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Effect of Fluorescence Visualization-Guided Surgery on Local Recurrence of Oral Squamous Cell Carcinoma: A Randomized Clinical Trial

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*From the **JAMA Otolaryngology Head Neck Surgery.** December 2020.*

Importance: High local recurrence rates with aggressive disease remain the main concern in oral cancer survival. Use of a translational device using fluorescence visualization (FV) approved by the US Food and Drug Administration and Health Canada, has shown a marked reduction in the 3-year local recurrence rate of high-grade oral lesions in a single-center observational study.

Objective: To determine whether FV- guided surgery can improve local control rates in the treatment of in situ or T1 to T2 category oral squamous cell carcinoma (OSCC).

Design, setting, and participants: A multicenter randomized clinical trial was conducted in a surgical setting. A total of 457 patients were enrolled between January 18, 2010, and April 30, 2015. Data analysis of the intention-to-treat population was performed from April 3, 2019, to March 20, 2020. Patients with histologically confirmed high-grade dysplasia/carcinoma in situ or T1 to T2 category OSCC were randomized to receive traditional peroral surgery or FV-guided surgery.

Intervention: Fluorescence visualization during surgery.

Main outcomes and measures: The primary outcome was local recurrence of OSCC. Secondary outcomes were failure of the first-pass margin, defined as a histologically confirmed positive margin for severe dysplasia or greater histologic change of the main specimen (i.e., not the margins taken from the resection bed), regional or distant metastasis, and death due to disease.

Results: Of the 457 patients enrolled in the study, 443 patients (264 [59.6%] men; mean [SD] age, 61.5 [13.3] years) completed the randomized treatment: 227 FV-guided and 216 non-FV guided surgery. The median follow-up was 52 (range, 0.29-90.8) months. In total, 45 patients (10.2%) experienced local recurrence. The 3-year local recurrence rate was 9.4% in the FV-guided group and 7.2% in the non-FV group (difference, 2.2%; 95% CI, -3.2% to 7.4%). Other similarities between the FV vs non-FV groups included failure of first-pass margin (68/227 [30.0%]) vs 65/216 [30.1%]), regional failure (39/227 [17.2%] vs 37/216 [17.1%]), disease-specific survival (23/227 [10.1%] vs 19/26 [8.8%]), and overall survival (41/227 [18.1%] vs 38/216 [17.6%]) were also similar between groups. No adverse events were judged to be related to the intervention.

Conclusions and relevance: In this randomized clinical trial, FV-guided surgery did not improve local control rates in the treatment of patients within situ or T1 to T2 category oral cancer. Under a controlled environment, FV-guided surgery did not have an evident effect in

reduction of local recurrence for localized OSCC. This result suggests that attention be directed to strategies other than improving definitions of nonapparent disease at clinical margins to identify the sources of local recurrence.

Summary statements:
This study randomized 261 patients undergoing primary surgery for T1-T2N0 oral cavity squamous cell carcinoma and 182 patients with high-grade premalignant oral lesions to undergo surgical margin planning either by clinical assessment alone or with assistance by the Velscope, a portable device that detects changes in tissue autofluorescence to detect high-risk tissues.

- No significant differences were observed between groups in the primary outcome, 3-year local recurrence, nor in any secondary outcomes (failure of fist pass margin, regional failure, overall survival, disease-specific survival)

Strengths:
Prospective, randomized multi-center trial design provides high level evidence about the role of fluorescence visualization in guiding surgical margins

- Trial design includes power analysis, clearly outlined randomization procedures, blinding protocols where possible, photo documentation, and auditing processes to minimize bias
- Discussion appropriately recognizes study limitations, including imbalanced use of adjuvant therapy between groups that may account for differences in local control, as well as lower than expected event rate that may impact study power

Weaknesses:
Multiple covariates that may impact the primary or secondary outcomes are not delineated, including perineural invasion, lymphovascular invasion, depth of invasion, or oral cavity subsite

- Supplement describes that training of study "fluorescence visualization specialists FVS", however it is not clear what training was performed or whether results were similar across study sites
- The study conclusion states that "to improve local recurrence, attention should be directed to strategies other than improving definitions of nonapparent disease at clinical margins", however, the study demonstrates no difference in first pass margin rates between groups, and while first-pass margins are reported, final margin status is unclear. It may a more valid conclusion to state that the Velscope was ineffective in defining nonapparent clinical margins and that it may remain valuable to continue efforts to improve detection of nonapparent disease.

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Equivalence Randomized Trial to Compare Treatment on the Basis of Sentinel Node Biopsy Versus Neck Node Dissection in Operable T1-T2N0 Oral and Oropharyngeal Cancer

Renaud Garrel, Gilles Poissonnet, Antoine Moyà Plana, Nicolas Fakhry,Gilles Dolivet,Benjamin Lallemant, Bastit, Fanny Richard, Valérie Costes, Paul Landais, Françoise Perriard; Jean Pierre Daures, Delphine de Verbizier, Valentin Favier, Marie de Boutray.

*From the **Clinical Oncology,** December 2020.*

Purpose: Sentinel node (SN) biopsy is accurate in operable oral and oropharyngeal cT1-T2N0 cancer (OC), but, to our knowledge, the oncologic equivalence of SN biopsy and neck lymph node dissection (ND; standard treatment) has never been evaluated.
Methods: In this phase III multicenter trial, 307 patients with OC were randomly assigned to (1) the ND arm or (2) the SN arm (experimental arm: biopsy alone if negative, or followed by ND if positive, during primary tumor surgery). The primary outcome was neck node recurrence-free survival (RFS) at 2 years. Secondary outcomes were 5-year neck node RFS, 2- and 5-year disease-specific survival (DSS), and overall survival (OS). Other outcomes were hospital stay length, neck and shoulder morbidity, and number of physiotherapy prescriptions during the 2 years after surgery.

Results: Data on 279 patients (139 ND and 140 SN) could be analyzed. Neck node RFS was 89.6% (95% CI, 0.83% to 0.94%) at 2 years in the ND arm and 90.7% (95% CI, 0.84% to 0.95%) in the SN arm, confirming the equivalence with $P < .01$. The 5-year RFS and the 2- and 5-year DSS and OS were not significantly different between arms. The median hospital stay length was 8 days in the ND arm and 7 days in the SN arm ($P < .01$). The functional outcomes were significantly worse in the ND arm until 6 months after surgery.

Conclusion: This study demonstrated the oncologic equivalence of the SN and ND approaches, with lower morbidity in the SN arm during the first 6 months after surgery, thus establishing SN as the standard of care in OC.

Summary Statements:

- Multicenter trial which randomly assigned 307 patients with oral or oropharyngeal cT1-T2N0 cancer to either neck dissection (ND) or sentinel node (SN) biopsy. Recurrence free survival (RFS) at 2 years was the primary outcome.
- 279 patients were analyzed with 139 in the ND arm and 140 in the SN arm with no differences in 2-year RFS (89.6% vs 90.7%, P < 0.01).
- Neck shoulder functional outcomes as assessed by self-reporting, an arm abduction test and physiotherapy course were worse in the ND arm until 6 months after surgery when this difference evaporated.

Strengths:

- The baseline clinical pathological characteristics were relatively evenly distributed among the two treatment arms. (However, note well and this is speculative there was a tendency towards more females in the SN group which questions how random the allocation was).

- Despite the pooling of oral and oropharyngeal cancer patients, oncologic equivalence was established between the ND and SN arms in terms of 2-year RFS (89.6% vs 90.7%, P < 0.01). There was no statically significant difference regarding 5-year RFS, 2 and 5 year disease specific survival (DSS) and overall survival (OS).
- Demonstrates quite well that functional outcomes for neck shoulder mobility are superior in the SN arm for at least the first 6 months following surgery.

Weaknesses:

- Oral and oropharyngeal cancer patients were pooled, with no mention regarding HPV status in the latter group (AJCC 7th Edition Used).
- Of the 140 SN patients there were 8 localization failures and 33 additional patients that went onto have ND (29.3%). Of this latter group 21 converted to ND at the same operation because of an intraoperative SN+ diagnosis, while 12 had a secondary ND following formal post-operative pathological analysis of the SN node that was initially deemed negative intraoperatively. However, depending on perspective this could also be considered a strength!
- The extent of the ND was not commented on in the ND group nor in the positive SN group (pSN+) apart from to say "Level IIb dissection was performed in 26 of 33 pSN+ patients (79%). It is not clear if there were further levels dissected.

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ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients with Locoregionally Advanced Head and Neck Squamous Cell Cancer

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From the ***Clinical Oncology.*** *January 2021.*

Purpose: We performed an open-label randomized controlled phase III study comparing treatment outcome and toxicity between radiotherapy (RT) with concomitant cisplatin versus concomitant cetuximab in patients with locoregionally advanced head and neck squamous cell carcinoma (HNSCC; stage III-IV according to the Union for International Cancer Control TNM classification, 7th edition).

Materials and methods: Eligible patients were randomly assigned 1:1 to receive either intravenous cetuximab 400 mg/m2 1 week before start of RT followed by 250 mg/m2/wk, or weekly intravenous cisplatin 40 mg/m2, during RT. RT was conventionally fractionated. Patients with T3-T4 tumors underwent a second random assignment 1:1 between standard RT dose 68.0 Gy to the primary tumor or dose escalation to 73.1 Gy. Primary end point was overall survival (OS) evaluated using adjusted Cox regression analysis. Secondary end points were locoregional control, local control with dose-escalated RT, pattern of failure, and adverse effects.

Results: Study inclusion was prematurely closed after an unplanned interim analysis when 298 patients had been randomly assigned. At 3 years, OS was 88% (95% CI, 83% to 94%) and 78% (95% CI, 71% to 85%) in the cisplatin and cetuximab groups, respectively (adjusted hazard ratio, 1.63; 95% CI, 0.93 to 2.86; P = .086). The cumulative incidence of locoregional failures at 3 years was 23% (95% CI, 16% to 31%) compared with 9% (95% CI, 4% to 14%) in the cetuximab versus the cisplatin group (Gray's test P = .0036). The cumulative incidence of distant failures did not differ between the treatment groups. Dose escalation in T3-T4 tumors did not increase local control.

Conclusion: Cetuximab is inferior to cisplatin regarding locoregional control for concomitant treatment with RT in patients with locoregionally advanced HNSCC. Additional studies are needed to identify possible subgroups that still may benefit from concomitant cetuximab treatment.

Strengths:

- Well-designed, adequately powered, multicenter phase III trial data comparing cetuximab to cisplatin based chemoradiotherapy.
- Clear advantage in locoregional control for cisplatin despite only 48% of patients in that arm receiving the recommended dose.
- Similar toxicity burden for the treatment arms.

Weaknesses:

- Largely a study of p16+ OPSCC patients (76%) thus confirming already seen inferior outcomes in HPV + oropharynx cancer with cetuximab-based chemoradiation in other phase III trials. Too few p16 negative patients to draw conclusions, but no major difference seen within that subgroup. Outcomes largely driven by the p16 + patients.
- Prematurely stopped study prevented analysis of the secondary question whether dose escalation to 73 Gy at the primary site improved outcomes for advanced T stage patients. Dose escalation did, however, seem to help in the cetuximab arm which further substantiates that the tumor response is largely driven by the radiation in patients receiving that agent.
- 7th edition staging.

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To Vaccinate or Not to Vaccinate: Should Adults Aged 26 to 45 Years Receive the Human Papillomavirus Vaccine?

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*From the **Laryngoscope.** January 2021.*

Background: The human papillomavirus (HPV) vaccine has been available in the United States (U.S.) since 2006 and was first approved by the Food and Drug Administration (FDA) for both men and women aged 9 to 26 years; this was increased to age 9 to 45 years in 2018. Despite FDA approval, the Advisory Committee on Immunization Practices (ACIP) did not recommend

routine vaccination for adults due to the rationale that the vaccine is most effective before any exposure to HPV has occurred, and several cost-effectiveness analyses have demonstrated little additional benefit in vaccinating adults on a population level. However, the number of new oropharyngeal cancer cases per year now outnumbers cases of cervical cancer in the U.S. and affect more men than women.

Clinical question: Despite the ACIP statement, should we be recommending HPV vaccination for our adult patients aged 26 to 45 years?

Evidence: 4 significant studies.

1. **Randomized controlled trial**. The VIVIANE (human papillomaVIrus: Vaccine Immunogenicity and Efficacy; clinical trial NCT00294047)[1] This phase 3, double-blind, randomized control trial included 4,917 women (90% 26–45 years old) followed over 7 years and focused on cervical cytology and serology for HPV.

Results: 50 to 70% efficacy in reducing both persistent infection over 6 months and low-grade squamous intraepithelial cervical lesions in the total vaccinated cohort, regardless of prior HPV status. The rate of serious adverse vaccine events were low in both vaccinated and control groups (0.2% and 0.3%, respectively).

Conclusion: The authors concluded that adult women do benefit from HPV vaccination, even if they may have had previous HPV infections.

2. **Retrospective cohort study**. Kang et al., 2013.[2] 737 female patients aged 20 to 45 years over a median 3.5 year period, all with high-grade cervical intraepithelial neoplasia (CIN) who had undergone a loop electrosurgical excision procedure for the lesion (LEEP). All of these patients presumably had already been exposed to HPV given their cervical pathology. 49% of the patients received the quadrivalent HPV vaccine after the LEEP, and 51% did not.

Results: Overall, the recurrence rate of CIN was 4.9%. Among recurrences caused by oncogenic HPV types 16 and 18 covered in the vaccine, 2.5% recurrence was seen in the vaccinated group versus 8.5% in the nonvaccinated group ($P < .01$). On multi-variate analysis, the authors demonstrated that an unvaccinated HPV status after LEEP was an independent risk factor for recurrent CIN.

Conclusion: The HPV vaccine can be considered to help reduce the risk of recurrent premalignant lesions in women who have already been infected by HPV.

3. **Retrospective cross-sectional analysis of survey data**. Chaturvedi et al.[3] used the National Health and Nutrition Examination Surveys from 2011 to 2014 to investigate men and women aged 18 to 33 years who had undergone screening for oral HPV. Oral infection = presence of HPV DNA in oral rinses.

Results: 18.3% had received at least one dose of the quadrivalent HPV vaccine (29.2% of women and only 6.9% of men). Prevalence of oral HPV infection with types 16, 18, 6, and 11 was significantly reduced in the vaccinated (even partially vaccinated) group (from 0.11% vs.

1.61% among the unvaccinated, *P* = .008), and also significantly reduced in vaccinated men (0.0% vs. 2.13%, *P* = .007).

4. **Prospective cohort study**: Parker et al.[4] reported findings of the multi-institutional Mid-Adult Men Trial Study of 150 men aged 27 to 45 years, immunized with the quadrivalent HPV vaccine and followed for 30 months.

Results: Antibodies against HPV 16 and 18 in the oral cavity (samples obtained from oral rinses) and serum peaked at 1 month after completing the three-dose vaccine series, and although those in the oral cavity decreased over time, seropositivity persisted for 2 years after vaccination in 98% and 80% of individuals against HPV types 16 and 18, respectively.

Conclusion: This study illustrated that the HPV vaccine generated a durable immune response even in adult men.

Recommendation: The current HPV vaccine is safe and proves efficacious in both adult women and men aged over 26 years, even in individuals with prior HPV exposure as supported by gynecologic and head and neck literature. **We should be recommending the HPV vaccine to our all our adult patients aged 26 to 45 years who have not yet been vaccinated.**

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Do predetermined surgical margins compromise oncological safety in computer-assisted head and neck reconstruction?

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*From the **Oral Oncology.** December 2020.*

Abstract Objectives: Computer assisted head and neck reconstruction has gained popularity over the past few years. In computer assisted surgery (CAS), surgical margins are predetermined in virtual surgery and resection guides are designed to be fitted intra-operatively. However, concerns have been raised regarding the oncological safety of predetermined surgical margins. Therefore, the aim of this study was to compare surgical margins, recurrence and survival outcomes in patients underwent CAS and non-CAS in head and neck reconstruction. Methods: We retrospectively reviewed the patients underwent oral and maxillofacial malignancies surgical excision and free flap reconstruction from October 2014 to December 2019 by the same chief surgeon. Patients were divided into two groups depending on whether CAS and predetermined surgical margins were adopted. The primary outcome was surgical resection margin and the secondary outcomes included recurrence and survival.

Results: A total of 66 subjects were recruited with 37 in the CAS group and 29 in the non-CAS group. The follow-up rate was 100%. The average follow-up time was 24.5 months. No significant difference in resection margin was identified between the groups (p = 0.387). Tumor staging, margin status, perineural invasion, lymphovascular invasion and extra nodal extension were identified as significant factors influencing survival.

Both before and after adjustment for these prognostic factors identified, CAS and non-CAS group showed no significant difference in survival outcome.

Conclusion: Predetermined surgical margins do not compromise oncological safety in terms of resection margin, disease recurrence and patient survival.

Strengths:

- Since 1995, the use of computer-assisted surgery and navigation has been described in head and neck oncology. In the last decade it has provided anatomical and diagnostic precision. This meta-analysis shows that computerized surgery represents surgical safety with anatomical orientation in real time, reduces surgery time, reconstruction precision, being a safe and desirable technique, this study prefigures as a contribution substantial and qualified scientist.
- It debuts as one of the first studies to investigate and compare the resection margin, recurrence pattern and survival outcomes with or without predetermined surgical margins in head and neck reconstruction, indicating that computer and non-computer-assisted surgery, produces similar clinical results in terms of resection margins, tumor recurrence, and survival.
- Compared with the other retrospective studies of computer-assisted surgery, this meta-analysis compared the state of the margins, the pattern of recurrence and survival in two groups with a similar level of surgical technique and adjuvant cancer therapy, demonstrating similar clinical results in both groups.
- This meta-analysis suggests that the optimization of the procedure consists of the incorporation of magnetic resonance and / or PETCT with tomography data in the planning of virtual surgery, three-dimensional intraoral exploration, intraoral digital exploration of the teeth and the tumor, merging and making 3D models for virtual surgical planning, which facilitates a direct and clear view of the tumor extension that can increase the precision for virtual planning, especially when the insertion of dental implants is planned preoperatively, allows to carefully evaluate the various types of images, which leading to better planned resection margins at precise positions, which can reduce errors in judgment during surgery; For this reason, the learning curve of young surgeons should be aimed at optimizing planning, which is established between two weeks between the taking of images and the actual surgery, which provides sufficient training and extensive experience for the surgical planning team.

Weaknesses:

- Limitation in the small number of cases with positive resection margins and tumor recurrence that could compromise statistical power. However, with this sample size, it was possible to identify all the adverse prognostic factors suggested by NCCN in the 2020 Guideline, including advanced disease staging, near / positive margin, perineural invasion, lymphovascular invasion, and extra nodal extension ($p = 0.002 - 0.035$ only in extra nodal extension), while the multivariate analysis of overall survival, disease-free survival, disease-specific survival, and local recurrence-free survival, in the two groups, was not detected with significant differences (all $p > 0.05$). This can demonstrate the reliability of statistical data and analysis.

- In all cases, an intraoperative frozen section of the tumor bed was performed. The closest distances from the resection margins to the tumor invasion fronts reported in the current study were related to the soft tissues, the pathology reports only indicated 'positive / negative' for the bone margins without indicating the closest distance.
- It has the limitation of retrospective studies in demographic history and clinicopathological characteristics.