Transoral Robotic Surgery in the Era of HPV Related Oropharyngeal Malignancy

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• No relevant financial disclosures
Objectives

- Review the association between HPV infection and HPV-OPSCC
- Role of TORS in treatment of HPV-OPSCC, specifically tonsil cancer
- Review Current research
Head & Neck SCC

- Head and neck squamous cell carcinomas (HNSCC) account for 4% of malignant neoplasms worldwide. Etiologic factors: tobacco, alcohol, HPV.
- Oropharyngeal squamous cell carcinoma (OPSCC) incidence significantly increased during 1984 to 2004 (28%), and continues to rise. New etiologic factor: Human Papillomavirus Virus (HPV).
- The subgroup of HPV+OPSCC is being recognized as a separate entity with a much better prognosis than HPV-negative oropharyngeal carcinoma.
• HPV is the most common sexually transmitted disease in US.
• Around 20-30% of adults in the U.S. have had an oral HPV infection, and HPV infection is more commonly found in men.
• Oral HPV is about three times more common in men than in women.
  • The prevalence of oral HPV infection is estimated as 10% in men and 4% in women aged 14-69
• >80% sexually active young adults have an anogenital infection with HPV.
• Only 1% of people have the high risk HPV that is found in oropharyngeal cancers (HPV type 16, 90% of cases). In some people, oral HPV infection leads to HPV-OSCC after many years.
  • Increased risk with increased number sexual partners (oral genital/anal contact).
  • Unclear if associated with deep kissing (although most experts feel this is UNLIKELY)
• HPV is transmitted to mouth by oral sex.
  • It may also be possible to get oral HPV by other ways.
HPV

- Most people clear the infections on their own within a year or two, but in some people HPV infection persists.
- We do not know the time from first oral HPV infection to cancer, but it takes many years (estimate 10-20y).
- Many patients with HPV-OSCC no longer have HPV detectable in their mouth after treatment, while others do.
- The HPV vaccine prevents people from getting new HPV infections, but will not help you clear an infection that’s already present.
  - Recommended for people ages nine to 26 years old (no current recommendations to prevent HN cancer per se) to prevent human papilloma infection.
- HPV vaccines (designed for cervical cancer) might also prevent oropharyngeal cancers, since the vaccines prevent an initial infection with
  - No study showing prevention of OPSCC(makes sense that it should work though)
HPV+ OPSCC

- Approximately 73% of OPSCC were HPV positive in the 2000’s (USA).
- HPV+ patients are usually younger (40-60 years), white male, bulky neck disease and small primary tumors, non-smokers.
- HPV + carries favorable prognostic significance in patients with OPSCC (Ang et al., NEJM, 2010)
  - 3 year overall survival 82% (57% HPV negative)
  - Improved progression free survival
- **HPV+ patients have a better outcome regardless of treatment modality.**
HPV OPSCC and the Family

- Some studies have suggested a 2-3 fold increase risk of OPSCC in partners of patients with HPV related cervical cancer.
- Partners of patients with OPSCC HPV may have a slightly elevated risk of HPV related cancers.
- No additional recommendations for screening for OPSCC in partners of patients with HPV OPSCC.
HPV and Tobacco

• Tobacco use associated with increased prevalence of oral HPV infection.
• Tobacco use (current and cumulative) associated with worse prognosis.
  – Increased risk death on local-regional progression.
• There is an association between HPV OPSCC and marijuana use.
Treatment of OPSCC and Role of TORS
NCCN Guidelines

Base of tongue/tonsil/posterior pharyngeal wall/soft palate

CLINICAL STAGING

T1-2, N0-1

TREATMENT OF PRIMARY AND NECK

Definitive RT©

Complete clinical response
Residual disease

or

No adverse features$f$

One positive node without adverse features$f$

Excision of primary ± ipsilateral or bilateral neck dissection$d$

Extracapsular spread ± positive margin

Positive margin

Other risk features

Complete clinical response
Residual disease

ADJUVANT TREATMENT

Salvage surgery

Consider RT©

Chemo/RT©,e (category 1)

Re-excision$g$ or RT©

RT© or Consider chemo/RT©,e

Salvage surgery

For T2, N1 only, RT© + systemic therapy$g$ (category 2B for systemic therapy)
Treatment of OP SCCA - OPEN

• Open surgery for treatment of OPSCC is invasive and carries high morbidity.
Treatment non-surgical

- Concurrent chemoradiotherapy has been the mainstay for treatment of locally advanced OPSCC. However, this treatment contributes to increased risk of long-term dysphagia with compromise in quality of life.
- Up to 78% of patients require PEG at some point during treatment.
- Long term morbidity – dysphagia, dry mouth
Background - TORS

- There is literature demonstrating appropriate oncologic and functional outcomes with a transoral approach to select oropharyngeal cancers.
- Laccourreye (2005) and Steiner (2003) have utilized minimally invasive approaches (headlight, laser) with acceptable oncologic and functional outcomes.
  - These approaches are useful for selected lesions given line of sight issues (especially lesions involving the inferior tonsil and BOT).
Background - TORS

• Disadvantages of traditional trans-oral approaches:
  – LACK OF EN BLOC RESECTION
  – Distance from surgical field
  – Limited exposure provided by the laryngoscope
  – Reduced depth of perception
  – Tremor
  – Lack of motion scaling
Background- TORS

- Resident research project at Upenn.
- Developed 2004-2009 by Hockstein, Weinstein, O’Malley.
- Feasibility and safety studies in mannequin and canine model, then cadaver.
- Preclinical and clinical trials leading to FDA approval 12, 2009.
Application in Otolaryngology

- In 2009, the Federal Drug Administration approved the use of TORS and the da Vinci robotic surgical system for T1 and T2 malignancies of the oropharynx, larynx and all benign diseases.

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Oropharynx</td>
<td>1. Benign tumors</td>
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<tr>
<td></td>
<td>2. Selected T1-T2, T3, T4a oropharyngeal carcinomas</td>
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<tr>
<td>Larynx/Hypopharynx</td>
<td>1. Benign tumors</td>
</tr>
<tr>
<td></td>
<td>2. Selected T1, T2 and T3 laryngeal and hypopharyngeal carcinomas</td>
</tr>
<tr>
<td>Parapharyngeal space/Infratemporal fossa</td>
<td>1. Benign tumors</td>
</tr>
</tbody>
</table>
TORS: Advantages

- Minimally invasive
- Exceptional 3 dimensional visualization
- Wristed instrumentation (six degrees of freedom)
- Tremor reduction
- Ergonomic operating position
- Motion scaling
- Decreased Morbidity
- Decreased operative time
- Decreased hospitalization time
- Decreased tracheostomy rates
- Improved swallowing function
- Lower cost than open approach
TORS Radical Tonsillectomy

- Discussing a new surgical technique.
- Better access and visualization.
- Better functional outcomes compared to gold standard.
Surgical Anatomy
Transoral robotic-assisted surgery set-up

Surgical Set-up
TORS Radical Tonsillectomy

1. Buccal Mucosa Incision
2. Lateral dissection (lateral to the pharyngeal constrictors) to level of styloglossus and stylopharyngeus
3. Soft Palate Resection
4. Elevation of constrictors off prevertebral fascia and transection of styloglossus and stylopharyngeus
5. Tongue Base
6. Pharyngoplasty (optional)
7. Uvula or buccal flap (optional)
Buccal Mucosa Incision

• Incision of Buccal mucosa

Lateral Dissection

- Develop a plane lateral to the pharyngeal constrictor
- Identify the pterygoid musculature
- Dissection brought to level of styloglossus and stylopharyngeus muscles
Soft Palate Resection

- Medial soft palate margin
- Dissection through soft palate and posterior tonsillar pillar to level of prevertebral fascia
- Elevation of constrictors off prevertebral fascia and transection of styloglossus and stylopharyngeus

Protection of Carotid

- Transection of tongue base muscle and extrinsic musculature
- Careful dissection of extrinsic musculature given proximity to carotids
Resection of Tongue Base Margins
Contraindications

- AJCC T4a disease (except unilateral deep extrinsic tongue muscle that did not require resection across the midline)
- AJCC T4b disease (carotid involvement)
- Tumors involving more than 50% of the posterior pharyngeal wall
- Invasion of the deep tissues lateral to the constrictor muscles or posterior invasion of the prevertebral fascia
- Retropharyngeal internal carotid artery (contraindication for TORS radical tonsillectomy)
- Benign causes of trismus or other anatomic findings that precludes transoral access
- Medical contraindication for having open wound heal by secondary intention, such as need for chronic anticoagulation
- Medical conditions that preclude general anesthesia
TORS Outcome

• Preliminary data relating to local control, disease-specific survival, and overall survival using upfront TORS are encouraging, with overall survival rates at 1 year exceeding 90%, and at 2 years exceeding 80%.
• Local failure rates for TORS are reported to be between 0% and 3%, with median follow-up rates ranging from 18 months to 2 years.
• Regional recurrence rates varied between 2% and 8%, while distant disease was reported in 1%–9%.
• Patients receiving TORS alone report better health-related quality of life (QOL) compared to individuals receiving TORS and adjuvant radiation or chemoradiation.
• Although initial feasibility and case series reports are encouraging, further validation through well-designed randomized control trials is required prior to widespread shifts in accepted treatment paradigms.
TORS: Oropharynx

- Two year overall survival estimates ranged:
  - 84-96% for IMRT
  - 82-94% for TORS
- Adverse events for IMRT included:
  - esophageal stenosis (4.8%)
  - osteoradionecrosis (2.6%)
  - gastrostomy tubes (43%)
- Adverse events for TORS included hemorrhage
  - (2.4%)
  - fistula (2.5%)
  - gastrostomy tubes at the time of surgery (1.4%) or during adjuvant treatment (30%)
  - Tracheostomy tubes were needed in 12% of patients at the time of surgery but most were decannulated prior to discharge

TORS Outcomes - Margins

- Ability to perform negative margin surgery consistently is of utmost importance.
- Weinstein 2010, pilot study
  - 98% negative margins (1/47)
  - Frozen sections not always utilized
- There are multiple studies confirming the ability to obtain adequate margins with TORS (up to 100% in large series, Moore 2009; 4.3% in multi-institutional prospective review, Weinstein et al 2012)
  - Historical data: Up to 25% of those undergoing an open approach may have positive margins (Zelesky 1993)
TORS Outcomes – Survival/Control- Early data

- Early data for transoral approach (non-robotic)
  - Moore 2009
    - 92.2% 2 year overall survival
  - Walveker 2008
    - 85% 3 year survival
- White 2010
  - N=89 (77 oropharyngeal), majority Stage 3/4,
  - *8% CRT failures
  - Mean f/u 26 month, 11 patients with recurrence
  - Recurrence free survival 86.3% @ 2 years (89.3% if TORS was primary treatment)
  - Comparable to standard treatment modalities
TORS Outcome Survival/Control

- Weinstein 2010
  - N=47, stage 3/4, mean f/u 26 months
  - 0 mortality
  - 2% local, 4% regional recurrence, 9% DM
  - Disease specific survival 98% @ 1 year, 90% @ 2 years
  - Pathologic risk stratification:
    - 38% avoided chemo
    - 11% avoided radiation
# TORS Outcomes-
Survival/Control

<table>
<thead>
<tr>
<th>Author/Institution</th>
<th>LR control</th>
<th>Progression free Survival</th>
<th>Distant Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stucken et al</td>
<td>100% / 2 years</td>
<td>95.2%</td>
<td>4.5%</td>
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<tr>
<td>Mt Sinai, N=55</td>
<td></td>
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<tr>
<td>Kaczmar et al,</td>
<td>96.6% / 2 year</td>
<td>N/A</td>
<td>8.4%</td>
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<tr>
<td>UPenn N=114</td>
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<tr>
<td>Ford et al.</td>
<td>N/A</td>
<td>91% / 2 year</td>
<td>N/A</td>
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<tr>
<td>UAB n=65</td>
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</tr>
<tr>
<td>Moore et al,</td>
<td>97% local 3 year</td>
<td>92.4% / 3 year</td>
<td>N/A</td>
</tr>
<tr>
<td>Mayo</td>
<td>94% regional 3 year</td>
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Safety

• Weinstein et al, 2012
• Pooled data UPenn, UAB, Mayo clinic, n=177, majority OP (78.5%)
  – 6.8% non exposure rate (no TORS), 1.5% “non-feasibility” rate – conversion to open.
  – EBL 83ml, no transfusion required
  – 12.4% elective tracheotomy, 2.3% at one year (larynx included as sub-site)
  – LOS 4.2 +- 2.7 days
  – No fatalities
  – 16% adverse event within 30 days of surgery
    • 2.3% grade 4 life threatening adverse event
    • 2.8% bleeding post-op requiring intervention
TORS compared to radiation

• Almeida et al. April 2014 have reported a systematic review of TORS vs intensity modulated radiotherapy (IMRT) for early oropharynx cancer.

• Twenty case-series including 8 IMRT studies (1287 patients) and 12 TORS studies (772 patients) were included.
  • Patients receiving definitive IMRT also received chemotherapy (43%) or neck dissections for persistent disease (30%).
  • Whereas patients receiving TORS required adjuvant radiotherapy (26%) or chemoradiotherapy (41%).

• Results:
  • 2 yr survival 84-96% IMRT, 82-94% TORS,
  • G tube 43% IMRT, 1.4% TORS post op, 30% during adjuvant therapy
  • Differences in adverse events

Functional Outcomes

• Historic rates of 20-47% for patients treated with Chemoradiation or open approach
  – More contemporary data: PEG rates at one year as low as 9% with concurrent chemotherapy and IMRT, most in range of 20-25% at 6 months
• Rates of permanent PEG tube (PEG at one year) with TORS:
  – < 5% (Moore 2009, Weinstein 2010, Kelly 2014)
  – More likely with adjuvant chemo + XRT
• Dysphagia as high as 50% at 3 years post CRT
“De-intensification” of Adjuvant Therapy

- 9-27% avoid XRT, 34-45% avoid CRT
- De-Intensified adjuvant radiation (IMRT)+ SND
  - N=31, median f/u 24 months
  - 84% Stage 3/4a (71% T2/T3)
- Allows pathologic upstaging of Neck and tailored treatment
  - Upstaged: N0 33%, N1 43%
  - N2B: 70% with ECE
  - 14% of clinically N1 down-staged to N0
De-Intensification

• De-intensify XRT:
  – 22.6% avoided adjuvant XRT (negative margins and no extra-capsular extension)
    • 29% of pt with N1 disease avoided radiation
• Avoid chemotherapy:
  – 86% of N1
  – 30% of N2
• Risk adapted strategies (TORS + SND treatment paradigm)
  – Organ preservation approach followed by pathologic stratification
    allows for risk-adapted approach to treatment
    • Decreased swallowing morbidity
TORS: HPV+ OPSCC

• Attention now focused on decreasing treatment toxicity related to standard chemoradiotherapy as the number of young HPV+ oropharyngeal cancer survivors increase
• TORS dramatically limits the morbidity of surgical exposure and reduces the acute and late effects of open surgery
• TORS offers a significant opportunity to impact positively on patient QOL and post-treatment function while retaining satisfactory oncologic control
• In addition, surgical resection can be a curative single modality for appropriately selected Stage I-III tumors, and for many Stage IV tumors when combined with standard adjuvant therapy.
Current Research

• HPV-associated OPSCC appears to be rapidly increasing in a younger population and seem particularly responsive to treatment with a better overall survival.

• While the organ-preservation chemoradiotherapy (CRT) approach has become a standard of care, there remain serious concerns about short and long term toxicity.

• Given the potential long-term sequelae of radiation therapy for a younger population, an alternative treatment paradigm is presently being investigated.
Current Research

ECOG3311: Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

• Primary Objective
  - To assess the oncologic efficacy following transoral resection and adjuvant therapy in patients determined to be at “intermediate risk” after surgical excision, the 2-year PFS rate will be examined.
Current Research

Schema

Step 1

REGISTER

Step 2

RANDOMIZE

Arm A: Observation

Arm B: Radiotherapy IMRT 50 Gy/25 Fx

Arm C: Radiotherapy IMRT 50 Gy/30 Fx

Arm D: Radiotherapy IMRT 90 Gy/53 Fx + CD3P 40 mg/m² weekly

Low Risk

Intermediate Risk

High Risk

Stratify: ≤ 10 pk-yr vs. > 10 pk-yr

Accrual: 377

1. Resectable oropharynx carcinoma, pT1b by IHC, PS 0-1
2. Credentialing of surgeon required as part of site participation, neck levels dissected and nodal yield (> nodal shrink)
3. Radiotherapy will be given with an intensity modulated radiotherapy (IMRT) technique. Standard ECOG credentialing through QARC will be required.
4. Stratify by current/former smoking history (≥ 10 pk-yr vs. > 10 pk-yr)
5. Low risk: T1-T2, N0/N1, 0-1 metastatic lymph nodes, negative margins
6. High risk: > 1 mm ECS or > 5 metastatic lymph nodes, positive margins
7. Intermediate risk: Close (< 3 mm) margins, < 1 mm ECS, 2-4 metastatic lymph nodes
8. If ≥ 2 events are observed among the first ten patients registered on Arm A within one year, currently enrolled and subsequently enrolled low risk patients who have not progressed will be treated with IMRT 50 Gy
Current Research

• ORATOR Trial, Canada
  – Randomized phase II trial
  – T1-T2, N0-N2, nodes 3 cm or less
• Arm 1: RT with/without chemotherapy
• Arm 2 TORS adjuvant therapy per pathology (XRT/CRT)
• Primary endpoint QOL 1 yr
• Secondary endpoints overall survival, PFS, toxicity, swallowing function
Conclusions

• TORS is an efficacious surgical option that allows open surgical techniques via a minimally invasive approach with reduced morbidity compared to traditional open approaches.

• TORS is an FDA approved treatment modality for T1 and T2 malignancies of the oropharynx, hypopharynx, larynx and all benign disease.

• TORS may offer superior quality of life and functional outcomes compared to traditional open surgery with a reduced complication profile.

• TORS has been most successfully applied in the management of HPV+oropharyngeal malignancy with reduced morbidity, excellent surgical outcomes, similar loco-regional control, and the ability to de-escalate therapy.
Conclusions

- Survival and outcomes research continues to accumulate as longer periods of follow-up are achieved with this relatively new technique in the management of OPSCC.

- Studies are underway evaluating the efficacy of TORS in not only successfully treating oropharyngeal malignancy, but in reducing the need for adjuvant therapy.

- The potential for reduced long-term effects and toxicity from radiation and chemotherapy is a main target in the application of TORS and the focus of research efforts.
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