Objectives: Patients who undergo surgery for obstructive sleep apnea (OSA) have increased perioperative morbidity. Transoral robotic surgery (TORS) has recently been applied to the treatment of OSA, but the perioperative management and postoperative complications still need to be elucidated in this patient population. The objective of this study is to perform the first large-scale evaluation of perioperative management and postoperative complications in patients who undergo TORS for OSA.

Methods: Consecutive patients who underwent surgical treatment of OSA between December 2010 and November 2013. There were 166 patients (average age 54.6; m:f 122:44) who underwent a comprehensive examination followed by drug induced sedated endoscopy (DISE) in the operating room. The average BMI, AHI and ASA were 29.0, 40.9, 2.26, respectively. All patients underwent TORS lingual tonsillectomy + direct multilevel procedures based on results of DISE. The average number of comorbidities was 1.8, with 29% (48) of patients on preoperative anticoagulation.

Results: The average length of stay in the SICU was one day, and the median overall hospital length of stay was two days. The first 16 patients were extubated on POD 1 in the SICU; we then transitioned to extubation in the operating room for the remaining 150 patients, none of whom required reintubation. There were 11 major complications including secondary bleeding requiring intervention (7), pulmonary embolism requiring anticoagulation (2), aspiration requiring prolonged hospitalization (1) and dysphagia requiring G-tube dependence (1). There were 29 minor complications, and the majority resolved without sequela. Preoperative ASA score predicted a postoperative complication (p=0.03). Age, BMI, AHI, lowest oxygen saturation, number of comorbidities, and number of adjunct multilevel procedures did not predict a complication.

Conclusions: TORS can be safely performed in patients with OSA with an acceptable SICU and overall length of stay. The decision to extubate in the OR versus the ICU on POD 1 did not affect length of stay. Complications are similar to those seen with other surgical treatments of OSA and were only predicted by ASA score. Minor complications such as globus sensation and dysguesia improve over several months but can persist.
Purpose: To determine the efficacy of the developed method of combined treatment in patients with malignant tumors of nasal cavity and paranasal sinus compared to the standard method of treatment.

Material and methods: A combined treatment was carried out in 116 patients with locally advanced forms of malignant neoplasms of different genesis. The group included patients who received the developed method of combined treatment including preoperative gammatherapy in the regimen: a single local dose (SFD) = 3 Gy, a total local dose (TFD) = 30 - 36 Gy (40 - 44 Gy by isoeffect). Surgery with intraoperative radiotherapy (IORT) with fast electrons of 6 MeV at a single dose which was determined according to the proposed formula with the limits of 10 ± 2 Gy depending on the total dose value of the preoperative course of gammatherapy before operation, replacing the postoperative defects using endoprosthesis made of porous titanium nickelide.

Results: Using the developed method of combined treatment of patients with malignant tumors of nasal cavity and paranasal sinuses including preoperative gammatherapy in TFD of 40 - 44 Gy by isoeffect, operation with IORT and one-moment rehabilitation of the postoperative defect using endoprosthesis made of porous titanium nickelide allows to increase the efficacy of the treatment and improve the long-term results. The indices of 5-year total and non-relapse survival rate made up in the developed group 61 ± 8,1 % and 66,2 ± 8,8 %.

Conclusion: The proposed method of combined treatment of nasal cavity and paranasal sinus tumors is well tolerated by the patients, allows to improve the long-term results, gives a good functional and cosmetic effect in most patients.
PROGNOSTIC FACTORS IN MERKEL CELL CARCINOMA OF THE HEAD AND NECK: AN ANALYSIS OF 4,718 PATIENTS

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IMPORTANCE: Merkel cell carcinoma (MCC) is a rare neuroendocrine malignancy that is most commonly found in the head and neck and is rapidly increasing in incidence. There is controversy regarding the role of elective neck dissection (END) and adjuvant chemoradiation (CRT) in the management of MCC of the head and neck.

OBJECTIVES: 1) To identify factors associated with survival in patients with MCC. 2) To determine the role of adjuvant CRT in MCC. 3) To determine the prognostic value of END in MCC.

DESIGN, SETTING, PARTICIPANTS: Retrospective review of adult patients with MCC who had surgery in the National Cancer Database (NCDB) from 1998 to 2011.

MAIN OUTCOMES AND MEASURES: Our main outcome was overall survival (OS). Statistical analysis included chi-square, t tests, Kaplan-Meier survival analysis, and Cox proportional hazards regression.

RESULTS: We identified 4718 patients; 92.0% had a surgical excision and 8.0% had Mohs surgery (Mohs). On multivariate analysis, tumors >5 cm (hazard ratio [HR], 2.8; 95% confidence interval [CI], 1.9-4.0) and positive margins (HR, 1.4; 95% CI, 1.0-1.8) were independently associated with decreased OS. Postoperative CRT (HR, 0.5; 95% CI, 0.3-0.7) and XRT (HR, 0.7; 95% CI, 0.6-0.9) provided a survival benefit over surgery alone. In clinically N0 patients, patients who had an END had improved 5-year OS compared with those who did not have an END (56.7% vs 38.6%, P< .001), and END was independently associated with improved survival (HR, 0.6; 95% CI, 0.4-0.9).

CONCLUSIONS AND RELEVANCE: To our knowledge, this is the largest cohort of patients with head and neck MCC. Results suggest that END and adjuvant CRT may help improve survival in these patients.
Background. Surgery followed by radiation has been considered a mainstay in the management of sinonasal adenocarcinoma, improving survival outcomes compared to single modality treatment. Moreover, endoscopic transnasal resection and advances in irradiation techniques (IMRT, intensity modulated radiotherapy) are emerging as a minimally invasive alternative to traditional open surgery and conventional radiotherapy. Recently, the favorable outcomes observed in patients with small primary tumors and wide resection margins suggested that they could be managed with surgery as a single treatment modality, without necessarily needing the addition of adjuvant radiotherapy. However, the appropriate management of this subset of patients remains still unclear due to the rarity of these tumors and the lack of comparative studies.

Methods. Longitudinal retrospective case-control study. From 2001 to 2013, we enrolled 79 patients affected by primary, early-stage (pT1-pT2) sinonasal adenocarcinoma radically resected using an endoscopic endonasal approach, with microscopic negative margins confirmed by final histology. The surgical resection was followed by adjuvant IMRT in 39 cases (Group A), while surgery as a single treatment modality was adopted for 40 patients (Group B). The study has been approved by the Institutional Review Board. Statistical analysis using the Kaplan-Meier method was performed to establish survival outcomes. The $\chi^2$ independent test was used to compare the survival rates between the two groups. For all tests, significance was set at $P<0.05$.

Results. Mean age of patients was 64 years. Tumors were staged pT1 in 42% of cases and pT2 in the remaining 58%. The 5-year overall (OS), disease-specific (DSS) and recurrence-free (RFS) survival rates were 89%, 100% and 92%, respectively, in Group A (mean follow-up, 51 months) and 81%, 86% and 79%, respectively, in Group B (mean follow-up, 59 months). Statistically significant differences were observed between the two groups in terms of DSS ($P=0.04$) and RFS ($P=0.02$), suggesting that the two treatment strategies were not equivalent for this subset of patients. The analysis was repeated excluding the 13 patients affected by high-grade tumors (poorly-differentiated adenocarcinoma and signet-ring variant): 9 patients were excluded from Group A obtaining the subgroup A2 (30 cases) and 4 patients from Group B creating the subgroup B2 (36 cases). When adopting these new inclusion criteria, the 5-year OS, DSS and RFS rates were 90%, 100% and 97%, respectively, in subgroup A2 (mean follow-up, 59 months) and 86%, 94% and 91%, respectively, in subgroup B2 (mean follow-up, 61 months). Remarkably, there was no statistically significant difference between these two new subgroups with regard to OS ($P=0.73$), DSS ($P=0.21$), and RFS ($P=0.14$).

Conclusions. Endoscopic transnasal surgery was recommended as a single treatment modality for primary early-stage low-grade histology sinonasal adenocarcinoma, resected with negative margins. Multimodality therapy with surgery followed by adjuvant IMRT remains the optimal treatment strategy not only for advanced stage lesions but also for high-grade histology adenocarcinomas regardless the stage of disease at presentation.
PROSPECTIVE EVALUATION OF ANTIBODIES TO HUMAN PAPILLOMAVIRUS IN OROPHARYNGEAL SQUAMOUS CELL CANCER SURVEILLANCE
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Background: Infection with high risk type human papillomavirus (HR-HPV) is an established independent risk factor for the development of oropharyngeal squamous cell carcinoma (OSCC). The aim of this study was to assess the course of serum antibody titers to HR-HPV before treatment and during follow-up.

Methods: From 11/09 till 04/12 51 patients (38 males, mean age 61 years (range 30-81y)) undergoing panendoscopy for evaluation of an untreated OSCC were prospectively enrolled. Serum antibodies to HPV16, 18, 31, 33, 45 and 58 late and early oncoproteins were measured as previously described at the time of diagnosis and during follow up. HPV-positivity of the tumor was defined by immunohistochemical p16 positivity and detection of HR-HPV by PCR amplification using two different consensus primer pairs (L1C1/L1C2 and GP5+/GP6+). The prevalence of HPV-associated OPSCC, the concordance of HPV-positivity in the tumor and type-specific serum antibodies as well as the correlation of tumor control with HPV-antibody titers were evaluated.

Results: 26/51 (53%) tumor samples were HR-HPV-positive (22 HPV type 16, 1 HPV type 16 and 33, 3 HPV type 33). Two of the HPV-negative tumor patients were positive for HR-HPV serum antibodies. In 19/51 patients serum antibodies to HPV type 16, in 5/51 to HPV type 16 as well as 33 and in 4/51 to type 33 could be detected with a highly significant concordance between the HPV-type specific positivity in tumor tissue and blood samples (Cohen's kappa 0.88). The mean observation and survival time of the whole patient cohort was 27 months (range 3 - 46 months). 6 months after treatment 23/28 patients had a significant decrease of antibody titer compared to the pretherapeutic titer. 5/28 patients developed recurrent disease after a median of 12 months (7-24 months). In 4/5 patients the antibody titer was increasing whereas in one patient the titer was initially decreasing and no antibody titer was measured at the time of recurrence whereas in only 2/23 patients without recurrence the antibody titer was increasing. An increase of the antibody titer was statistically significantly associated with recurrence (p=0.003) as calculated by Fisher exact test.

Conclusions: In line with the literature we found a high concordance rate between positive HPV-status of OSCC tissue and positivity for HR-HPV serum antibodies. Furthermore we observed a significant decrease of HR-HPV antibody titers after tumor treatment. Tumor recurrence during follow up was associated with a statistically significant antibody titer increase. Therefore we believe that HR-HPV serum antibodies could serve as markers for tumor surveillance.
ENDOSCOPIC RESECTION WITH TRANSNASAL CRANIECTOMY: A RELIABLE SURGICAL PROCEDURE FOR SELECTED SINONASAL MALIGNANCIES.

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Objectives: To assess the outcomes of endoscopic resection with transnasal craniectomy (ERTC) in terms of disease control and morbidity. To identify factors influencing recurrence and survival in patients treated with ERTC.

Patients and methods: The records of all the patients who underwent ERTC for a sinonasal malignancy with radical intent, from April 2004 to November 2013, at two referral hospitals were retrospectively reviewed. The associations between complication and age, histology, pT status (pT1-2 VS pT3-4a VS pT4b) were analyzed by using logistics regression models. Overall Survival (OS) was calculated according to Kaplan-Meier method. Furthermore, the significant factors at univariate analysis were entered into Cox proportional hazard models to determine the adjusted HR.

Results: 185 patients (136 males and 49 females) were eligible for this study. Median and median age at presentation were 64 and 60.6 years, respectively (range 22-84). Forty-six (24.86%) patients were previously treated at other institutions; 29 received surgery, 17 radiotherapy, and 13 chemotherapy. Bilateral dural resection was performed in 145 (78.38%) cases. Definitive pT status was: pT1 in 23 (12.44%) patients, pT2 in 52 (28.11%), pT3 in 38 (20.54%), pT4a in 19 (10.27%), and pT4b in 53 (28.65%); 48 (48/53; 90.57%) pT4b cases had a focal dural invasion. The breakdown by histology was the following: 107 (57.84%) adenocarcinomas, 36 (19.46%) carcinomas other than adenocarcinoma, 30 (16.22%) olfactory neuroblastoma, and 12 (6.49%) other tumors. Surgical margins were involved in 21 (11.68%) specimens. Median hospitalization time was 12 days (range 2-43). Adjuvant treatment was added in 122 (65.95%) patients: 108 received radiotherapy, 13 chemo-radiation, and 1 chemotherapy. Postoperative complications occurred in 14 (7.57%) patients. Eleven (5.95%) patients experienced cerebrospinal fluid leak. No intraoperative or perioperative fatal event was observed. Recurrence occurred in 44 (23.78%) patients: 24 (58.54%) local recurrences, 7 (17.95%) regional, and 17 (43.59%) distant metastases. Median follow-up was 40 months. Patients were: alive without disease in 146 (78.92%) cases, 23 (12.43%) died for the disease, 11 (5.59%) were alive with disease, and 5 (2.70%) died for other causes.

At multivariate analysis, risk of complications was not related to any of the analyzed factors. Five-year OS was 77.52% (±4.26%), and was significantly related to pT category (p<0.001), dural involvement (p<0.001), and surgical margins (p=0.002), at the univariate analysis. At multivariate analysis, only pT4b status was significantly associated with an increased risk of death (HR=17.97, p=0.008), while gender, age, pT3-4a and involved margins were not significant.

Conclusions: ERTC, when properly selected, is a reliable oncological surgical procedure, with a low risk of complications. In this series, pT4b cases were mostly due to a limited dural invasion, so that the prognostic role of this histologic finding may not be assessed, as it overlaps the pT4b category.
IMPLEMENTATION OF A COMPREHENSIVE COMPETENCY-BASED TRANSORAL ROBOTIC SURGERY TRAINING CURRICULUM WITH EX VIVO DISSECTION MODELS

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BACKGROUND: Transoral robotic surgery (TORS) has become an accepted treatment option for patients with oropharyngeal cancer and obstructive sleep apnea. Despite its increasingly widespread adoption, there is no uniform training curriculum. The ideal curriculum would be TORS-specific, low-cost, high-fidelity, easy to implement across residency programs, objectively measured, and free from industry bias. We describe the results of our novel TORS curriculum training program in which we introduce ex vivo dissection models for radical tonsillectomy (RT) and base of tongue (BOT) resections.

METHODS: Twelve otolaryngology residents from an academic hospital participated in the curriculum using the da Vinci robotic surgical system. The curriculum is outlined in Figure 1. Trainee performance was video-recorded and reviewed by a blinded rater who scored the trainee on various objective structured assessment of technical skills (OSATS) performance metrics as well as resection time and margin analysis. Additionally, four expert TORS surgeons completed the ex vivo dissections for performance comparison with the trainees.

RESULTS: The curriculum ranged from three to six once-weekly sessions. Each session ranged from 86.7 to 104.6 minutes, with an average total training time of 387.8 minutes (SD 57). Data are provided in Table 1. Compared with their pre-training performance, the curriculum-trained residents achieved a significantly higher OSATS score in the BOT resection. Trainees achieved OSATS scores similar to those of experts in both the BOT resection and RT models, although they had a longer time to resection. Peripheral and deep surgical margin measurements in the BOT model were significantly improved following training and comparable to experts.

CONCLUSIONS: We present the results of a comprehensive TORS training curriculum with ex vivo oropharyngeal porcine models to a cohort of TORS-naive resident trainees. Trainees' measures of surgical margin accuracy and OSATS scores achieved equivalence with that of experts. The results confirm acquisition of a sound level of robotic proficiency on par with expert performance. This graduated curriculum provides a realistic training experience to develop competency with oropharyngeal resections prior to transition to the operating room.

<table>
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<th>Cohort</th>
<th>Composite Score</th>
<th>Pvalue</th>
<th>Resection Time(sec)</th>
<th>Pvalue</th>
<th>Peripheral Margins(mm)</th>
<th>Pvalue</th>
<th>Deep Margins(mm)</th>
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<tr>
<td>Pre-trained</td>
<td>11.33(SD1.33)</td>
<td>&lt;0.0001</td>
<td>897(SD413)</td>
<td>0.799</td>
<td>3.3(SD1.75)</td>
<td>0.0026</td>
<td>2.9(SD2.5)</td>
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<tr>
<td>Post-trained</td>
<td>18.58(SD0.49)</td>
<td></td>
<td>863(SD197)</td>
<td>5.2</td>
<td>5.1(SD1.11)</td>
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**Figure 1. Outline of TORS Training Curriculum***

1. Online educational module and observed TORS videos
2. da Vinci virtual reality Skills Simulator tasks
3. Initial base of tongue resection on porcine model (i.e. pre-training performance)
4. Basic robotic skills tasks (transfer/manipulation, sharp dissection, electocautery, blunt dissection, robot set-up and docking)
5. Radical tonsillectomy on porcine model
6. Final base of tongue dissection on porcine model (i.e. post-training performance)

*Progression to each successive step in the curriculum is dependent on achievement of a threshold competency score attained at each task.
SENTEL LYMPH NODE BIOPSY FOR HEAD AND NECK MELANOMA IS ASSOCIATED WITH IMPROVED SURVIVAL - A SEER ANALYSIS
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Importance: Sentinel lymph node biopsy (SLNB) provides important prognostic information for melanoma; however, a survival benefit has not been proven.

Objective: To assess the association of SLNB with survival for head and neck melanoma (HNM).

Design: Propensity score-matched case-control study using the population-based Surveillance Epidemiology and End Results (SEER) database to compare patients with HNM initially treated with SLNB to those initially treated without SLNB or neck dissection.

Setting: SEER database in the United States

Patients: Melanoma arising in head and neck subsites meeting current recommendations for SLNB, initially treated during the years 1998-2010 with either a) SLNB +/- neck dissection, or b) no SLNB or neck dissection.

Intervention: SLNB +/- neck dissection

Main Outcome Measures: Observed survival (OS) and disease-specific survival (DSS) estimates based on the Kaplan-Meier method, and Cox proportional-hazards modeling to compare survival outcomes between the matched-pair cohorts

Results: 9056 HNM patients meeting study criteria were initially identified from the SEER database. To minimize bias in treatment selection, matching of SLNB treatment cohorts was performed utilizing propensity scores modeled on 10 covariates known to be associated with SLNB treatment or melanoma survival. Cohort matching and balance was optimized based on available covariates, but the matching was unable to control for confounding effects from unrecognized factors influencing treatment assignment to SLNB - such as comorbidity. This might especially influence the result amongst the oldest patients; therefore, cohorts were matched and analyzed separately by stratifying young patients aged 18-64 and older patients age 65-84. Stratification was also done for thin (0.75-1mm) versus intermediate (1-4mm) Breslow depth tumors. In the age 18-64 intermediate cohort, 1484 HNM patients were matched and balanced by propensity score for SLNB treatment; the KM 5-year survival estimate for those treated by SLNB was 82% versus 77% for those not treated with SLNB (HR 1.44, 95% CI 1.10-1.90, p-value .009). The 5-year DSS for SLNB versus no SLNB was 87% versus 86%, respectively (HR 1.40, 95% CI 1.20-1.64, p-value <.0001). Sensitivity analysis suggested that an unrecognized covariate influencing the selection of SLNB treatment by 25% with near perfect association with mortality would account for the treatment effect associated with SLNB assignment identified in this study for young patients with intermediate thickness HNM. No significant difference in survival based on SLNB was seen in the thin melanoma cohort.

Conclusions and Relevance: This SEER cohort analysis demonstrates an association between SLNB and improved survival for young patients with HNM between 1-4mm Breslow depth. However, the possibility of an unmeasured confounding variable remains present. This study may signify a therapeutic benefit of SLNB for HNM, but use of data beyond that provided by SEER is recommended.
Background

For patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN), chemotherapy may offer palliation and life extension. However, effects are often marginal and do not necessarily outweigh side effects. Treatment choice is therefore much dependent on physician and patient preference. Real-world data on treatment patterns, overall survival, adverse events and costs is scarce. We conducted a study to provide insight into systemic treatments and outcomes in daily clinical practice for patients with R/M SCCHN in The Netherlands.

Methods

A retrospective, observational study was conducted in six Dutch head and neck treatment centers. Medical records of patients fulfilling the following criteria were reviewed: diagnosis of recurrent (<2cm normal mucosa between the two tumor locations and <5 years) and/or metastasized (M+) squamous cell carcinoma of the head and neck (ICD-O C01-C14 and C30-C32), between January 2006 and July 2013. Information on treatment patterns was collected for all selected patients. For patients receiving one or more lines of palliative, non-trial pharmacotherapy, further data were collected on patient characteristics, tumor characteristics, disease progression, treatment, survival, adverse events, and resource use. Resource use included: in-patient hospital days, day care hospital treatments, out-patient visits, consultations, laboratory services, imaging services, surgical and other procedures, radiotherapy and use of medication. Estimates of costs of R/M SCCHN were obtained using resource use combined with Dutch unit cost data. A hospital perspective was chosen.

Results

893 R/M SCCHN patients fulfilled selection criteria, of whom only 125 (14%) received palliative, non-trial first-line systemic treatment. Most common: cetuximab added to platinum-fluorouracil (32%), methotrexate monotherapy (27%), capecitabine monotherapy (14%), and platinum combination therapy (various combinations, 13%). Patients treated with monotherapy are older than patients treated with combination therapy. Median progression free survival and overall survival are 3.4 and 6.0 months, respectively. 34 out of 125 patients experienced serious adverse events (SAEs) associated with the first treatment line. 21 hospital admissions were related to adverse events, median 8 days. Combination therapies are associated with more SAEs than monotherapies, with cetuximab plus platinum-fluorouracil being most toxic (19 SAEs, 48%). Mean total costs range from €10,075 [±€9,891] (methotrexate monotherapy) to €39,459 [±€21,149] (cetuximab plus platinum-fluorouracil). Primary cost drivers are hospitalizations and anticancer drug treatments.

Conclusion
In the Netherlands, systemic treatment is given to a minority of patients with R/M SCCHN. Compared to other European countries\(^1\), Dutch head and neck cancer specialists seem to take a conservative approach to prescribing chemotherapy in general, and cetuximab plus platinum-fluorouracil specifically.

References