PROGNOSTIC FACTORS IN PATIENTS UNDERGOING SALVAGE SURGERY OF THE PHARYNX AND LARYNX

Dennis M Tang, BS, Chad Zender, MD, Rod Rezaee, MD, Michael Gibson, MD, PhD, Pingfu Fu, PhD, Minggen Lu, PhD, Min Yao, MD, PhD, Pierre Lavertu, MD; University Hospitals, Case Western Reserve University

Purpose/Objectives: Radiation therapy has become the primary treatment modality for cancer of the pharynx and larynx in many institutions in the United States. In patients with recurrent head and neck cancer that have failed radiation with or without chemotherapy, salvage surgery is the preferred treatment modality for curative intent. Salvage surgery in the post radiation setting is a significant undertaking frequently requiring major ablative and reconstructive efforts. We sought to identify patient and treatment related factors that could help predict outcomes from salvage surgery for recurrent/persistent squamous cell carcinoma of the oropharynx, hypopharynx, and larynx.

Materials/Methods: A retrospective chart review of patients with head and neck squamous cell carcinoma treated at University Hospitals Case Medical Center between 2006-2012 was performed. Patients identified as having recurrent squamous cell carcinoma of the oropharynx, hypopharynx, and larynx after initial treatment with radiation or chemoradiation therapy were included. Primary outcome variables were disease-free survival (DFS) and overall survival (OS). Co-variates included: demographics, tobacco and alcohol exposure, original stage, p16 staining, type and length of radiation and chemotherapy, disease-free interval, location of recurrence, unilateral or bilateral recurrence, salvage surgery pathology, and time to second recurrence. Univariate analyses were used to determine hazard ratios by using simple Cox proportional hazard regression models. Time-to-event data analysis using Kaplan-Meier method and multiple Cox regression models were used to evaluate the impact of significant co-variates.

Results: Comprehensive data on 73 consecutive patients from 2006-2012 was collected. It consisted of 53 males and 20 females with a mean age of 59 years at the time of recurrence and a mean follow-up of 23.3 months. The patient database consisted of 41 oropharyngeal, 10 hypopharyngeal, and 22 laryngeal tumors. The overall DFS was 49.9% and 41.6% at 2 yr and 5 yr respectively. The overall OS was 63.8% and 51.6% at 2 yr and 5 yr respectively. With regards to DFS, bilateral recurrence (p=0.0001, HR=3.8, CI=1.8-7.8), positive margins (p=0.008, HR=3.2, CI=1.3-8.2), perineural invasion (p=0.036, HR=2.4, CI=1.03-5.6), and disease-free interval less than 9 mo (p=0.011, HR=3.3, CI=1.3-10) were correlated with worse outcomes. With regards to OS, bilateral recurrence (p=0.0002, HR=4, CI=1.8-9), positive margins (p=0.001, HR=4.5, CI=1.7-12), perineural invasion (p=0.022, HR=3, CI=1.1-8), and disease-free interval less than 9 mo (p=0.021, HR=3.3, CI=1.1-10) were correlated with worse outcomes.

Conclusions: Multiple factors exist that predict poorer outcomes with salvage surgery after recurrent head and neck squamous cell carcinoma including a shorter (<9mo) disease-free interval, bilateral recurrence, and positive surgical margins. P16 status showed a trend towards improved overall survival but it was not significant. Patients with these high-risk features may benefit from re-treatment protocols, which need to be investigated further through prospective multi-institutional studies.
Background Primary squamous cell carcinoma of the larynx and hypopharynx commonly metastasises to level II, III, IV lymph nodes. There is good evidence to support bilateral level II, II, IV selective neck dissection (SND) in patients with an N0 neck undergoing primary laryngectomy. The evidence base for this approach in patients undergoing salvage laryngectomy for radiotherapy failure is less clear-cut.

Methods Retrospective case note review of patients undergoing salvage laryngectomy, pharyngolaryngectomy or pharyngolaryngoesophagectomy and neck dissection at Queen's Medical Centre, Nottingham, United Kingdom between 2000 and 2012.

Results Forty-five patients were identified, the majority of whom were male and over 50 years of age and bilateral SND was performed on 37 of these. A combination of SND and radical neck dissection (RND) or modified RND was performed on four patients. Three patients underwent ipsilateral SND or RND and one patient underwent a contralateral SND only, having already undergone an ipsilateral neck dissection for a previous tonsil carcinoma on the same side.

Thirty-nine of the 45 salvage surgery patients were reported as clinically/radiologically (c/r) N0 pre-operatively and 35 of the 45 patients were confirmed on pathology as pN0. Seven patients assessed as c/rN0 pre-operatively were found to be pN+ on pathology. In these seven patients positive lymph nodes were found in the ipsilateral neck in all cases and in the contralateral neck in one case. In the ipsilateral neck the levels involved were recorded as II (n = 2), III (n = 2) and IV (n = 1) and in two cases it was not recorded. In the contralateral neck there were 5 positive nodes in level II.

Of the 32 c/rN0 pN0 patients, 8 developed recurrence - 6 locally, 1 regionally and 1 developed a second primary and of the 7 c/rN0 pN+ patients, 6 developed recurrence - 1 locally, 2 regionally and 3 developed distant metastasis.

Conclusion There is a significant risk of leaving residual disease in the clinically and radiologically N0 neck during salvage laryngectomy if bilateral elective neck dissection is not performed. The 7 c/rN0 pN+ patients in particular had a poor prognosis, with 6 of the 7 going on to develop recurrence. We would advocate bilateral level II, III, IV selective neck dissection as part of salvage laryngectomy to minimise the chance of regional recurrence.
THE EFFECT OF PERIOPERATIVE PROTON PUMP INHIBITORS ON THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULA FOLLOWING TOTAL LARYNGECTOMY: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

K A Stephenson, FCORL, FRCS, MMed, J J Fagan, FCORL, MMed; Groote Schuur Hospital / University of Cape Town, South Africa

BACKGROUND:

Pharyngocutaneous fistula is a common complication of total laryngectomy. We hypothesized that perioperative proton pump inhibitor (PPI) treatment could reduce the incidence of pharyngocutaneous fistulae.

METHODS:

This prospective placebo-controlled double-blind randomized controlled trial compared PPI treatment (14 days enteral omeprazole) with a placebo in patients undergoing total laryngectomy.

RESULTS:

Forty patients were randomized into PPI (N = 21) and placebo arms (N = 19). One of 21 patients receiving omeprazole developed a fistula in comparison to 6 of 19 placebo group patients (p=0.04). No other statistically significant risk factors for pharyngocutaneous fistula were identified. The mean hospital stay of patients with and without a fistula was 32 and 7.5 days respectively.

CONCLUSIONS:

Pharyngocutaneous fistulae result in prolonged hospitalization and morbidity. We observed a statistically significant reduction in fistulae with PPI prophylaxis. Further research to better define the role of reflux and antacid management is suggested.
NEW TOTAL LARYNGECTOMY: AN AT-RISK POPULATION FOR 30-DAY UNPLANNED READMISSION

Evan M Graboyes, MD, Zao Yang, BS, Dorina Kallogjeri, MD, MPH, Jason A Diaz, MD, Brian Nussenbaum, MD, FACS; Washington University School of Medicine in St. Louis

Background: Previous research identified that patients who undergo a total laryngectomy are at a nearly five-fold increased risk of 30-day unplanned readmission. In this prior study, specific details about readmissions in this patient population were not elucidated. We, therefore, designed a new study to analyze this group of patients.

Objectives: To determine the rate, describe the characteristics, and identify the risk factors that predict 30-day unplanned readmission in patients undergoing total laryngectomy.

Study Design: Retrospective cohort study.

Setting: Single academic hospital.

Subjects and Methods: The medical charts for all patients who had a total laryngectomy performed between January 1, 2007 and December 31, 2012 were reviewed. Data related to sociodemographics, comorbidities, oncologic and surgical details, hospital course and complications, and post-discharge follow up were collected. Univariate and multivariate logistic regression were performed to identify risk factors for unplanned readmission to the hospital within thirty days of discharge from the otolaryngology service.

Results: The study identified 155 patients with a new total laryngectomy for analysis. The 30-day unplanned readmission rate for patients following discharge after total laryngectomy was 26.5% (41/155). The median length of index hospitalization was 10 days (range 5-53 days). The median time to unplanned readmission was seven days (range 1-28 days), although 27% (11/41) of readmissions occurred within two days discharge. The most common cause of unplanned readmission was a complication that occurred after discharge. The two most common complications that caused a 30-day unplanned readmission were pharyngocutaneous fistula (27% of unplanned readmissions) and stomal cellulitis (17% of unplanned readmissions). Significant predictors identified on univariate analysis were presence of a new postoperative complication after discharge ([Odds Ratio (OR) 29.81, 95%], first postoperative contact with Emergency Room rather than treatment team (OR 3.21, 95% CI 1.26-8.16), salvage total laryngectomy (OR 2.56, 95% CI 1.16-5.64), and chronic steroid use (OR 7.78, 95% CI 1.45-41.83). Neither the presence of a complication during the index hospitalization (OR 1.01, 95% CI 0.50-2.07), nor the number of complications during the index hospital stay, predicted readmission (OR 0.98, 95% CI 0.68-1.39). A primary tracheo-oesophageal puncture was associated with a decreased risk of readmission (OR 0.45, 95% CI 0.21-0.95).

Conclusion: New total laryngectomees are an at-risk patient population with a very high rate of unplanned readmission within 30 days of discharge. Nearly 30% of readmissions occur within 2 days of hospital discharge. The reasons for readmission are diverse. Complications during the index hospitalization did not predict readmission, but complications after discharge were found to be the most significant predictor of unplanned readmission within 30 days. These data can be used to design and implement quality improvement interventions to decrease the readmission rate in this patient population.
THE IMPACT OF CETUXIMAB ON TRENDS IN CHEMORADIATION USE IN ELDERLY PATIENTS WITH HEAD AND NECK CANCER
Shrujal S Baxi, MD, MPH, Caitriona O'Neill, Eric J Sherman, MD, Coral L Atoria, MPH, Nancy X Lee, MD, Matthew G Fury, MD, PhD, Elena B Elkin, PhD, David G Pfister, MD; Memorial Sloan-Kettering Cancer Center and Weil Medical College of Cornell University

Background: The use of chemoradiation (CTRT) for the management of locally advanced head and neck cancer (LAHNC) is increasing. CTRT is associated with more toxicity than radiation alone, especially in older and sicker patients. In 2006, the FDA approved cetuximab for use with radiation in LAHNC. Cetuximab with radiation has a perceived lower side effect profile compared to standard chemotherapies used in CTRT, but its benefit in the elderly is unclear. Our objective was to examine the impact of cetuximab on the use of CTRT in elderly patients with LAHNC and compare the drug costs of different standard regimens.

Methods: We identified patients aged 66 and older diagnosed with LAHNC between 1999 and 2007 in the Surveillance Epidemiology and End Results (SEER)-Medicare linked database. Treatment was categorized as CTRT or other based on Medicare claims within 6 months of diagnosis. We excluded patients who did not receive definitive treatment. In patients who had CTRT, we identified use of cetuximab based on drug-specific billing codes. We assessed trends in the use of CTRT over the entire study period and in the use of cetuximab since 2006. We examined the influence of age and comorbidity on the likelihood of receiving CTRT before and after 2006 adjusting for clinical and demographic factors. The costs of selected standard chemotherapy regimens were estimated using the US Food and Drug Administration's Orange Book.

Results: We identified 2,837 patients with locally advanced HNSCC. About 20% were >=80 years and 18% had a Charlson comorbidity score (CCS) of >=2. The use of CTRT increased from 21% of patients diagnosed in 2000 to 48% in 2007 (p<0.001). The use of radiation alone declined from 33% to 23% while primary surgery declined from 45% to 29% of patients diagnosed in 2000 to 2007, respectively (p<0.001). Prior to 2006, patients who were >=80 years or those with a CCS of >=2 were less likely to be treated with CTRT, but for those diagnosed in 2006 or 2007, neither age nor comorbidity was associated with receipt of CTRT. Of the 442 patients who received CTRT after 2005, 45% received cetuximab. The estimated drug costs, not including supportive medications or chemotherapy administration charges, for a course of cetuximab is over a hundred times that of other regimens used in CTRT.

Conclusions: In this population-based cohort of older adults, the use of CTRT increased substantially over time. Not only is cetuximab replacing other chemotherapies in CTRT, but the availability of cetuximab, with a perceived gentler side effect profile, may have increased the use of CTRT, especially in older and sicker patients. Given the lack of prospective data confirming the benefit of cetuximab and radiation in this population and the significantly higher cost of this regimen, there is a real need to assess the comparative effectiveness of different treatment strategies in elderly patients with LAHNC.
S102  HEAD AND NECK CANCER TREATMENT OUTCOMES IN THE HMO CANCER RESEARCH NETWORK

Steven S Chang, MD, Gabriel G Calzada, MD, Thuy-Anh Melvin, MD, Michael Friduss, MD, Erich Sturgis, MD, MPH, Christine Johnson, MPH, PhD, Randall Weber, MD; Henry Ford Health System, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Midatlantic, University of Texas MD Anderson Cancer Center

Introduction:

The Health Maintenance Organization Cancer Research Network (HMOCRN) is a consortium of 19 nonprofit research centers based in large, vertically integrated health care delivery organizations across the United States. They represent a geographically, racially and socioeconomically diverse population. These organizations provide care to approximately 19 million individuals. The HMOCRN has been continuously funded by the NCI since its formation in 1999. The NCI's goal was to enhance research on cancer etiology, prevention, detection, and management through collaboration with these community based organizations that served large, stable populations of patients (>92% retention after cancer diagnosis/treatment) and maintained electronic databases with a rich array of patient information. These health organizations are structured to allow the evaluation of the entire continuum of cancer care from primary care to long term surveillance. The NCI also funds the maintenance of a pooled tumor registry called the virtual data warehouse (VDW) which is extracted from each of the 19 different health systems electronic medical records. This registry contains detailed demographic, pathology, surgery, chemotherapy, radiation and survival data for each patient. This registry is updated annually by data abstractors at each site using a standardized coding system. In this study, we demonstrate that it is feasible to conduct high quality observational studies within the HMOCRN using the VDW. We also identified a unique and unstudied population of head and neck cancers patients.

Methods:

Head and neck cancer patients were queried within the HMOCRN VDW spanning from 1995 to 2013. Search criteria included all tumors of the upper aerodigestive tract (larynx, pharynx, oral cavity, nasal cavity), salivary gland and thyroid/parathyroid glands. Dermatologic malignancies were excluded. All histologic types for each site were included. Data analysis was performed on the Henry Ford site VDW. Statistical analysis was performed using chi-squared test. Statistical significance was considered positive if p<.05.

Results:

80,000 unique head and neck cancer patients were identified in the HMOCRN. Of these tumors, approximately 30,000 thyroid/parathyroid gland, 10,000 laryngeal, 4,000 salivary gland, 12,000 oropharyngeal, 15,000 oral cavity. Over-all survival analysis was performed for each tumor type. Using the dataset we were able to identify statistically significant racial, gender and socioeconomic differences in patient outcomes for several tumor types. We demonstrate that the current AJCC staging system for oropharynx cancer survival does not accurately predict survival. We also show that incorporating HPV status into the staging system improves the accuracy of the staging system.

Conclusions:
We demonstrate that there are a sufficient number of head and neck cancer patients within the HMOCRN to create study cohorts. We show that we can utilize the HMOCRN VDW to perform outcomes research for head and neck cancer patients in a community setting. Lastly, we demonstrate that ancillary testing such as HPV status can be queried from pathology databases and included into our analysis. We propose that the design of the HMOCRN is uniquely equipped to study cancer survivorship, treatment costs, and cancer treatment quality. Additionally, because of the HMO health system design, the HMOCRN allows for powerful collaborative multi-institutional prospective studies.
TRIPLE POSITIVE PATHOLOGICAL FINDING IN HEAD AND NECK CANCER IS RELATED TO A WORSE PROGNOSIS

Yu-Tsai Lin, MD, Hui-Ching Chuang, MD, PhD, FACS, Cheng-Tung Lu, MD, Chih-Yen Chien, MD, FACS; Kaohsiung Chang Gung Memorial Hospital, Taiwan

**Purposes:** Perineural invasion, lymphvascular invasion, large tumor size, poor differentiation of cancer cell and extrascapsular spread (ECS) in lymph nodes are major adverse prognostic factors in patients with head and neck squamous cell carcinoma (HNSCC). Usually, patients with advanced head and neck cancer will at least have one or more risk factors that induced poor survival results. Our aim was to analyze the prognosis outcome of the HNSCC patient with perineural invasion, lymphvascular invasion, large tumor size (T3+ or T4+), poor differentiation of cancer cell, ECS and triple positive (Triple factors-1 including perineural invasion, lymphvascular invasion and ECS; Triple factors-2 including tumor size, poor differentiation of cancer cell and ECS) in pathological study.

**Methods:** We retrospectively examined 582 patients who were diagnosed oral cavity cancer and surgery was performed in years 2006 to 2008 in Kaohsiung Chang Gung Memorial Hospital. Clinical data including age, gender, stage, T classification and N classification was recorded. The prognostic factors of perineural invasion, lymphvascular invasion, tumor size, histology differentiation of cancer cell and ECS were obtained from pathology reports. The 5-year control and survival rates were the main outcome measures. Statistical analyses were performed to determine the disease related parameters as well as survival rates.

**Results:** The study included 41 women and 541 men with an average age of 51.88 years (range, 23-85 years). The follow up time is up to 5 years (60 months) and the mean is 38.77 months (std =19.20) in the range of 0 to 60 months. In 5-year overall survival rate, the T classifications (T3+ or T4+), poor differentiation, perineural invasion, lymphvascular invasion, ECS, triple positive-1 and triple positive-2 were 73.9%, 67.1% 61.9%, 56.1%, 35.7%, 18.8% and 14.3%, respectively. Patients with triple positive in pathological study had a significantly lower 5-year overall survival rate than patients without triple positive (p < 0.001). The multivariate analysis using Cox's regression model revealed that the age at time of surgery (< 65 years vs.>=65 years), triple positive 1 or 2 (negative vs. positive), T classifications (T1 or T2 vs. T3+ or T4+), histology differentiation (well or moderate differentiation vs. poor differentiation) and N classifications (N1 or N2 vs. N3+ or N4+) were independent prognostic factors for the 5-year overall survival rates.

**Conclusions:** Perineural invasion, lymphvascular invasion, poor differentiation of cancer cell, advanced T stage and extrascapsular spread in lymph nodes are all independently important prognostic factors. However, patients of HNSCC with triple positive adverse factors will have the poor 5-year survival rate even underwent adjuvant CCRT.
THE EFFECT OF TUMOR-TARGETED RADIONUCLIDE THERAPY USING MESENCHYMAL STEM CELL MEDIATED DELIVERY OF THE SODIUM IODIDE SYMPORTER IN METASTATIC SQUAMOUS CELL CARCINOMA OF HEAD AND NECK; IN VITRO EXPERIMENT

IkJoon Choi, MD, MyungChul Lee, MD, PhD; Department of Otolaryngology-Head and Neck Surgery, Korea Cancer Center Hospital

Objectives: The aim of this study was to introduce functional sodium iodide symporter (NIS) expression into mesenchymal stem cells (MSCs) and evaluate the effect of 131I therapy in squamous cell carcinoma cell line in vitro based on the bystander effect from NIS-expressing MSCs.

Methods: MSCs (PCS-50010, ATCC®) isolated from human umbilical cord were cultured. After recombinant adenovirus rAd-pCMV-hNIS-GFP was manufactured, rAd-pCMV-hNIS-GFP was transfected into MSCs. 125I uptake and efflux analysis to evaluate function of NIS-MSCs were performed. A clonogenic assay was then performed to determine whether 131I sequestered by NIS-MSCs would be able to kill adjacent squamous cell carcinoma (SqCCa) cells through the crossfire effect of 131I.

Results: NIS-transfected MSCs showed a 12-fold increase in NIS-mediated iodide uptake activity, which could be blocked upon treatment with the perchlorate. In wild-type (WT)-MSCs, iodide uptake above background level was observed.

NIS protein expression in NIS-MSCs was confirmed by western blot analysis and GFP expression. Radionuclides were rapidly washed out from NIS-MSCs. The halftime (T1/2) of 125I was about 12 min. In a clonogenic assay, SqCCa cells, cocultured with WT-MSCs (ratio 1:10) showed no significant cell killing after incubation with 131I. In contrast, in cocultures of SqCCa cells and NIS-MSCs (ratio 1:10) revealed a 55% reduction in cell survival.

Conclusion: The NIS-MSCs was found to increase the accumulation of radioactive iodine uptake, and showed cytotoxic effect to SqCCa cells. These results suggest the potential of radioactive iodine therapy of iodine non-concentrating tumors by MSCs-mediated NIS gene delivery.
SOFT TISSUE METASTASIS IN P16-POSITIVE OROPHARYNX CANCER: PREVALENCE AND RELATIONSHIP TO DISTANT METASTASIS

Parul Sinha, MBBS, James S Lewis Jr., MD, Brian Nussenbaum, MD, Bruce H Haughey, MBChB; Washington University School of Medicine

Objective: Extracapsular spread (ECS) varies in definition, extent and impact on outcomes. Studies that grade extent of ECS in p16-positively surgically-treated oropharynx squamous cell carcinoma (OPSCC) are sparse, but do not demonstrate prognostic significance for ECS. Soft tissue metastasis (STM), however, is preliminarily reported to have prognostic impact, although negated by adjuvant therapy. Definitions of STM vary across studies from "gross irregular tumor masses in the neck" to "tumor masses with no residual nodal tissue/ architecture." The objective of this study is to assess uniformly defined STM for its prevalence in p16-positive OPSCC patients and its relationship to distant metastasis (DM), the most frequent category of the infrequent recurrences observed in this population.

Methods: A prospectively assembled transoral (TOS) database was used to identify primary p16-positive OPSCC patients treated with TOS, neck dissection ± adjuvant therapy from 10/1996-9/2012. Histology was reviewed by a single pathologist to define ECS and STM ("STM-def"). STM was also recorded from pathology reports ("STM-rep"). Patients were sub-divided into Group A (pN0), Group B (pN+ without ECS), Group C (pN+ with ECS) and Group D (STM-def). Distant metastatic and regional recurrence (RR) rates, and distant metastasis-free survival (DMFS) were study end-points.

Results: 222 of 225 p16-positive OPSCC patients underwent histology review. Median follow-up was 58 (15-189) months. Group A, B, C and D had 21 (10%), 107 (48%), 40 (18%) and 54 (24%) patients; STM-rep was noted in 94 (42%). DM alone occurred in 12, RR in 5 and both in 2. DM frequencies were 0 (0%) in group A, 4 (4%) in group B, 2 (5%) in group C and 8 (15%) in group D. RR rate was similar (2.5-5.6%) across the 4 groups. Five-year DMFS for group D was 84% versus 100% in Group A (p=0.005), 96% in Group B (p=0.006), and 95% in Group C (p=0.006). DM frequencies for patients with versus without STM-rep was 6 (6.4%) and 8 (7.5%); five-year DMFS was 93% and 90% (p=0.451). In pN+ necks, Group D was significantly associated with poorer DMFS versus group B (HR =4.6, 95% CI: 1.38-15.2, p=0.013) but not versus group C (HR=3.4, 95% CI: 0.73-16.2, p=0.118). Prognostic significance for STM-def was lost, however, in multivariate analysis (adjusted for adjuvant treatment) in which only pT3-T4 remained significant (Hazard Ratio=4.2, 95% CI: 1.3-13.7, p=0.017). Amongst the 54 group D patients, 34 underwent adjuvant chemoradiation, with DM occurring in 5 (15%) while the 17 who underwent radiation alone had DM in 2 (17%); three had no adjuvant, with DM in one. Five-year DMFS for group D patients was 84.5% in chemoradiation (38% pT3-T4) and 85.6% in radiation (35% pT3-T4).

Conclusions: A traditionally negative prognosticator, STM-def was present in about one-quarter of this p16-positive cohort but had no impact on RR. It associated significantly with DM and DMFS at the univariate level, versus ECS and STM-rep, but significance of STM-def was lost in multivariate analysis for DMFS; only high T-stage was prognostic, confirming T-stage as a major driver in this disease. Neither adjuvant therapy regimen (radiation or chemoradiation) was associated with superior DM rates or DMFS in patients with STM.