Clinical Trials in Transoral Endoscopic Head & Neck Surgery
ECOG3311 and RTOG1221

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Disclosure

- I have no conflicts of interest to disclose
Robotic H&N Surgery: Transoral
Transoral Resection of Pharynx Cancer

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ECOG3311 HPV+
- Descalation (?) with surgery

RTOG1221 HPV-
- Surgical Intensification
Phase II Randomized Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer (E3311)

- p16+, Stage III/IV (cT1-2N1-N2b) OPSCC
- Credentialing of surgeon required as part of site participation in the trial
- Stratify by stage and smoking status
ECOG 3311 p16+ trial schema

Assess Eligibility:
- HPV (p16)+
- SCC oropharynx
- Stage III-IV: t1-2, n1-2b

Baseline Functional/QOL Assessment

Randomize

Low Risk:
- T1-T2N0-N1 negative margins
- Observation
- Transoral Resection (any approach) with neck dissection

Randomize

Intermediate:
- Clear/close margins < 1mm ECS
- 2-4 metastatic LN PNI, LVI
- Radiation Therapy IMRT 60 Gy/30 Fx

Randomize

High Risk:
- Positive Margins > 1mm ECS or ≥5 metastatic LN
- Radiation Therapy IMRT 60 Gy/30 Fx +
- Radiation Therapy IMRT 66 Gy/33 Fx + CDDP 40 mg/m² weekly

Evaluate 2-year PFS Local-Regional Recurrence, Functional Outcomes/QOL

Accrual goal = 377
**E3311 Trial Design**

- Patients with pT1-T2N0-N1 will be observed (Arm A)

- Patients with clear/close margins, ≤1 mm ECS, PNI/LVI, and/or 2–4 metastatic LN will be randomized to 50 Gy vs. 60 Gy (Arms B & C)

- Patients with positive margins, ≥ 5 metastatic LN, and/or >1 mm ECS will be treated with standard-dose (66Gy) RT + cisplatin (Arm D)

- **Primary objective** is to evaluate the 2-yr PFS in HPV+ SCC patients treated with low-dose RT (assume 85% per arm)

- **Secondary end points**: Early/late toxicities, swallowing function, QOL, and oral/serum/tissue biomarkers in predicting clinical outcome
RTOG 1221: Phase II Schema

**T Stage**
1. T1
2. T2

**N stage**
1. N1
2. N2

**Zubrod Status**
1. 0
2. 1

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**Eligible**
- Oropharyngeal SCC: Tonsil, BOT, GPC
- Stage III-IV: T1-2, N1-2b
- p16 NEGATIVE (IHC)

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**Arm 1: eHNS* + Neck Dissection** (Experimental Arm)
“Risk-based” post-operative Adjuvant Therapy, +/- IMRT (60 Gy) +/- Weekly cisplatin **for high-risk patients with ≥5 metastatic nodes, extracapsular extension, or positive surgical margins on final surgical pathology**

**Arm 2: Chemoradiotherapy** (Control Arm)
IMRT (70 Gy)
+ Weekly cisplatin

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* eHNS = TLM or TORS
**Italicized text will be added at next protocol amendment (in progress)**
Primary Objective

- **Primary:** To determine if surgical intensification for patients with HPV-negative OPC will improve progression-free survival by 15%
  - Based on stage-matched patients enrolled in RTOG 0129, we estimate that 2-year PFS for patients in the control arm of the proposed trial is 55%.
Phase II-b Design: Experimental (Surgical) Arm

• Transoral Surgery (TORS vs. TLM) and Neck Dissection

• Risk-based post-operative adjuvant therapy will be guided by pathological findings of the primary tumor and within cervical nodes.
Phase II-b Design (Control Arm)

- Radiotherapy w/concurrent chemotherapy
  - IMRT: 70 Gy over 6 weeks: 2 Gy, 35 fractions
  - Concurrent weekly cisplatin (40 mg/m^2 IV)
  - Unilateral neck IMRT can be used
    - For T1-2 lateralized tonsil tumors with < 1 cm invasion into the soft palate
    - No or limited lateral invasion of BOT
    - N1 neck involvement
  - For “big T2” or N2b, bilateral IMRT allowed
Post-Op RT only

- Patients with “close” margins, lymphovascular (LVI) or perineural invasion (PNI), >1 metastatic lymph nodes will receive IMRT (60 Gy at 2 Gy) in 30 fractions over 6 weeks.
- Subclinical regions at risk for microscopic disease (e.g. contralateral hemineck, when indicated) will receive 54 Gy (1.8 Gy/fraction, using integrated boost technique)
Post-Op ChemoRT

• Patients with positive margins or extracapsular spread (ECS) in cervical nodes (or with ≥ 5 metastatic nodes without ECS) will receive postoperative cisplatin, 40 mg/m² IV on days 1, 8, 15, 22, 29, and 36, for a total of 6 weekly doses concurrent with IMRT (60 Gy at 2 Gy in 30 fractions over 6 weeks).

• Patients with involved surgical margins or ECS may receive a 6 Gy boost at 2 Gy per fraction to the area of the positive margin or ECS.
No PORT

No Indication for Post-operative Radiation Therapy

- For patients with negative margins, no adverse features, such as LVI or PNI, pathologic T1-2 tumor, pN0 neck, and no adjuvant therapy would be given.
Neck Dissection

• Levels II-IV; 20 nodes minimum per side
• Neck Dissection Impairment Index
  – NDII, Taylor et al. OTOHNS 2002
  – 10-item validated PRO instrument used to specifically measure QOL-related shoulder dysfunction in patients who have undergone neck dissection
Patient-reported Outcomes: Swallowing

- To assess swallowing function, the MDADI, MBS, and PSS-HN will be administered in both arms
  - Defined endpoints, pre and post treatment
  - Post-Tx: post-op, 3-6 months, 1 and 2yrs
  - MDADI and PSS-HN are collected at post surgery (Arm 1 only), 3, 6, 12 and 24 months from end of RT.

- To enhance the PRO data, objective correlates include a MBS performed at baseline, post-surgery (Arm 1 only), 6 and 24 months after treatment and clinician grading (CTCAE, v.4) to compare with patient-reported MDADI scores.
Function: Prospective baseline MBS data to predict swallowing outcomes
Stopping Rules and Q/A

- Severe bleeding rate > 10% (defined as return to OR or "catastrophic" grade 4), and >3% grade 5 toxicity