Head and neck squamous cell carcinoma (HNSCC), which includes a variety of primary sites in the upper aerodigestive tract, is a histologically homogeneous but etiologically and clinically heterogeneous entity. Chemoradiotherapy (CRT) is one of the treatment options for locally advanced HNSCC. It is not well established whether pretreatment 18F-FDG PET/CT can predict local response of HNSCC to CRT. In attempt to elucidate primary site of HNSCC whose local response to CRT is predictable by pretreatment 18F-FDG PET/CT, and also PET/CT parameter which is the best predictor, we examined 118 patients: 11 with nasopharyngeal cancer (NPC), 30 with oropharyngeal cancer (OPC), and 77 with laryngohypopharyngeal cancer (LHC) who had completed CRT >=66 Gy concurrent with docetaxel plus cisplatin. OPC was assessed for human papillomavirus (HPV) infexction status. PET/CT parameters of primary tumor, including metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum and mean standardized uptake value (SUVmax and SUVmean), were correlated with local response to CRT, according to primary site and HPV status. Receiver operating characteristic curve analyses were generated to assess the predictive efficacy of PET/CT parameters, with complete response as the gold standard. Optimal cutoff values to divide patients into high- and low-risk groups were determined so that the sum of sensitivity and specificity was maximal. Logistic regression analyses were used to identify independent predictors. Area under the curve (AUC) of the PET/CT parameters ranged from 0.53 to 0.63 in NPC and from 0.50 to 0.54 in OPC. HPV-negative OPC showed AUC ranging from 0.51 to 0.58, while all of HPV-positive OPCs showed complete response. In contrast, AUC ranged from 0.71 to 0.90 in LHC. Moreover, AUCs of MTV and TLG were significantly higher than those of SUVmax and SUVmean (P<0.01). After multivariate analysis, high MTV >25.0 mL and high TLG >144.8 g remained as independent, significant predictors of incomplete response compared with low MTV (odds ratio [OR], 13.4; 95% confidence interval [CI], 2.5-72.9; P=0.003) and low TLG (OR, 12.8; 95% CI, 2.4-67.9; P=0.003), respectively. We conclude that the predictive efficacy of pretreatment 18F-FDG PET/CT varies with different primary sites and chosen parameters, and that local response is highly predictable by volume-based PET/CT parameters in LHC, but not in NPC and OPC. Volume-based PET/CT parameters may serve as a prognostic factor for patients with LHC treated with CRT in the setting of larynx preservation.
S188 ULTRASOUND IN THE SEARCH FOR THE PRIMARY SITE OF UNKNOWN PRIMARY HEAD AND NECK SQUAMOUS CELL CANCERS

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Background: Head and neck squamous cell cancers (HNSCC) arising from an unknown primary (UP) site are a challenging clinical entity. Although human papillomavirus (HPV) detection can localize a tumor to the oropharynx (OP), clinical and histologic confirmation can remain elusive in up to 60% of UPs of HNSCC. Traditional imaging modalities (computed tomography, magnetic resonance imaging) and operative approaches (direct laryngoscopy [DL]/exam under anesthesia [EUA], biopsies) have had limited success in the identification of unknown primaries. Positron-emission tomography may improve detection. We have used ultrasound (US) to visualize base of tongue (BOT) cancers and were therefore interested in evaluating US to identify the primary tumor site of patients with HNSCC of UP.

Methods: Patients with HNSCC of UP after clinical evaluation (physical exam and fiberoptic laryngoscopy) by a head and neck surgical oncologist were eligible. Controls were subjects without known cancer. A Toshiba US (SSA-580A) was used with a convex transducer for the transcervical examination (3.75-6.0 Mega hertz [MHz]). For the intraoral examination, an endocavitary multifrequency convex probe (5-7.5 MHz) was used. US examination was performed in a standardized fashion. An US impression was ascertained and communicated with the surgeon. US findings were compared with operative examination (DL, EUA and biopsies).

Results: 10 patients with HNSCC of UP were eligible. PET/CT scans performed for staging purposes were negative (7 of 10), indeterminate (2 of 10) or suspicious (1 of 10) for a primary lesion. On US examination, an OP primary tumor site was identified in 10 of 10 cases (100%), with 7 in BOT and 3 in tonsil. The suspected lesions were largely hypoechoic (90%). Largest dimensions ranged from 6-20mm. On operative examination 5 of 10 were appreciated on DL or palpation. Two additional primaries were histologically confirmed with directed biopsies. 100% of cases were HPV-positive. Assuming that HPV-positive HNSCC localizes to the OP, DL successfully diagnosed 70% of these tumors, while US visualized 100%. The 3 cases that were not histologically confirmed appeared to be BOT tumors on US and underwent lingual tonsillectomy. However, this could represent a false positive, misclassification (e.g. tonsil) or the depth of dissection may have been too superficial. No lesions were suspected among 20 controls.

Conclusion: Ultrasound is a promising imaging modality to visualize the primary site for patients presenting as HNSCC of UP. Detection rates are similar to those using TORS diagnostic strategies (palatine/lingual tonsillectomy) which have potential risks. US before DL and biopsy has lower risk and similar success rate and therefore warrants further investigation in the visualization of OP cancers and UPs.
PROGNOSTIC VALUE OF PRETREATMENT 18F-FDG PET/CT VOLUME-BASED PARAMETERS IN PATIENTS WITH OROPHARYNGEAL SQUAMOUS CELL CARCINOMA WHOSE P16 AND P53 STATUS ARE KNOWN

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BACKGROUND:

Human papilloma virus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) patients respond well to any type of treatment and then it is widely expected to deintensify or modify treatment with less toxicity while maintaining the same excellent clinical outcome for those patients.

However, several studies have demonstrated no survival advantage in patients with HPV-positive OPSCC and this may be because the influence of HPV infection on survival of OPSCC patients differs in relation to exposure to other carcinogenic factors, such as smoking or alcohol. Hence, the identification of another objective risk-stratifying factor in HPV-positive OPSCC is of major importance in guiding future clinical decision-making to select patients for tailored deintensified treatment.

The purpose of this study was to determine whether pretreatment FDG-PET/CT volume-based parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) add more prognostic information to OPSCC patients.

METHODS:

Forty-seven patients with histologically proven OPSCC, who underwent FDG-PET/CT scan just before any treatment followed by a definitive therapy, were retrospectively analyzed.

For each patient, we calculated each SUVmax for primary tumor and each MTV and TLG for primary tumor, lymph node metastases if any, and summation of them. To define MTV, the threshold was set at 2 standard deviations above the mean SUV in mediastinal blood pool. Tumor p16 and p53 status were also evaluated by immunohistochemical staining as a surrogate marker of HPV-status and smoking status respectively. The cut-off value for the percentage of p16-or p53-positive cells were set at 50%.

Univariate and multivariate analyses of clinical risk factors including FDG PET/CT parameters, p16 status, p53 status, clinical stage, and definitive treatment modality for disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS) were performed using Cox proportional hazards model. In addition, a scoring system for DFS, DSS and OS was formulated based on p16 status, p53 and the most significant FDG-PET/CT variable which was determined in this study. Patients were classified from 0 to 3 (0: no risk factor, 1: one risk factor, 2: two risk factors).

RESULTS:

Almost all parameters from MTV and TLG for primary lesion, lymph nodes, and total tumor lesions were found to be significant prognostic factors for DFS, DSS or OS, although SUVmax for primary lesion was found not to be significant in univariate analysis. Multivariate Cox regression analysis revealed that only MTV for total tumor lesions (cut-off 65) retained their independence for all DFS, DSS and OS (HR; 3.2, 11.4 and 6.0. P =0.040, 0.008 and 0.011 respectively) indicating that it refers to the most significant FDG-
PET/CT variable. According to the scoring system, the score 0 subgroups showed significantly better DFS, DSS and OS than other groups.

CONCLUSIONS:

Our data revealed that volume-based PET parameters such as MTV for total tumor lesions could act as predictive markers for survival outcomes in OPSCC patients with either p16 / p53 status. Using our scoring scale with these parameters, it may be possible to select OPSCC patients for tailored de-intensified treatment.
INDOCYANINE GREEN BASED NIR FLUORESCENT IMAGING TO GUIDE SURGICAL RESECTIONS DURING TORS
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Background: Transoral robotic surgical (TORS) resection of the tonsil and tongue base offers a promising alternative to the more traditional organ-preserving chemo-radiotherapy route providing a similar oncological outcome with an improved side effect profile. Use of near infrared guided imaging to guide surgical resections has been demonstrated as feasible in preclinical models to improve accuracy of oncological resection. Absence of tactile feedback during TORS may be compensated by use of indocyanine green contrast enhancement of tumors to accurately identify the edge of the tumor. Successful implementation of image guided surgery would be able to both decrease intra-operative time and spare uninvolved tissue potentially decreasing surgical morbidity. We hypothesize that ICG has a higher affinity for tumor cells than histologically normal cells and can be used to image cancer during TORS using the Firefly fluorescence imaging system.

Objective: To determine if the use of dynamic ICG fluorescence imaging during trans-oral robotic resection of oropharyngeal tumors can be used to determine tumor margins.

Methods: Using the Firefly™ Fluorescence Imaging for the da Vinci® Si™ System, 8 patients underwent TORS as part of primary treatment for oropharyngeal SCC. Half an hour prior to surgical resection, the patients were injected with ICG 0.5mg/kg. Surgical resection was carried out according to the standard of care, however observation of normal and tumor tissues using the Firefly™ imaging system was performed multiple times throughout the resection.

Results: There was no inter-operative distinction between tumor and normal tissue. Intra-operatively the ICG was retained in both the involved and uninvolved palatine tonsil at a similar rate. Comparison with the contralateral tonsil demonstrated no distinction between the malignant and tonsillar tissue on the unaffected side. Furthermore, observation of contrast change in the tongue base tissue was hampered by venous stasis in the tongue from compression by the tongue blade retractor used to obtain surgical access.

Conclusion: Preoperative systemic injection with ICG at the time of surgical resection is nonspecific for tumor tissue and does not improve detection surgical margins for malignant tumors of the oropharynx.
THE ROLE OF POST-TREATMENT IMAGING IN THE MANAGEMENT OF OROPHARYNGEAL SQUAMOUS CELL CARCINOMA
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Background: Cancer surveillance of oropharyngeal squamous cell carcinoma is with CT and PET/CT scan at 8 and 12 weeks post-treatment, respectively, as per current treatment guidelines. We investigated whether imaging results in these time frames have an impact on clinical decision-making.

Methods: Retrospective review of patients with oropharyngeal squamous cell carcinoma treated with chemotherapy and/or radiation, with or without surgery. All had post-treatment CT and PET/CT scan at 8 and 12 weeks, respectively. CT scan within 6-8 weeks post-treatment and PET/CT within 10-14 weeks was accepted. CT and PET/CT impression was recorded as positive, negative, or equivocal, and equivocal impressions were clarified by the clinical impression at that time point. Clinical impression at the time of CT and PET/CT scan was recorded as positive or negative for persistent disease.

Results: Fifty-one patients met inclusion criteria, 44 men and 7 women. Thirty-two were smokers or had a history of smoking, and 19 never smoked. Overall disease-free survival was 90.2%, with only 5 patients having a recurrence. Mean disease-free survival was 45.42 months using Kaplan-Meier method and 2-year disease-free survival was 94.1%. There was no significant difference in clinical impression at the time of CT versus PET/CT (p=0.424). The agreement between the imaging report and concurrent clinical exam impression were compared for CT and 6-week clinical exam versus PET/CT and 12-week clinical exam, and there was no significant difference (p=0.8238).

Conclusion: Current treatment guidelines suggest post-treatment CT at 8 weeks and PET/CT at 12 weeks as appropriate surveillance for oropharyngeal squamous cell carcinoma. Our results suggest performing both of these imaging modalities may not be necessary in the absence of suspicion of disease progression, as clinical impression at the time of CT versus PET/CT is not significantly different. In our cohort, the decision to perform neck dissection or biopsy was made based on impression at PET/CT and not at time of CT scan. These findings suggest the results of CT at 8 weeks to possibly be inconsequential in decision making.
IMPACT OF POST-TREATMENT SURVEILLANCE ON HEAD AND NECK CANCER OUTCOMES

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Objective: To determine how compliance with post-treatment surveillance (PTS) among other patient characteristics affect clinical outcomes in patients with head and neck cancer.

Methods: A retrospective cohort study was performed on squamous cell head and neck cancer (HNSCC) patients. 332 patients met inclusion criteria, which included completion of both prescribed treatment and PTS at the study institution. Patient characteristics, tumor characteristics, clinical follow-up, socioeconomic, and geographic data were collected. Outcome measures were defined as overall survival, disease-free survival, and recurrence. Kaplan-Meier survival models were used to compare patients based on diagnostic, geographic, and patient behavior categories.

Results: Nearly two-thirds of the included patients were male (69%). The mean age at diagnosis was 60 years (SD=11.6). Tobacco use was common as expected among patients with 54% actively smoking at the time of diagnosis and an additional 30% with a history of tobacco use. Stage IV patients were the most common, representing 57% of the cohort, while Stage I and III each included an additional 17%. Treatment prescriptions included various combinations of surgery, radiation therapy, and chemotherapy, with the largest proportion receiving radiation therapy plus chemo. Recurrence occurred in 36% of the patients. The mean length of follow-up for the full cohort was 46 months (SD=30 months). Thirty-seven percent of patients died from disease, while 15 percent died from other or unknown causes. The mean age at death was 65 (SD=11.9). First, patients compliant with the prescribed treatment and PTS show a statistically significant difference in mean survival at 48 months versus 39 months for the non-compliant patients (p-value=0.033). Secondly, those patients that quit smoking (58%) survive significantly longer, with 48% surviving at 60 months versus 28% among those that continued to smoke(p=0.009). We also found significantly improved outcomes based on the distance patients lived from the treatment center. Median survival was 60 months for those living less than 100 miles away from the treatment center versus 48 months and 40 months for those living 100-200 miles away and greater than 200 miles away, respectively. Lastly, there was improved survival in higher income patients, although the lowest income group had the best survival.

Conclusions: Survival among HNSCC patients is significantly impacted by compliance with post-treatment surveillance. Differences were also found for comparisons including smoking cessation, socioeconomic status, and the distance travelled to the treatment center. More work is needed to further understand the impact of these patient behaviors and characteristics on cancer outcomes. Understanding the impact of the various characteristics may aid the head and neck cancer practitioner in increasing patient compliance, and education about outcomes.
Cancer patients could benefit from a surgical procedure that helps the surgeon to determine adequate tumor resection margins. Systemic injection of tumor-specific fluorescence agents with subsequent intraoperative optical imaging can guide the surgeon in this process. This way, complete resection of tumor tissue would result in improved patient survival while decreasing the morbidity associated with damage to normal structures.

At present, clinical trials of fluorescence-guided tumor resection are starting all over the world in many different fields of cancer research. Although optical imaging has high potential to improve oncological care, identification of the photons coming from the fluorescent contrast agent is complicated by autofluorescence and optical tissue properties. These factors have an important influence on the image that is presented to the head and neck surgeon. Considering the clinical consequences at stake, it is a prerequisite to answer the questions that are essential for the surgeon. What is optical image-guided surgery and how can it improve patient care? What should the head and neck surgeon know about the fundamental principles of optical imaging to understand which conclusions can be drawn from the images? And how do the limitations influence the clinical decision-making? In our presentation, we will discuss these questions and provide a clear overview of the basic principles and practical applications for optical image-guided head and neck cancer surgery.

Next to the technical possibilities and limitations of optical imaging, we will go into some very important fundamental questions that the scientific field is currently dealing with: the difficulties of tumor heterogeneity that hampers most approaches of tumor-specific targeting, and the issue of invasive tumor strands that challenges determination of adequate resection margins because they can be very difficult to resolve. We then describe how point optical spectroscopy can be used to scrutinize suspect tissue that is difficult to differentiate from normal tissue by measuring the local tissue optical properties to recover a local intrinsic fluorescence measurement.

In conclusion, although there are limitations to the intrinsic capacity of the technique, when practical and technical surgical possibilities are considered, optical imaging can be a very powerful intraoperative tool in guiding the future head and neck surgeon towards radical resection and optimal clinical results.

References


EFFECTIVENESS OF NARROW BAND IMAGING IN THE DETECTION OF PRE-MALIGNANT AND MALIGNANT LESIONS OF THE LARYNX: VALIDATION OF A NEW ENDOSCOPIC CLINICAL CLASSIFICATION

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Background: This study aims to assess the value of Narrow Band Imaging (NBI) endoscopy in the diagnosis of pharyngo-laryngeal lesions and to demonstrate the validity of a new NBI-based classification of their vascular pattern.

Methods: In 2009-2011, 248 pharyngo-laryngeal lesions underwent NBI-endoscopic evaluation. NBI findings were classified into 5 types according to the Niclassification and were compared with histopathological reports. Sensitivity, specificity, accuracy, positive and negative predictive values were calculated.

Results: Sensitivity, specificity, accuracy, positive and negative predictive values were 97.4%; 84.6%, 92.7%, 91.6% and 95.1% respectively. Ninety-eight% of histologically malignant lesions corresponded to type V endoscopic pattern, while 84.8% of the non neoplastic lesions corresponded to a type I-IV pattern.

Conclusions: the NBI ability to detect changes in the mucosal microvasculature can be useful for distinguishing non-malignant from malignant lesions. An internationally accepted NBI-endoscopic classification may contribute to the further definition of the diagnostic validity of this technique.
EARLY DETECTION AND ENDOSCOPE ASSISTED RESECTION OF PHARYNGEAL CANCER WITH NARROW BAND IMAGING TECHNIQUE
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[Background and purpose]

Pharyngeal cancer is often advanced when detected and has relatively poor prognosis. Early detection of the tumor is important because it not only improves survival rate but also minimizes functional loss of swallowing and voice. We have previously reported that narrow band imaging (NBI) combined with magnifying endoscopy is useful in detecting early superficial pharyngeal cancers, which are difficult to detect with a standard endoscopy. For such cases, we are performing endoscope assisted submucosal dissection applying endoscopic submucosal dissection technique which is increasingly used for early esophageal cancer. In this study, we investigated the usefulness of endoscope assisted submucosal dissection for early pharyngeal cancer.

[Operation procedure]

The procedure is performed by an otolaryngologist and a gastroenterologist assists the procedure by manipulating a gastroscope to obtain an optimal surgical field. Under general anesthesia, specially designed curved laryngoscope was inserted to allow a working space in the pharyngeal lumen and a gastroenterologist inserts a magnifying gastroscope (GIF TYPE H260Z; Olympus, Tokyo) with high resolution transorally to visualize the field. The extent of the lesion was determined by NBI and iodine staining and the margins of the lesion are marked with coagulation. Cutting and dissection procedure was performed with an orally inserted curved electric knife. Fasting period was usually 1-2 days after operation.

[Results]

Since September 2007, 111 cancer lesions were removed from 71 patients with superficial pharyngeal cancer. Tumor origin was 68% in the hypopharynx and 32% in the oropharynx. Regarding adverse effects, subcutaneous emphysema temporally occurred in 8 cases, all of which treated conservatively. Two cases needed emergency tracheostomy, one of which was due to post operative bleeding and the other was post operative musosal edema in addition to the preexisting bilateral vocal fold paralysis.

During the median follow-up period of 24 months, local recurrence occurred in 3 cases, one of which controlled by the same procedure and two cases controlled by concurrent chemoradiotherapy. Post operative neck lymph node metastasis occurred in 2 cases and both were controlled by neck dissection. All patients survive with no evidence of disease and retain their speaking, breathing, and swallowing functions.

[Conclusions]

Endoscope assisted submucosal dissection for early pharyngeal cancer allows excellent survival and the preservation of swallowing and voice functions. Early detection of superficial pharyngeal cancer with narrow band imaging technology and the treatment with endoscopic submucosal dissection can be a new treatment strategy for the head and neck cancer.