PROGNOSTIC SIGNIFICANCE OF QUALITATIVE AND QUANTITATIVE PERINEURAL INVASION IN SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

Brittany E Howard, MD, Matthew A Zarka, MD, Longwen Chen, MD, Richard E Hayden, MD, Michael L Hinni, MD; Mayo Clinic Arizona

Introduction:

The clinical and prognostic significance of perineural invasion in squamous cell carcinomas of the oropharynx has long been debated. This is especially true when considering the varying degrees of perineural invasion and their clinical implications. We present the prognostic implications of qualitative and quantitative perineural invasion in primary squamous cell carcinomas of the oropharynx treated by primary surgical resection with or without adjuvant therapy.

Methods:

After obtaining an IRB approval, a retrospective chart review was performed at a single tertiary academic medical center. Patients with previously untreated primary oropharyngeal squamous cell carcinomas undergoing transoral surgical resection between the years 1999 and 2012 were identified. These patients' pathology slides were reevaluated by a single reviewer with identification and quantification of perineural invasion. Evaluated characteristics of involved nerves included nerve diameter, number, location relative to tumor, and degree of nerve involvement. All findings were reviewed and confirmed by a senior pathologist. Results were then assessed for association with oncologic outcomes including local, regional, and distant disease recurrence as well as disease free survival, disease specific survival, and overall survival.

Results:

Two hundred and nineteen patients with oropharyngeal squamous cell carcinoma treated by primary surgical resection with or without adjuvant therapy were included in the study. Perineural invasion was identified in 61 (27.9%) patients. Comparing oncologic outcomes between patients with perineural invasion and those without revealed no significant difference in local (3/61, 4.9% verses 5/158, 3.2% respectively; p=0.6885), regional (8/61, 13.1% verses 11/158, 7.0% respectively; p=0.1803), or distant disease recurrence (1/61, 1.6% verses 8/158, 5.1% respectively; p=0.4502). Similarly, 5 year Kaplan-Meier estimation showed no significant difference between patients with perineural invasion verses those without in disease free survival (84% vs. 87% respectively; p=0.49), disease specific survival (93% vs. 97% respectively; p=0.26), and overall survival (85% vs. 91% respectively; p=0.20). There was a significant increased risk of regional recurrence when nerves with diameter greater than 2 mm were involved (p=0.0418). There was no significant association between diameter of involved nerves with local or distant disease recurrence. There was no significant association between number of nerves involved, location, or degree of involvement with oncologic outcomes. Subgroup analysis of patients with perineural invasion showed a reduction in regional recurrences with utilization of adjuvant therapy (2/34; 5.6%) verses no adjuvant therapy (6/16; 37.5%); this was statistically significant (p=0.0053). In patients with perineural invasion, adjuvant therapy was not associated with a significant reduction in local or distant disease recurrence.

Conclusions:
In this study, patients with primary squamous cell carcinomas of the oropharynx treated by surgery with or without adjuvant therapy demonstrated no significant difference in oncologic outcomes based upon presence or absence of perineural invasion within the primary tumor. However, perineural invasion of nerves larger than 2mm was associated with an increased risk of regional recurrence.
COMPARISON OF TREATMENT OUTCOMES AFTER TRANSORAL ROBOTIC SURGERY AND SUPRAGLOTTIC PARTIAL LARYNGECTOMY: OUR EXPERIENCE WITH SEVENTEEN AND SEVENTEEN PATIENTS RESPECTIVELY

Se-Heon Kim, MD, Young Min Park, MD; Department of Otorhinolaryngology, Yonsei University College of Medicine, Seoul, Korea

Introduction: We performed transoral robotic surgery and supraglottic partial laryngectomy in patients diagnosed with supraglottic carcinoma and retrospectively analysed their treatment and functional outcomes to confirm a validity of transoral robotic surgery as a minimally invasive surgery.

Method: Between May 2009 and April 2012, 34 patients were enrolled in the study. During the period of the study, 17 patients received transoral robotic surgery and 17 patients received supraglottic partial laryngectomy. Clinicopathologic information, operative time, time to decannulation, feeding tube dependence, admission period and complications were collected and analysed. The M.D. Anderson Dysphagia Inventory was conducted 6 months post-operatively to evaluate subjective swallowing function. Acoustic waveform analysis was performed to objectively evaluate post-operative voice status.

Results: There was a significant difference in the average operation time between the groups (P = 0.019). There was no significant difference between overall and disease-free survival between the groups. There were significant differences in swallowing function, time to decannulation and hospital stay between the groups (P = 0.001, P = 0.013, P = 0.015). Using the M.D. Anderson Dysphagia Inventory conducted 6 months post-operatively, the transoral robotic surgery group showed better subjective swallowing status than the conventional surgery group (P = 0.038). On acoustic waveform analysis, there were no significant differences in the various voice parameters between the groups.

Conclusion: Transoral robotic surgery removed the tumour transorally without an external incision. Therefore, it showed rapid functional recovery and less morbidity compared with conventional supraglottic partial laryngectomy (return to an oral diet: 9.0 and 16.0 days, decannulation: 10.0 and 11.5 days, hospitalisation: 18.0 and 22.0 days).
TRANSORAL VIDEOLARYNGOSCOPIC SURGERY (TOVS), A NOVEL ENDOSCOPIC SURGERY FOR SUPRAGLOTTIC AND HYPOPHARYNGEAL CANCERS

Akihiro Shiotani, MD, Masayuki Tomifuji, MD, Koji Araki, MD, Taku Yamashita, MD; National Defense Medical College of Japan

Backgrounds

Transoral CO2 laser microsurgery is a well-known minimally invasive procedure for laryngeal/hypopharyngeal cancers that preserves laryngeal function. This procedure employs fractionated resection; therefore, surgeons accustomed to conventional en bloc resection must be trained before performing fractionated resection. Another limitation of this method is that pathological evaluation can be complicated.

Recently, the minimally invasive transoral robotic surgery has been described as successful in the treatment of supraglottic/hypopharyngeal cancers. However, although surgical robots are widely used in some countries, they are expensive and may not be available in some places.

To address these problems, we developed a novel easy-to-use surgical environment that combines a distending laryngoscope, rigid high-definition endoscope, and surgical forceps for laparoscopic surgery. This environment provides a wider field of view, which makes it possible to operate with both hands and perform transoral en bloc resection for supraglottic/hypopharyngeal cancers. We named this surgery "Transoral Videolaryngoscopic Surgery (TOVS)".

Methods

Fifty three patients with T1, T2 and selected T3 supraglottic/hypopharyngeal cancer (stage I: 14, stage II: 16, stage III: 5, stage IVA: 18) underwent TOVS.

Under general anesthesia with oral endotracheal intubation, the most appropriate surgical view was obtained using an FK retractor (Gyrus ACMI, Southborough, Massachusetts) or a Weerda distending laryngoscope (Karl Storz, Tuttlingen, Germany). A laryngeal rigid endoscope with a high-definition camera (Karl Storz) or Endoeye Flex rigid endoscope (Olympus Medical Systems, Tokyo, Japan), which has a flexible part at its tip, was used for monitoring. The tumor was resected en bloc using 3-mm-diameter laparoscopic surgical instruments (Karl Storz) bimanually while watching the video images on the monitor. Neck dissections were performed for node-positive patients.

Survival rate, local control rate, laryngeal preservation rate, and postoperative swallowing function were investigated.

Results

This surgical environment enabled us to perform transoral en bloc resection in all cases. Postoperative (chemo[t2])radiotherapy was administered to 14 patients, because of multiple cervical lymph node metastases or extracapsular spread, and to 3 patients, because of positive surgical margin. The 5-year disease-specific and overall survival rates and the laryngeal preservation rate were 93.4%, 80.3% and 93.2% respectively. Postoperative swallowing function was satisfactory: 94.3% of cases scored <= 2 on the functional outcome swallowing scale (FOSS). Tracheostomy was performed for 3 patients as a
prophylactic measure, for 1 patient because of a postoperative hemorrhage and for 1 patient because of a difficult intubation.

Conclusions

TOVS made it possible to perform a safe and reliable transoral en bloc resection for T1-T3 supraglottic/hypopharyngeal cancers with satisfactory oncological and functional outcomes, indicating that it could be one of the minimally invasive treatment options for these cancers. TOVS may also be an easy-to-use and less expensive alternative surgical environment for robotic surgery.

References


TRANSORAL LASER MICROSCUREGY FOR SQUAMOUS CELL CARCINOMA OF THE
HYPOPHARYNX

Thomas H Nagel, MD, Parul Sinha, MBBS, MS, Bruce H Haughey, MBChB, Michael L Hinni, MD, Richard E
Hayden, MD; Mayo Clinic Arizona, Mayo Clinic Florida, Washington University School of Medicine

Objective: To evaluate outcomes of transoral laser microsurgery (TLM) as the primary treatment for
squamous cell carcinoma of the hypopharynx.

Methods: Prospectively assembled case-series study of 74 patients with squamous cell carcinoma of the
hypopharynx treated with transoral CO2 laser microsurgery from 1996 to 2011 at 3 centers. The intent
was a margin negative resection at the primary hypopharynx tumor site. Locoregional control and
functional outcomes were recorded. Kaplan-Meier estimates were computed for disease-specific
survival (DSS), overall survival (OS), and disease-free survival (DFS).

Results: The median follow-up period for alive patients was 56 months (minimum-maximum, 5.3-173
months). All except one patient had a follow-up of at least 12 months. Three patients were lost to
follow-up and excluded from the study resulting in a final cohort of 71 patients. Primary tumor
classification according to American Joint Committee on Cancer (AJCC) was 13 pT1, 38 pT2, 11 pT3, and
9 pT4. 71.8% of patients had Stages III and IV disease. Patients were treated with surgery (TLM with neck
dissection) alone in 44% of cases, with 56% of patients receiving adjuvant radiation or chemoradiation
therapy. 3- and 5-year DSS estimates were 84.3% and 77.0%. 3- and 5-year OS estimates were 66% and
56%, while 3- and 5-year DFS estimates were 53% and 36%. Local control rate was 88.7%. Neck
recurrences occurred in 12.7% of patients and distant metastases developed in 9.9% of patients. 15
patients remained dependent on long-term gastrostomy feeding after treatment.

Conclusion: Transoral laser microsurgery with or without adjuvant therapy is a valid treatment option
for squamous cell carcinoma of the hypopharynx.
TRANS-ORAL MICRO-ENDOSCOPIC KTP-532 LASER ASSISTED SURGERY FOR SUPRAGLOTTIC CANCER
Dipak R Nayak, Prof, Balakrishnan Ramaswamy, Prof, V.v K Sandeep, Dr, Suraj S Nair, Dr; Department of ENT-Head & Neck Surgery Kasturba Medical College, Manipal University, Manipal, Karnataka, India

Background: Laser assisted endoscopic supraglottic laryngectomy for selected supraglottic cancers is as effective as the conventional external approach but is less morbid with better preservation of the laryngeal functions. CO2 laser is often used in such cases. KTP-532 laser has advantages of better hemostasis and in addition it can be used through optical fiber.

Objective: This retrospective study was intended to determine the role of endoscopic KTP-532 laser assisted approach in surgically treating selected supraglottic malignancy.

Materials and Methods: This is a retrospective study of 38 patients with squamous cell carcinoma of the supraglottis who underwent KTP-532 Laser assisted Micro-endoscopic supraglottic/extended supraglottic laryngectomy of various types depending on their extent, between 2000 and 2012 (13 years). Age of these patients varied from 39 to 87 years with a mean of 61 years. 35 patients were males and 3 females. Of the 38 patients with supraglottic malignancy, (T1-5, T2-21 and T3-12 cases), three T2 and five T3 cases underwent salvage surgery for radio-residual tumors. 19 patients underwent neck dissection in the same/second sitting (Modified/Radical neck dissection in 11 and lateral neck dissection in 8 patients). Twenty three patients underwent post operative radiotherapy for stage II/III disease.

Results: Of the 38 cases included in this study 31 had no loco-regional residual disease on their last follow-up. The follow-up period ranged from 1 to 13 years. Six patients had loco-regional recurrence of whom two died of residual disease, 2 underwent total laryngectomy and were disease free till last follow up and two were surviving with disease on their last follow up. One patient died of non cancer cause 3 weeks after surgery. The overall survival rate was 81.57% (31/38 cases) and three year disease free survival rate was 76.19% (16/21 cases). Commonest complication encountered was aspiration seen in 6 cases. This was resolved within 3-7 weeks in 4 cases. Tracheostomy was done post-operatively in 3 cases (in one due to post radiation cartilage necrosis and in other two for persistent aspiration).

Conclusions: Trans oral KTP-532 Laser assisted Micro-endoscopic Supraglottic Laryngectomy for supraglottic cancer is a viable alternative technique with less morbidity and achieves good disease control and survival rate.
Objectives:

To determine survival outcomes of advanced stage hypopharyngeal squamous cell carcinoma (SCC) patients treated at a single institution with either primary surgery with adjuvant radiation (RT)/chemoradiation (CRT) or definitive CRT.

Methods:

Retrospective analysis of a prospectively collected institutional database was performed for patients with newly-diagnosed squamous cell carcinoma of the hypopharynx between January 1999 to December 2011. Demographic, clinic-pathologic data, and survival information as well as smoking status, alcohol use, and Karnofsky Performance Status (KPS) were analyzed and compared between treatment groups. Overall (OS) and disease free survival (DFS) statistics were calculated and compared between treatment groups using the Kaplan-Meir method with Cox regression analysis for multivariate analysis.

Results:

166 consecutively treated patients with hypopharyngeal SCC were identified. Patients with early stage (T1-2N0) disease, metastatic disease at diagnosis, those treated with palliative intent, or lost to follow-up within 3 months were excluded. The remaining 118 patients were included in the survival analysis, of whom 46.6% were treated with definitive CRT and 53.4 % underwent S+RT/CRT. No significant differences were identified between S+RT/CRT vs CRT treatment groups in terms of age (p=0.74), gender (p=0.19), smoking history (p=0.45), alcohol use (p=0.75) and KPS (p=0.76). Five year OS and DFS for patients who received S+RT/CRT was 56.6 % and 55.8 % respectively. For patients treated with CRT, 5 year OS and DFS were 53.8 % and 76.8% respectively. No significant differences were seen in OS (p=0.87) or DFS (p=0.75) between patients treated with CRT or S+RT/CRT. Multivariate Cox regression analysis showed no significant hazard ratios of survival associated with age, gender, treatment, alcohol use, smoking history or KPS (p>0.05, for all).

Conclusions:

Advanced stage hypopharyngeal SCC patients in the present analysis demonstrate comparable DFS and OS with primary surgical management or definitive CRT.
COMPLEX TREATMENT OF HYPOPHARYNGEAL CANCER STAGE III-IV USING INDUCTION CHEMOTHERAPY

Elena Novozhilova, PhD, Daniil Stroyakovsky, PhD, Leonid Vinogradov, MD; Moscow City Oncology Hospital N62, Moscow, Russia

A combined treatment of hypopharyngeal cancer including extended organ resection. Since this approach negatively affects quality of life, attempts are made to save the organ by using chemoradiotherapy (CRT). The goal of this study is to compare effectiveness of induction chemotherapy (ICT) and CRT for treatment of locally advanced hypopharyngeal cancer.

Materials and methods: Patients with confirmed primary hypopharyngeal cancer stage (?3,4 N0-3, ?0) were enrolled in the study. The 1st cohort - 35 patients received 3 cycles of ICT according to the following protocol: cisplatin at 100 mg/m2 (1 day); 5-FU as a continuous 24 hr infusion of 1250 mg/m2 (days 1-5); docetaxel at 75 mg/m2 (1 day). This was followed by 3D conformal hypofractionated irradiation in a linear accelerator, to a total accumulated dose of 68 Gy. Patients with no residual tumor were left under close surveillance, in case of remaining tumor and/or metastases, the surgery was applied. The 2nd cohort of 48 patients received 30 mg/m2 of cisplatin once a week, simultaneously they were subjected to 3D RT according to the same schedule as the 1st cohort.

Results: In the 1st cohort, 31 of 35 patients completed the treatment. One patient died from cardiac infarction. Another patient was surgically treated after RT a dose of 40 Gy due to tumor progression. Two patients were withdrawn from chemotherapy due to either trombocytopenia or leukopenia. In the 2nd cohort, all patients completed CRT as scheduled. All patients in both cohorts developed radioepithelitis by the end of the therapy. This was successfully treated by Hydrolactivin (hydrolyzed milk serum with Ca lactate, Russia). In the 1st cohort, 20 patients (64%) developed complete response (CR), 11 patients (36%) developed partial response. Five of the 16 patients with N1-3, achieved complete regression of metastases. No detectable tumor was observed in 18 patients from cohort 1 after half time of the treatment. During 1st year after completion of the treatment, 3 patients from cohort 1 with initial total resorption of primary tumor, developed disease progression. They were subjected to laryngectomy with resection of pharynx. During 5 years of observation more 3 patients from cohort 1 were treated with laryngectomy, and 56% of the patients developed regionary metastases. In the 2nd cohort, 19 patients (40%) achieved CR at the primary tumor site. No patients from cohort 2 demonstrated resorption of nodal metastases. The 5 year overall survival rates for cohorts 1 and 2 were 68,2% and 56,4% for T3 patients; and 44,0% and 24,0% for T4 patients.

Conclusions: ICT demonstrated higher efficiency comparing with classical CRT despite its higher toxicity. Half of the patients were able to avoid resection of pharynx and to maintain higher quality of life. Even for relatively small number of patients treated in this study, observations during 5 years of follow-up surveillance demonstrated significant increase in overall survival rates after application of ICT protocol followed by RT.
Roles of Algorithm-Based "ChemoRadioSelection" for the Treatment of Advanced Hypopharyngeal Carcinoma

Muneyuki Masuda, MD, Mioko Matsuo, MD, Takeihiro Aso, MD, Hideyuki Kiyohara, MD, Fumihide Rikimaru, MD, Naonobu Kunitake, Yuichiro Higaki, MD; Department of Head and Neck Surgery, National Kyushu Cancer Center

Background: The mainstay for the treatment of advanced head and neck squamous cell carcinoma (HNSCC) has shifted from the radical surgery plus postoperative radiation to the organ preserving dose-intensified modality, achieving quite favorable organ preservation as well as survival of patients. However, these approaches appear to reach the limits of human tolerance due to severe late toxicities and treatment related deaths. Optimization of the therapeutic ratio seems to be an urgent task. In this context, we have evaluated the role of "chemoradioselection" strategy in the treatment of advanced hypopharyngeal carcinoma (HPC), focusing on the overall survival, functional laryngeal preservation reflected by the laryngo-oesophageal dysfunction free survival (LEDFS), and the survival benefit of radical surgery that has been denied in the current dose-intensified modality.

Patients and Methods: Fifty-five patients with advanced HPC were enrolled to our algorithm-based protocol as follows. After 40Gy of concurrent chemoradiation (CCRT) composed of cisplatin (15 mg/m², day 1-5) and 2Gy /day of irradiation, the tumor response was evaluated. Those who demonstrated complete response at the primary site: i.e., chemoradioselected (CRS) proceeded to further 30 Gy of CCRT up to 70 Gy and planned neck dissection, while the non-responders: i.e., non-chemoradioselected (N-CRS) underwent radical surgery. All 55 patients were followed up more than 36 months; the median follow up period was 69 ranging from 5 to 181 months.

Results: Based on this algorithm, 27 patients were CRS, while 28 N-CRS. The 5-year cumulative disease specific and overall survival rates were 76.2% and 65%, respectively. The CRS patients revealed significantly (p = 0.0167) better 5-yr survival (77.3%) compared to the N-CRS population (53.3%). The rates of tumor related death and distant metastasis in the CRS cohort: 11% and 7% were significantly lower than those in the N-CRS cohort: 32% and 18%. CRS patients demonstrated favorable LEDFS: 77.3% at 3-year and 57.1% at 5-year, although the overall 3-yr and 5-yr LEDFS remained 41.7% and 29.7%. No laryngo-oesophageal dysfunction was observed in the survivors with larynx. Among T, N and clinical stage, T stage was significant predictor of chemoradioselection. Intriguingly, the patients' survival was not affected by T stages, indicating that in this regimen radical surgery seems to have surgical benefit, probably saving the advanced T stage tumors in N-CRS patients. Thus, it appears that chemoradioselection can sufficiently segregate tumors that are cured by CCRT alone from biologically aggressive tumors that are better treated by radical surgery at relatively early phase of treatment.

Conclusions: The quite favorable survival data of the present study is quite comparable to or better than those of recent milestone studies that treated stage III and IV HNSCC such as RTOG-91-11or Tax 324 study. In addition, the data of LEDFS is not so inferior to these studies, although it should be improved. Our results indicate that algorithm-based chemoradioselection might provide a novel platform for the treatment of advanced HPC, taking full advantages of CCRT and radical surgery, and thereby optimizing the therapeutic ratio. By boosting chemoradioselection, further improved results might be feasible.