

**Head & Neck Steering Committee
Transoral Resection of Pharynx Cancer
November 6-7, 2011
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Introduction/ Meeting Description

✚ The Head & Neck Cancer Steering Committee convened a Clinical Trials Planning Meeting on Transoral Resection of Pharynx Cancer on November 6-7, 2011 at the Sheraton Hotel in Crystal City, Arlington VA.

Goals of the meeting were to:

- Develop a clinical trial related to HPV oropharynx cancers that reduces surgical morbidity without compromising overall survival.
- Develop a clinical trial for tobacco-related oropharynx cancer that can limit toxicities by re-introducing surgical resection into the treatment algorithm so that it may improve both local/regional control and survival.
- Determine the steps needed to perform exemplar trials that include:
 - Feasibility studies
 - Appropriate end points
 - Address obstacles related/associated with correlative science in order to successfully conduct this trial
 - Need to enlist investigators and patient advocates, surgical, medical and radiation oncologists
 - Monitor Quality of life(QoL), functional outcomes, cost effectiveness expertise, imaging and statistics

✚ The meeting was attended by clinical and translational investigators, pathologists, radiation oncologists, cost effectiveness experts, quality of life and functional outcomes experts, statisticians and patient advocates. There were approximately 65 attendees at the meeting who were assigned to the two breakout sessions on the second day of the meeting based on their expertise with the subject matter.

Background and Summary of Discussions Leading to Recommendations:

- In the US, 13,000 new cancers of the oropharynx were diagnosed in 2011;

- Of the 13,000, 4500 were caused by tobacco and alcohol. It was noted that these tumors have a significantly worse prognosis, with local recurrence being a major problem;
 - Of the 13,000, 8500 were caused by the human papilloma virus (HPV) and the incidence is rising about 4% per year (Ang, KK, et al. NEJM, 201:363: 24-35);
 - Historically, standard of care has been an open surgical resection followed by external beam radiotherapy;
 - The present treatment standard is concurrent chemo-radiation that is associated with major acute and late toxicities;
 - It was noted that HPV tumors have a better prognosis and may not need concurrent chemo-radiation.
- ✚ Technological advances now permit resection through the open mouth that avoids performing a mandibulectomy and limits pharyngeal injury to tumor site;
- This transoral resection approach:
 - increases local and regional control;
 - the intensity of the therapy is directed by the pathology;
 - reduces acute and late side effects;
 - improves QOL
- ✚ The DaVinci Robot was approved by the FDA in December 2009 for T1-T2 oropharynx resections.
- At present, > 1000 transoral resections (TORS) have been performed;
 - There is no prospective multi-institutional trial underway, which impedes evaluation of outcome and tissue specimen collection;
 - Development of these concepts will engage surgeons in the clinical trial process;
 - More than a hundred surgeons have been certified in the TORS technique in the United States. The number with sufficient “experience” remains to be determined, since the criteria have yet to be defined as to what constitutes sufficient “experience” to participate in a trial. It is estimated that there is probably on the order of 25 surgeons at more than 10 institutions.

Current Treatment Expectations

- ✚ Surgery and radiotherapy (RT) are both highly effective and equivalent modalities for the management of early stage disease (T1- T2, N0);

- ✦ Several standards of care exist for intermediate to advanced stage presentations (T1N1-T4, N3), Stage III disease (T1N1, T2N1) can be treated with radiotherapy alone;
- ✦ The addition of epidermal growth factor receptor (EGFR) inhibition to radiotherapy constitutes a treatment option for presentations where radiotherapy alone might not be the optimal treatment;
- ✦ The most commonly employed non-surgical strategy for the management of locally advanced head and neck cancer is radiotherapy and concurrent chemotherapy (CRT);
- ✦ Minimally invasive and Endoscopic Head and Neck Surgery is a crucial part of “personalized medicine” and provides true multi-disciplinary care to the head and neck cancer patient.

Transoral Robotic Surgery (TORS)

- ✦ Transoral Robotic Surgery (TORS) en bloc resection is equivalent to open surgical technique for there is no disassembly of the neck. The muscular and neurovascular innervations of the laryngopharynx are left mostly undisturbed, which enhances functional outcomes and reduces patients’ relying on feeding tubes.

Transoral Laser Microsurgery (TLM)

- ✦ Transoral Laser Microsurgery (TLM) allows for complete surgical resection of aerodigestive tract primary tumors using an approach:
 - through the mouth,
 - a laser, (or other cutting tool for debulking),
 - a microscope for illumination and viewing.
- ✦ The rationale for using TLM is:
 - Tumors have predictable, known patterns of spread, deep to the mucosa;
 - Tumor host interface can be clearly detected and followed;
 - Negative resection margins confer high levels of control, leading to de-intensified adjuvant treatment;
 - Only the tumor needs to be destroyed;
 - Second treatment options are highly desirable.

TLM Outcomes:

- Disease control
- Improved survival
- Better swallowing function
- Reduced morbidity and complications

- Reduced cost

Management of the Neck with Definitive non-operative treatment

- ✦ Radiotherapy is effective in the eradication of regional lymph node disease and is especially effective for “overt” and “elective” disease provided that dose intensity is adjusted;
- ✦ There is always the potential for damage to the normal tissue that will result in impaired pharyngeal dysfunction. This is directly related to the treatment of the superior constrictor muscle;
- ✦ There will be salivary damage resulting in xerostomia;
- ✦ There is a direct dose effect resulting in bone damage;
- ✦ Patients achieving a CR after chemo-radiation have a high probability of regional control and may be safely observed without planned neck dissection.

External Beam Radiotherapy

- ✦ The most significant advantage of External Beam Radiation Therapy (EBRT), as a primary management of neck disease, is that treatment can be rendered without surgery;
- ✦ Additionally, EBRT has been shown effective for the treatment of the retropharyngeal lymph node basin;
- ✦ The disadvantages of EBRT are largely related to the morbidity of treatment, including chronic pain syndrome, neck stiffness, xerostomia, and osteoradionecrosis;
- ✦ Surgical neck dissection achieves equivalent treatment results when compared to EBRT while providing the opportunity to pathologically evaluate the neck disease;
- ✦ Factors, such as disease volume and extracapsular spread (ECS), can be identified as a result of neck dissection. This information can be used to prognosticate the disease and tailor the therapeutic approach accordingly;
- ✦ These prognostic factors may guide adjuvant therapy;
- ✦ When considering the options for management of the neck following transoral surgery, the morbidity and limitations associated with each option deserve consideration.

Post Surgical Adjuvant Treatment

- ✦ If local control is adequately addressed by the TORS surgeon, patients with T1/T2 tonsil and base of tongue cancer, who have pN0 or possibly pN1 neck node dissections, should be able to avoid both chemotherapy and radiation and still should achieve a 90% cure rate.
- ✦ For more advanced disease (e.g., T Resectable, N2B, Base of Tongue (BOT) or Tonsil), randomizing patients to TORS or TLM with bilateral node dissection, retropharyngeal node sampling, tailored XRT vs. chemo-radiation should be considered.

Functional and QoL Outcomes after TORS

- ✦ “In multivariate analysis, T stage 4 was found to be significant and is associated with persistently poor swallowing at the 2-year point after surgery (odds ratio of 15.20 when compared to T stages 1–3). This finding is clinically intuitive and most likely due to resection of greater volume with higher stage tumors.” (quote from Rich et al)
- ✦ If the cancer does fit within the confines of the pre-determined en bloc resection, standardized en bloc TORS resection necessitates tumor related contraindications. This translates to fewer T4 and T3 than TLM but possible and lower reported G-tube dependence. (Weinstein, G.)
- ✦ Appropriate measurement tools must be used to validate results.

After Chemo-Radiotherapy

- ✦ Use of FACT – HN Tool – these QoL measures are valuable tools, providing insight into the impact of treatment to a patient;
- ✦ Non-surgical treatment related symptoms can persist but do not directly affect global QoL measures. This appears to be related to:
 - patient factors,
 - severity of the side effect, and
 - may differ for the HPV + population;
- ✦ Developing treatment approaches that reduce PEG dependency rates are likely to have a meaningful impact on the global QoL for HPV+ OP carcinoma patients;
- ✦ Reducing less severe forms of swallowing complications are likely to have a smaller impact on global QoL.

After Neck Dissection

- ✦ Neck dissection related QoL can be assessed with single questions. Examples of head and neck quality of life measures are the University of Washington Quality of Life (UW QoL), the University of Michigan Head and Neck Quality of Life (UM H&NQoL) and the Quality of Life 30 (QLQ C30) and the SF 36 [1, 2]
- ✦ These measures lack specificity but show sensitivity for patients, who have undergone neck dissection and suffer from pain and stiffness. If the trial is going to focus on general measures of QoL, these instruments are adequate [3].
- ✦ Neck dissection related QoL is more accurately assessed with instruments that were specifically designed for the assessment of the neck and shoulder.

- ✦ The instrument that has been used the most in head and neck cancer patients is the Shoulder Disability Questionnaire (SDQ) [4]. This is one of the simplest instruments available but is limited because the responses are dichotomous (yes/no) and may affect the ability of this instrument's intent to assess subtler changes in clinical outcome.
- ✦ There is also the question of when to administer the instrument(s). The measurement of the neck related quality of life should be performed prior to treatment to establish baseline. If only one other assessment is made, then the optimal time for assessment would be 12 months after the completion of treatment. This allows sufficient time for the regeneration of nerves the completion of healing of the wound and also allows for evaluation of late effects of therapy.

Research Opportunities:

- ✦ De-intensify the dose of radiation especially in patient populations with a favorable prognosis to decrease the late effects of injury to swallowing muscles;
- ✦ In the HPV- patients who have a higher local regional recurrence rate after CRT, treatment de-intensifications with surgery might improve local regional control by removing the patient's disease and permit a risk based use of post-operative adjuvant therapy with observation for patients with favorable pathology;
- ✦ Radiation alone for intermediate risk patients;
- ✦ Chemoradiation for high risk individuals;
- ✦ Prospective tissue banking on HPV- and HPV + tumors with established protocols for tissue collection, processing and storage to lead to the creation of large shared tissue repositories.

Comparative & Cost Effectiveness Research (CER):

- ✦ Important to include as concepts are being developed as it will compare the benefits and /or harms of alternative methods to treat oropharyngeal cancer and ultimately improve the outcome(s) for patients;
- ✦ It will provide head to head comparisons of competing treatments;
- ✦ It will lead to better clinical decision making;
- ✦ It will reduce variation in care while at the same time reducing medical expenditures;
- ✦ Relevant endpoints for CER studies can include, pain, quality of life, functional status, patient preferences for health states, adverse events, caregiver burden, survival, and costs of care;
- ✦ Caregiver burden was identified as a major problem for many patients as the treatments had several toxicities.

Background/Importance of Research Topic/Disease/Limitations

- ✦ The rationale for a primary surgical role is the opportunity to biologically stage disease so that adjuvant therapy and dose can be used in a judicious manner. The advent of transoral approaches and improved surgical tools allow for better access, exposure and, consequently, control of surgical margins and lead to a decrease in surgical morbidity, more accurate staging and personalization of therapy.

Consensus & Recommendations:

Short Term Goals:

- ✦ The investigators from ECOG and RTOG will develop concepts to address the HPV+ and HPV – population and bring forth these concepts to the respective task forces for intellectual input. The concepts will then be formalized for review by the **Head & Neck Steering Committee**;
- ✦ A working group of the CTPM will develop what specific credentialing criteria will be appropriate for surgeons to participate in these prospective trials e.g.,
 - adequate training in TORS,
 - performed minimum of 20 cases independently,
 - demonstrate continuing proficiency in the performance of at least 5 TORS in the past 12 months;
- ✦ Functional outcome assessment tools will be integrated into the concepts;
- ✦ Cost effectiveness analysis will also be incorporated into the concept development.

Long Term:

- ✦ Development of at least two (maybe more) concepts to address this patient population will be brought forth during the next 12 months for HNSC consideration.