
<tr>
<th>Cumulative Proportion Surviving</th>
<th>Months from Presentation</th>
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<tbody>
<tr>
<td>Previously Untreated, n = 96</td>
<td>60</td>
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<tr>
<td>Recurrence Disease, n = 28</td>
<td>60</td>
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<tr>
<td>Persistent Disease, n = 78</td>
<td>60</td>
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Previously Untreated vs. Persistent Disease

Log Rank p = 0.00064
Importance of Adequate Initial Treatment

Diagnosis Scan

Status Post Endoscopic Debulking with Subtotal Resection/Positive Margins

3 Months Status Post IMRT (54 Gy)

Adenoid Cystic Carcinoma with Orbital/Anterior Skull Base Involvement
Overall Survival of Sinonasal Malignancy Patients Treated with Endoscopic Surgery by Site and Type of Surgery

- Died
- Last Contact

- Purely Endoscopic Outside, n = 122
- Purely Endoscopic at MDACC, n = 95
- Endoscopic-Assisted Outside, n = 15
- Endoscopic-Assisted at MDACC, n = 48

Endoscopic-MDA vs. Endo-Assisted-Outside: p = 0.018
Endoscopic-MDA vs. Endoscopic-Outside: p = 0.080
Training and Expertise
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 parynchemal invasion

Extent of disease
Overall Survival of Patients with Sinonasal Malignancies by Histology

- Died
- Last Contact

Cumulative Proportion Surviving

- CARCINOMA, SQUAMOUS
- CARCINOMA, UNCLASSIFIED
- ADENOCARCINOMA
- OTHER NEOPLASMS
- CARCINOMA
- SARCOMA
- MELANOMA, MALIGNANT
- CARCINOMA, ADENOID CYSTIC
- NEUROBLASTOMA

N=3564 patients
Overall Ten-Year Survival of Sinonasal Malignancy Patients by Histology (Simpler)

Died  Last Contact

N=3564 patients
Olfactory Neuroblastoma

Neuroendocrine Carcinoma

Sinonasal Undifferentiated Carcinoma
Neuroendocrine Tumors – Overall Survival

5y-OS
ENB 93.1%
NEC 64.2%
SNUC 62.5%
SmCC 28.6%
Cordes et al., 2007

- Neuroendocrine: Chromo/Synap
  - +
  - -

- Muscle: Desmin
  - CD99
  - Melanocytic: PanMel/S100

- Myogenin +

- NEC
- ENB
- RMS
- ES/PNET
- Melanoma
Advances in Histopathologic Classification
Integrated Multidisciplinary Approach

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

Ahamad et al, AHNS 2007
Complication Free Rate

Bristol IJ, Ahamad A, Garden AS, Morrison WH, Hanna EY, Papadimitrakopoulou VA, Rosenthal DI, Ang KK.

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Ocular</th>
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Total: 13 34 17 36 8 23 12 0

Complications between the Two Groups

Proton Therapy
33 yo female
Adenoid cystic carcinoma
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+**
  - SCC and Undiff: (N = 100)
  - Other: (N = 47)
  - **P = 0.007**

- **Recurrent N+**
  - SCC and Undiff
  - Other
  - **P = 0.025**
Nodal Control Rate in Patients with SCC or Undifferentiated Histology ± ENI

\[ P = 0.0004 \]
Improvement/Limitations/Future Directions

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

After induction chemotherapy
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

○ Died  + Last Contact

50 patients with T3/T4 SCC

Partial Response or Stable Disease
N = 37

Progressive Disease
N = 13

p = 0.009

Cumulative Proportion Surviving

Months from End of Treatment for Initial Disease
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
Phase II Trial of Induction Chemotherapy in Advanced Sinonasal Cancers
Protocol Schema

1. **DIAGNOSIS & STAGING + BIOPSIES**

2. **INDUCTION CHEMOTHERAPY**

3. **RESPONSE ASSESSMENT + BIOPSIES**

   - <PR>
     - Surgery & postop RT
   - **PR/CR**
     - CHEMORADIOTherAPY
       - observe
       - CR
       - <CR> surgery
Correlative Study

• To identify biological markers that could serve as surrogates for response and predictors of long-term outcome.
Summary

• Diagnostic imaging
• Craniofacial skull base surgery
• Endoscopic and Robotic Approaches
• Conformal Radiation
• Active chemotherapeutic agents
• Treatment intensification
MDACC
Skull Base Surgery

Franco DeMonte
1992
Neurosurgery

Ehab Hanna
2004
HNS

Paul Gidley
2005
Neuro-Otology

Michael Kupferman
2007
HNS

Shirley Su
2013
HNS

Shaan Razza
2014
Neurosurgery

Marc Elie Nader
2017
Neuro-Otology
MDACC Head and Neck Team

- Head and Neck Surgery
- Thoracic/Head and Neck Medical Oncology
- Radiation Oncology/Medical Physics
- Oncologic Dentistry
- Speech Pathology
- Neuroradiology
- Pathology
Thank you