Objectives

- Epidemiology of HPV+ oropharynx squamous cell carcinoma (OPSCC)
- Prognosis of oropharynx cancer
- Treatment options and outcomes
- Role of TORS in the era of HPV+ OPSCC
- TORS outcomes
- Updated AJCC staging
- Future directions
Background

- Incidence of oropharynx cancer rising
  - Despite overall decline in head and neck cancer
  - Decreased smoking
  - Increased HPV+ disease
- HPV+ OPSCC > cervical cancer by 2020
- Double-stranded circular DNA virus
- Replicates exclusively in keratinocytes
- E6 and E7 viral oncogenes promoting cell growth by inactivation of p53 and pRb
- High risk subtypes 16 and 18
HPV+ OPSCC

- HPV-16 causes 90% of HPV+ cancer
- Gillison et al. showed 26 or more vaginal sex partners or 6 or more oral sex partners dramatically increases risk; OR = 3.1 and OR 3.4 respectively
- Differing phenotypic and biological profile of HPV+ OPSCC
  - Better DFS and OS compared to HPV- disease
Oncologic Outcomes

- Ang et al. Performed retrospective analysis of RTOG 0129
- Overall Survival of HPV (+) at 3 yrs: 82%
- Overall Survival of HPV (-) at 3 yrs: 57.1%
- Progression-free Survival in HPV (+): 73.7%
- Progression-free Survival in HPV (-): 43.4%
- Locoregional recurrence in HPV (+): 13.6%
- Locoregional recurrence in HPV (-): 35.1%
Risk Stratification

- Smoking factor
Treatment
Evolving vs. Revolving Treatment Paradigms
Chemoradiation Therapy Era

- The Department of Veteran Affairs Laryngeal Cancer Study Group
  - Induction chemotherapy followed by radiation therapy in stage III and IV laryngeal cancers
  - 2 yr survival 68% for both groups, overall rates of recurrence were similar, larynx preservation rate 64%
  - Changed standard of care to non-surgical

- RTOG 91-11
  - RT along vs. induction chemo + RT vs. concurrent CRT
  - Concurrent cisplatin/XRT provided best rates of laryngeal preservation, disease free survival, superior overall survival due to suppression of distant metastases, presumably from the addition of chemotherapy.
  - Concurrent chemoXRT became standard
Non-Surgical Treatment

- Standard chemoradiation therapy is once daily XRT in fractions of 2 Gy/fx for a total dose of 70-74 Gy (7 weeks)
- Concurrent Cisplatin
- Salvage Neck Dissections for PET+ lymph nodes 3 months s/p treatment or clinically concerning neck masses
Toxicity

- Loss of Taste
- Xerostomia
- Need for Feeding Tubes/Dysphagia
- Febrile Neutropenia
- Radiation Dermatitis
- Pain
Severe Late Toxicity After Concurrent Chemoradiation

- Machtay et al. reviewed RTOG Analysis of 3 trials
- 43% of assessable patients had a severe late toxicity
- 35% in patients with OPSCC
- Older age (odds ratio 1.05 per year; \( P = .001 \))
- Advanced T stage (odds ratio, 3.07; \( P = .0036 \))
- Larynx/hypopharynx primary site (odds ratio, 4.17; \( P = .0041 \))
- Neck dissection after CRT (odds ratio, 2.39; \( P = .018 \))
Traditional Surgery

Mandibulotomy

Pharyngotomy
Traditional Surgery

- Transmandibular or transpharyngeal open approaches
  - High morbidity
  - Poor function
- Transoral laser microsurgery
  - Lower morbidity
  - Technically more challenging
Superior Oncologic Outcomes with Upfront Surgery

- Head & Neck 2004
- 16,188 cases from the National Cancer Data Base
- Early-stage disease, surgery with or without XRT had higher survival than irradiation alone
- Advanced-stage disease, surgery with irradiation had the highest survival
Five-year disease-specific survival by treatment for early-stage (I–II) base of tongue SCC
Five-year disease-specific survival by treatment for advanced-stage (III–IV) base of tongue SCC
Transoral Robotic Surgery

Increased Range of motion

Improved access and magnification
Transoral Robotic Surgery
Not experimental, just a new tool

- TORS first described in 2005 at Penn
- FDA approved in 2009 for T1/2 tumors
- NCCN guidelines recognize transoral surgery as useful modality in select patients
- Poses new challenges and questions for oncologists (esp Radiation Oncologists)

Review
Oral Oncology
Transoral robotic surgery: The radiation oncologist’s perspective
Matthew C. Ward M.D., Shlomo A. Koyfman M.D. *
Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, United States
TORS Candidacy Factors

- **Primary site**
  - $T_{1/2}$
  - Absence of midline soft palate
  - Resection of less than 50% BOT or posterior pharyngeal wall

- **Gross ECS in neck**

- **Trismus**

- **Retropharyngeal carotid**
Early Stage Disease

- T1-2 No-1
- Generally good outcomes no matter the modality
- Goal: achieve optimum oncologic outcomes while minimizing acute and late toxicities
- Modern XRT techniques, severe late toxicity is decreasing
- Patient and tumor factors determine surgical vs. non-surgical approach
Preop Patient Selection

- Active smokers unwilling to quit
  - Decreased efficacy of XRT
  - Increased stroke risk
  - Second malignancies
- Live a great distance from treating facility
- Previous radiation history
  - Lymphoma or skin cancer
- Poor social support and non-compliance
Tumor Factors

- Small exophytic tumors with minimal invasion
  - Negative margins likely
  - Good function postop
- Borderline PET findings for adenopathy
  - Downstaging of N1 to No in 1/3 of patients
- Pathologic upstaging in 30-40% of No
Poor Candidates for TORS
TORS Radical Tonsillectomy
TORS BOT Resection
Oncologic Outcomes

- Retrospective multi-institutional review of 410 patients undergoing TORS
- 31.3% received radiation therapy alone
- 21.3% received radiation therapy with concurrent chemotherapy
- Neck dissection was performed in 78.8%
- Mean follow-up time was 20 months
- Local, regional, and distant recurrence occurred in 4.4%, 3.7%, and 2.4%
- 4.1% died of disease, and 3.2% died of other causes
OncoLogic Outcomes

- 2-year locoregional control rate was 91.8% (95% CI, 87.6%-94.7%)
- DSS 94.5% (95% CI, 90.6%-96.8%)
- OS 91% (95% CI, 86.5%-94.0%)
- Improved survival among women (P = .05) and tonsil (P = .01)
- Smoking was associated with worse overall all-cause mortality (P = .01)
- Adverse histopathologic features did not remain significant on multivariate analysis.
Efficacy of TORS Alone

Prospective, single-center, observational study
30 pts underwent TORS +/- SND without adjuvant therapy (minimum follow-up 18 mos)
1 local recurrence
3 pts with perineural invasion (10%)
1 pt with lymphovascular invasion (3%)
16 pts with Stage III/IV disease
Functional Outcomes

Transoral Robotic-Assisted Surgery for Head and Neck Squamous Cell Carcinoma

One- and 2-Year Survival Analysis

Hilliary N. White, MD; Eric J. Moore, MD; Eben L. Rosenthal, MD; William R. Carroll, MD; Kerry D. Olsen, MD; Renée A. Desmond, DVM, PhD; J. Scott Magnuson, MD

- 0% of patient Gtube dependent
- In a prospective comparative study, 11 patients treated with TORS had significantly better eating ability and dietary intake 2 weeks after treatment compared with patients treated with chemoradiation
- Surgical patients experienced a return of their oral dietary intake 1 year after surgery, whereas patients treated with chemoradiation continued to have decreased oral diet as assessed by the Performance Status Scale questionnaire.
Prospective nonrandomized clinical trial
40 patients with stage III or stage IVA oropharynx and supraglottic SCC
Group 1: TORS + adjuvant therapy
Group 2: Primary chemoradiotherapy
Patients completed the M.D. Anderson Dysphagia Inventory (MDADI) before treatment and then at 3, 6, and 12 months
Functional Outcomes

No statistically significant differences before treatment or at 3-month follow-up visit

Difference was significant at the posttreatment visits at 6 months ($P=0.004$) and 12 months ($P=0.006$)
Adjuvant Therapy with TORS

- Dose reduction from 70 Gy to 60 Gy
  - Less acute and late toxicity effects possible
    - Preliminary results from ECOG 1308 trial
  - ORATOR trial
    - Phase II trial comparing TORS with risk adapted adjuvant treatment
    - QOL as primary endpoint

- Spare chemotherapy
- Target volume reduction
De-Intensifying Through Reducing the Volume of Irradiation

Slides courtesy of Harry Quon, MD
Radiation Oncology
Johns Hopkins
Implications of TOS on Radiotherapy Treatment Planning

Max: 45-50 Gy
D50: <30 Gy

Quon et al. ORL 73(3):121-30, 2011
Implications of TOS on Radiotherapy Treatment Planning

Max: 45-50 Gy
D50: <30 Gy

Quon et al. ORL 73(3):121-30, 2011
Radiation Limited to the Primary Invasive Base

Max: 45-50 Gy
D50: <30 Gy

Quon et al. ORL 73(3):121-30,2011
Unknown Primary

- 89% detection rate
- Rapidly evolving paradigm
- Dramatic decrease in overall toxicity with TORS detection
Future Directions

- Decoupling of primary and neck
  - Reduction in target volume
  - ADEPT trial omits primary site XRT in pT1-2 resected with negative margins
  - TORS only to primary without ND followed by neck XRT

- Lateralize XRT
  - Spare contralateral neck XRT

- ECS and chemotherapy
- HPV vaccine
Case

- 54 yo M presented with biopsy proven HPV+ SCC of right BOT
  - Clinically staged at T2 N2c Mo stage IVa
  - TB discussion
  - Concern for ECS on CT
  - Patient desired upfront surgery, TORS and bilateral neck dissections
Case
Case

- Final path
  - Negative margins
  - No adverse features
  - Contralateral neck negative
  - 3 positive ipsilateral nodes
  - No ECS

- Discharged POD #4
  - Soft diet without feeding tube
  - All drains removed
Conclusions

- HPV+ OPSCC patients are younger, healthier, nonsmokers
- TORS is a safe and effective treatment that is at least equivalent to non-surgical treatment
- Good functional outcomes with TORS
- Careful selection is key
- Late toxicities from chemoXRT may be avoided or reduced
- De-intensification strategies will continue to shape the future of treatment paradigms