

A Phase I Randomized Controlled Trial of Intratumoral Lidocaine Injection Before Transoral Robotic Surgery (TORS) and Neck Dissection for HPV-Associated Oropharyngeal Squamous Cell Carcinoma

Regulatory Sponsor: Ryan M. Carey, MD
University of Pennsylvania
Department of Otorhinolaryngology – Head & Neck Surgery
5th Floor Ravdin Bldg
3400 Spruce Street
Philadelphia, PA 19104
(610)-790-9202
Ryan.Carey@pennmedicine.upenn.edu

Sub-Investigators: Radiation Oncology: Alexander Lin, MD
Otorhinolaryngology: Robert M. Brody, MD
Otorhinolaryngology: Gregory S. Weinstein, MD
Otorhinolaryngology: Devraj Basu, MD, PhD
Otorhinolaryngology: Karthik Rajasekaran, MD
Pathology: Timothy Chao, MD, PhD

Biostatistics: Xingmei Wang, MS

Protocol Number: 856397

UPCC Number: 12324

CONFIDENTIAL

This document is confidential and the property of the University of Pennsylvania. No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorization from the study sponsor.

Table of Contents

STUDY SUMMARY	3
1 INTRODUCTION	6
2 STUDY OBJECTIVES	9
3 STUDY DESIGN	9
4 SUBJECT SELECTION AND WITHDRAWAL.....	10
5 STUDY PROCEDURES	13
6 STATISTICAL PLAN	16
7 SAFETY AND ADVERSE EVENTS.....	17
8 DATA HANDLING AND RECORD KEEPING	21
9 DATA AND SAFETY MONITORING PLAN.....	22
10 ETHICAL CONSIDERATIONS	23
11 STUDY FINANCES	24
12 PUBLICATION PLAN	25
13 REFERENCES	25

List of Abbreviations

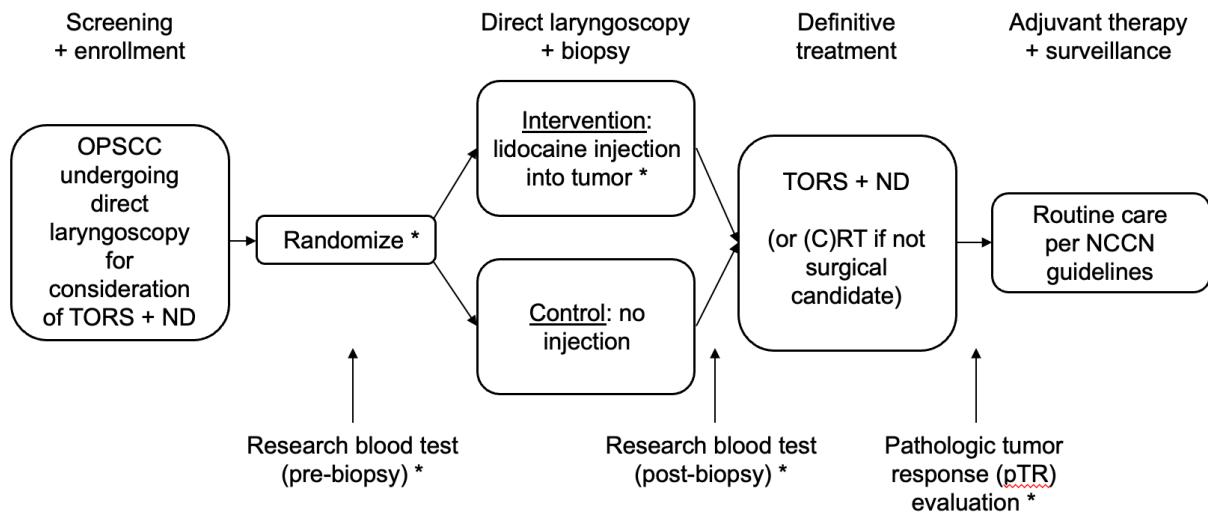
Oropharyngeal squamous cell carcinoma	OPSCC
Human papillomavirus	HPV
Transoral Robotic Surgery	TORS
Chemoradiotherapy	CRT
Intensity-modulated radiation therapy	IMRT
Perineural invasion	PNI
Extranodal extension	ENE
Quality of Life	QOL
Bitter taste receptor	T2Rs
Voltage gated sodium channel	VGSC
Pathologic tumor response	pTR

Study Summary

Title	A Phase I Randomized Controlled Trial of Intratumoral Lidocaine Injection Before Transoral Robotic Surgery (TORS) and Neck Dissection for HPV-Associated Oropharyngeal Squamous Cell Carcinoma
Short Title	Intratumoral Lidocaine Injection Before Oropharyngeal Cancer Surgery
Protocol Number	
Phase	Phase I
Study Duration	2-years
Study Center(s)	Single-center
Objectives	<p><i>Primary:</i> To determine if intratumoral lidocaine injection prior to TORS and neck dissection for HPV associated OPSCC is 1) safe and 2) causes a major pathologic treatment effect.</p> <p><i>Secondary:</i> To determine if intratumoral lidocaine injection prior to TORS and neck dissection for HPV associated OPSCC improves the locoregional control rates, progression-free survival, metastasis-free survival, and overall survival.</p>
Number of Subjects	30 evaluable subjects
Diagnosis and Main Inclusion Criteria	<ul style="list-style-type: none"> - ≥18 years old with OPSCC undergoing direct laryngoscopy for consideration of TORS and neck dissection.
Study Regimen	<ul style="list-style-type: none"> - Patients will be randomized and blinded to intratumoral injection of 1% lidocaine (intervention arm) or no injection (control arm) at the time of direct laryngoscopy and biopsy prior to TORS and neck dissection. <ul style="list-style-type: none"> o Intervention arm: While under general anesthesia after direct laryngoscopy with biopsy, 1% lidocaine will be injected under direct visualization (not exceeding the maximum tolerated dose of 4.5 mg/kg body weight) into the primary tumor with the aim to distribute the lidocaine evenly into the tumor. o Control arm: Direct laryngoscopy with biopsy with no injection. - Blood samples will be obtained before and after direct laryngoscopy/study intervention. - Pathologic tumor response (pTR) will be determined from surgical specimens.

Statistical Methodology	<p>This is a patient-blinded, randomized phase I study assessing safety, pathologic treatment effects, and oncologic outcomes from intratumoral lidocaine injection vs no injection at the time of direct laryngoscopy prior to TORS and neck dissection for HPV associated OPSCC. The total sample size is estimated to be 30 patients total (split approximately equally between the two groups). The proportion of patients with a pathologic tumor response (pTR) $\geq 50\%$ (pTR-2) in the primary tumor following surgical resection will be compared between intervention and control arms using a one-sided Fisher's exact test with a significance level of 0.05. The 2-year locoregional control (LRC) rates, progression-free survival (PFS), metastasis-free survival (MFS), and overall survival (OS) will be estimated using the Kaplan–Meier method and compared using log-rank test between the two arms.</p>
-------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Study Schema



Primary endpoints: 1) safety, 2) proportion of patients with pTR-2

Secondary endpoints: 2-year LRC, MFS, PFS, OS

* Denotes trial-related (i.e., not institutional standard of care)

1 Introduction

Based on evidence that lidocaine may activate apoptosis in cancer cells and/or limit metastasis, this randomized phase I study will establish the safety and efficacy of intratumoral lidocaine injection at the time of direct laryngoscopy prior to TransOral Robotic Surgery (TORS) and neck dissection for oropharyngeal squamous cell carcinoma (OPSCC). The primary objective of the study is to determine if intratumoral lidocaine injection is safe and causes a major pathologic treatment effect in the primary tumor following surgical resection. The secondary objectives will be to determine if intratumoral lidocaine injection improves locoregional control (LRC) rates, progression-free survival (PFS), metastasis-free survival (MFS), and overall survival (OS) compared to no injection (standard of care).

Background

Oral squamous cell carcinomas, which are located in the oral cavity and pharynx, accounted for roughly 50,000 new cancer diagnoses in the US in 2020 with an anticipated increase to 76,000 by 2040.¹ The increase in incidence is predominantly attributed to the rise in human papillomavirus (HPV)-associated OPSCCs which now represent most OPSCC cases and typically occur in the tonsils or base of tongue.² Compared to HPV-negative OPSCCs, HPV associated OPSCCs tend to have relatively higher nodal burden at presentation and generally affect younger patients with higher performance status and fewer co-morbid conditions.^{3, 4} Treatment for OPSCCs is selected based on the clinical and pathologic features and typically includes either definitive chemoradiation or surgery (TORS and selective neck dissection) followed by adjuvant radiation (+/- chemotherapy).⁵⁻⁸ Candidacy for TORS is typically assessed with direct laryngoscopy (with biopsy when indicated) to help evaluate the tumor extent and relevant anatomy. Primary surgery or primary radiation for HPV associated OPSCC both allow for favorable disease control (>95% LRC rates) and OS (~90% 3-year OS);⁹⁻¹³ however, a subset of patients recur and are unable to be successfully salvaged.^{13, 14} Furthermore, the available treatments have associated toxicities including life-threatening sequelae or side-effects that impact quality of life (QoL) such as dysphagia, xerostomia, dysgeusia, neck fibrosis, and chronic pain.¹⁵⁻¹⁸ Several completed and ongoing de-escalation trials have sought to limit treatment-related morbidity by de-intensifying therapy for HPV associated OPSCC.¹⁹⁻²² However, there is a clear need for novel therapies with low side-effect profiles to improve disease outcomes while maintaining QoL.

Study Rationale, Preliminary Data, and Significance

Lidocaine, a commonly used local anesthetic, has potential relevance for OPSCC treatment through its activation of bitter taste receptors (T2Rs) and inhibition of voltage gated sodium channels (VGSCs). T2Rs are G-protein-coupled receptors (GPCRs) that bind bitter agonists and are best known for their gustatory role on the tongue²³. These receptors are also

expressed in other normal tissues throughout the body where they serve a diverse array of chemosensory and immune functions.²⁴⁻²⁹ More recently, T2Rs have been investigated in several cancers including GI,³⁰⁻³⁶ pancreatic,^{37, 38} breast,³⁹ thyroid,⁴⁰ acute myeloid leukemia,⁴¹ and head and neck squamous cell carcinoma including HPV associated OPSCCs.⁴² T2Rs in head and neck squamous cell carcinoma cells are activated by bitter compounds which trigger downstream Ca^{2+} responses, mitochondrial depolarization, caspase activation, and apoptosis.⁴² T2R expression levels have been shown to correlate with survival in head and neck squamous cell carcinomas⁴² and several other solid tumors including lung, prostate, and esophageal cancer.⁴³ Of the 25 T2R isoforms in humans, T2R14 is being studied most actively.^{24, 44, 45} Interestingly, the local anesthetic lidocaine is a bitter agonist for T2R14.⁴⁶ In head and neck squamous cell carcinoma, lidocaine decreases cancer viability, depolarizes the mitochondrial membrane potential, elevates mitochondrial reactive oxygen species, induces apoptosis, and can inhibit the proteasome in a T2R14-dependent manner.⁴⁷ Furthermore, analysis of The Cancer Genome Atlas (TCGA) data suggests that T2R14 expression is increased in HPV associated OPSCCs compared to HPV-negative OPSCCs.

In addition to the newly described T2R14-mediated effects and increased receptor expression in HPV associated OPSCCs,⁴⁷ lidocaine has been shown to also have beneficial effects in certain cancer types through its inhibitory effects on VGSCs.⁴⁸⁻⁵⁶ VGSCs have been shown to be expressed in human cancers including prostate⁵⁷, breast cancer,⁵⁸⁻⁶⁰ and head and neck squamous cell carcinoma.⁵⁴⁻⁵⁶ It has been suggested that VGSCs are involved in oncogenic processes and are associated with metastatic behavior.⁴⁸⁻⁵⁶ For example, sodium channel protein type 5 subunit alpha, also known as Nav1.5, is highly expressed in head and neck squamous cell carcinomas and associated with TNM stage, lymph node metastasis, and other clinical features. *In vitro* inhibition of Nav1.5 promotes apoptosis and decreases proliferation, migration, and invasion. Additionally, Nav1.5 is thought to potentially be involved in the progression of head and neck squamous cell carcinomas through the Wnt/β-catenin signaling pathway.⁵⁶ To our knowledge, there are no published studies evaluating oncologic outcomes for the *in vivo* clinical use of local anesthetics such as lidocaine in patients with OPSCC, though these drugs have been studied in other solid tumors including breast cancer.^{48, 52, 61, 62}

In vitro inhibition of VGSCs in breast cancer has been shown to reduce cell proliferation, motility, and invasion while encouraging focal adhesion, potentially reducing the metastatic capability of primary tumors.⁶⁰ Clinical studies in patients undergoing breast cancer tumor resection suggested possible improved outcomes with use of local anesthetic, specifically lidocaine, at the primary tumor site.⁶³⁻⁶⁵ These observations led to the design of a recently published randomized controlled trial in the *Journal of Clinical Oncology* assessing the effect of lidocaine infiltration around the primary breast tumor prior to surgical resection in women with early breast cancer. This multi-institutional trial of nearly 1600 patients

demonstrated significantly increased 5-year DFS (86.6% vs 82.6%) and OS (90.1% and 86.4%) in the peritumoral lidocaine injection group compared to the no injection group.⁶⁶

Surgery for solid tumors is known to modify gene expression and metastatic potential, cause dissemination of tumor cells, stimulate growth of micrometastasis, and inhibit the immune system.⁶⁷⁻⁷² Simple interventions before or during oncologic surgery that can improve outcomes and potentially reduce metastasis are appealing, especially when they are not particularly time-consuming or expensive. Injection of local anesthetic such as lidocaine (with or without vasoconstrictive agents like epinephrine) is already commonly used during head and neck surgery to reduce general anesthetic requirements and provide hemostasis.⁷³ Therefore, lidocaine injection into the primary tumor in OPSCC would likely be easy to implement at the time of direct laryngoscopy while a patient is already under general anesthesia. Given the potential oncologic benefits and limited side-effects, intratumoral lidocaine injection may be particularly beneficial in HPV associated OPSCC prior to definitive TORS and neck dissection.

Dosing Rationale

Subcutaneous injection of 1% lidocaine (40 mM) is frequently used for local anesthesia during surgical operations and minor procedures.⁷³ Concentrations of lidocaine lower than 1% or 40 mM (including 10 mM) were sufficient to decrease head and neck SCC viability and cell proliferation and induce apoptosis *in vitro*; this effect was reduced or lost at lower concentrations of 5 mM or 1 mM.⁴⁷ The previously referenced breast cancer randomized controlled trial demonstrated that 1% lidocaine injected around the primary tumor was associated with ~4% higher DFS and OS compared to no injection.⁶⁶ Therefore, the current study will use 1% lidocaine injected under direct visualization (not exceeding the maximum tolerated dose of 4.5 mg/kg body weight) into the primary tumor with the aim to distribute the lidocaine evenly into the tumor. The maximum tolerated dose of 1% lidocaine (4.5 mg/kg body weight) is ~31.5 mL total for a 70 kg person.

Most tumors are stage T1 or T2 with greatest dimension 2 or 4 cm, respectively. A spherical tumor with diameter of 2 cm corresponds to a volume of 4.2 mL. A spherical tumor with diameter of 4 cm corresponds to a volume of 33.5 mL. However, in our experience injecting oropharyngeal tumors or abscesses with lidocaine for anesthetic purposes for biopsy or drainage, respectively, it is typically not feasible to inject more than 10 mL before the injection begins to extravasate from the tissues, likely due to the anatomic constraints of the oropharynx. A total volume of 10 mL is significantly lower than the maximum tolerated dose of 1% lidocaine (31.5 mL for a 70 kg individual). Therefore, tumors will be injected with 1% lidocaine until the injection appears to be evenly distributed into the tumor and begins to extravasate, with a total volume not to exceed 10 mL. The exact volume injected will be recorded for each subject. Notably, the previously referenced breast cancer clinical trial with 1600 patients reported no adverse events related to lidocaine injection.⁶⁶

Biological Correlate for Early Evaluation of Intervention: Pathologic Tumor Response

Advancements in neoadjuvant therapies have led to several systems for evaluating the pathologic treatment response in tumors following surgical removal. Pathological complete response (pCR, eradication of all cancer cells) and major pathologic response (MPR, presence of $\leq 10\%$ viable tumor cells) are commonly used as surrogate clinical markers for predicting long-term survival.⁷⁴⁻⁷⁷ Despite being regarded as the “gold standard” for immunotherapy, pCR and MPR do not fully consider the varying degrees of treatment response within the tumor that may influence clinical outcomes. Therefore, some researchers have also implemented a metric known as the pathological tumor response (pTR) defined as the presence of tumor cell necrosis, keratinous debris, and giant cell/histiocytic reaction, quantified as a percentage of the overall tumor bed (area pathologic response/area pathologic response plus viable tumor).^{78, 79} The calculated pTR rate is scored in increments of 10% and often grouped into pTR-0 ($\leq 10\%$), pTR-1 ($\leq 10-49\%$), and pTR-2 ($\geq 50\%$) to categorize the degree of response. Recent clinical trials in HPV associated OPSCC have successfully used pTR rates as primary endpoints for assessing responses to neoadjuvant pembrolizumab.⁷⁸ pTR scoring will serve as an early metric for evaluating the study intervention.

2 Study Objectives

2.1 Primary Objectives

Determine if intratumoral 1% lidocaine injection at the time of direct laryngoscopy prior to TORS and neck dissection for HPV associated OPSCC is safe and causes a major pathologic treatment effect.

2.2 Secondary Objectives

Determine if intratumoral 1% lidocaine injection at the time of direct laryngoscopy prior to TORS and neck dissection for HPV associated OPSCC improves the locoregional control rates, progression-free survival, metastasis-free survival, and overall survival compared to no injection.

3 Study Design

3.1 General Design

This is a phase I patient-blinded, randomized controlled trial evaluating intratumoral lidocaine injection prior to definitive surgery in HPV associated OPSCC. Patients with OPSCC undergoing direct laryngoscopy who are being considered for definitive TORS

and selective neck dissection, will be eligible. Patients will be randomized and blinded to intratumoral injection of 1% lidocaine (intervention arm) or no injection (control arm) at the time of direct laryngoscopy. After administration of general anesthesia and biopsy, lidocaine will be injected under direct visualization (not exceeding the maximum tolerated dose of 4.5 mg/kg body weight) into the primary tumor. The control arm will receive no injection.

Blood samples will be obtained prior to direct laryngoscopy/study intervention (pre-biopsy) and again after the intervention (post-biopsy). The pTR rate (defined above and in published literature^{78, 79}) will be determined by the designated study pathologist (Timothy Chao, MD, PhD) with head and neck expertise using increments of 10% for the biopsy and surgery specimens. The scores will be grouped as pTR-0 (<10%), pTR-1 (10%–49%), and pTR-2 (≥50%).

Patients will otherwise receive institutional standard of care treatment including TORS primary site resection, selective neck dissection, and additional indicated adjuvant radiation therapy with or without chemotherapy. All enrolled patients will be assessed for safety measured by adverse events. If a patient does not ultimately receive primary surgery following their direct laryngoscopy/study intervention (based on surgical candidacy, patient preference, or other reasons), then they will not be counted as an evaluable subject, as the primary endpoint pTR requires a surgical specimen for evaluation. If a patient is determined to have a pathology other than HPV associated OPSCC after their direct laryngoscopy, then they will not be counted as an evaluable subject.

3.2 Primary Study Endpoints

- 1) Safety measured by occurrence of adverse events.
- 2) Pathological tumor response (pTR) in the primary tumor following surgical resection.

3.3 Secondary Study Endpoints

2-year locoregional control rates, progression-free survival, metastasis-free survival, and overall survival.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- 4.1.1 Patients ≥ 18 years old.**

- 4.1.2** Histologically confirmed diagnosis of squamous cell carcinoma of the oropharynx or neck.
- 4.1.3** Clinical T1, T2, T3, or T4 stage disease of the oropharynx (per AJCC 8th Ed).
- 4.1.4** Any clinical N stage disease (per AJCC 8th Ed).
- 4.1.5** Patients must be undergoing direct laryngoscopy +/- biopsy at the University of Pennsylvania as part of their work-up for consideration of definitive TORS and selective neck dissection.
- 4.1.6** Patients must sign an informed consent document that indicates they are aware of the investigational nature of the treatment in this protocol as well as the potential risks and benefits.
- 4.1.7** Ability to understand and the willingness to provide written informed consent.

4.2 Exclusion Criteria

- 4.2.1** Prior external beam radiation therapy to the head and neck.
- 4.2.2** Prior chemotherapy for head and neck cancer.
- 4.2.3** Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery (i.e. AJCC 7th Ed. T4b for OPSCC).
- 4.2.4** Presence of distant metastatic disease.
- 4.2.5** Uncontrolled inter-current illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, connective tissue disease or psychiatric illness/social situations that would limit compliance with study requirements.
- 4.2.6** Known history of hypersensitivity to lidocaine or other amide local anesthetics.
- 4.2.7** Pregnant or breastfeeding.

4.3 Patient Selection and Inclusion

OPSCC is now the most common head and neck cancer diagnosed in the United States

with most cases attributed to HPV. HPV associated OPSCC is most frequently seen in middle-aged, white males (not Hispanic or Latino). We expect to have similar eligibility and enrollment demographics as other published trials on HPV associated OPSCC. For reference, RTOG 1016, which compared radiotherapy with cetuximab vs cisplatin, is the largest published randomized trial of HPV associated OPSCC in the United States with the following study demographics:⁸⁰

	IMRT + Cisplatin (n=406)	IMRT + Cetuximab (n=399)	Total (n=805)
Age (years)			
≤ 65	344 (85%)	345 (86%)	689 (86%)
> 65	62 (15%)	54 (14%)	116 (14%)
Mean (standard deviation)	57.7 (8.1)	57.4 (7.8)	57.6 (8.0)
Median (1 st - 3 rd quartile)	58 (52-63)	58 (52-63)	58 (52-63)
Min - max	33 - 83	33 - 80	33 - 83
Gender			
Male	373 (92%)	355 (89%)	728 (90%)
Female	33 (8%)	44 (11%)	77 (10%)
Race			
White	380 (94%)	367 (92%)	747 (93%)
Black or African American	17 (4%)	19 (5%)	36 (4%)
Other	2 (<1%)	8 (2%)	10 (1%)
Unknown	7 (2%)	5 (1%)	12 (1%)
Ethnicity			
Hispanic or Latino	11 (3%)	15 (4%)	26 (3%)
Not Hispanic or Latino	383 (94%)	369 (92%)	752 (93%)
Unknown	12 (3%)	15 (4%)	27 (3%)

4.4 *Subject Recruitment and Screening*

Subjects will be recruited from the practices of Otorhinolaryngology and Radiation Oncology at the University of Pennsylvania. The study CRC will verify eligibility using the criteria outlined in Section 4.1 and 4.2. Patients will be consented either in clinic or in the hospital.

4.5 *Clinical Evaluation and Staging Criteria*

- History and physical examination:
 - Primary tumor extent will be documented by the head and neck surgeon, with a particular focus on the degree (if any) of involvement of the soft palate and/or base of tongue.
- Laboratory studies:
 - HPV status will be determined based on p16-positivity by immunohistochemistry or HPV-positivity by in-situ hybridization.
 - Research blood tests will be drawn 1) prior to direct laryngoscopy/study intervention and 2) after the direct laryngoscopy/study intervention (but before definitive treatment).
- Pathologic evaluation
 - In addition to standard pathologic evaluation of biopsy and surgical

specimens, pTR will be calculated and categorized as pTR-0 ($\leq 10\%$), pTR-1 ($\leq 10-49\%$), and pTR-2 ($\geq 50\%$) by the designated study pathologist (Timothy Chao, MD, PhD).

- Staging imaging studies will be dictated by standard of care.
- Eligibility for this study will be according to AJCC 7th and 8th Edition staging. AJCC 7th Edition staging data will be collected and recorded in the electronic medical record (Epic) for all patients as this staging is currently being used clinically to determine indications for adjuvant radiotherapy.

4.6 Off-Study Criteria

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the subject's health, the subject will be removed from protocol therapy. In this event, the reasons for withdrawal will be documented if possible.
- Subject's refusal to continue treatment or decision for non-surgical treatment: In this event, the reasons for withdrawal or decision for non-surgical treatment will be documented if possible.
- Patients may be taken off study at any time at the discretion of the Principal Investigator.

4.7 Study Duration

With an estimated accrual of 1-2 patients per month, it is anticipated that accrual will continue for approximately 2-years. The anticipated accrual rate is based on accrual to our prior TORS trial protocols. We find that most of our patients with HPV associated OPSCC are highly motivated to enroll on clinical trials, as they are often referred to Penn Medicine specifically for that reason.

5 Study Procedures

5.1 General study design

Patients will be enrolled to reach 30 evaluable subjects on this phase I patient-blinded, randomized controlled trial investigating the feasibility and safety of intratumoral 1% lidocaine injection at the time of direct laryngoscopy prior to definitive surgery in HPV associated OPSCC patients. Patients with a clinically apparent primary tumor (i.e. clinical T1-T4), any clinical N stage, and M0 disease (per AJCC 8th Edition) undergoing direct laryngoscopy who are being considered for definitive TORS and selective neck dissection, will be eligible. Patients will be blinded to the intervention which will be administered as dictated by the protocol, according to Section 3.1 above. Randomization will be performed using the “Clinical Trial Randomization Tool” from The National Cancer Institute's Division of Cancer Prevention.⁸¹

Clinical evaluations will be performed according to routine clinical care, which is left to the discretion of the treating physician. This will include a baseline evaluation prior to direct laryngoscopy/study intervention.

All patients will be asked to take a short survey about pain (2 questions) at their follow up appointment after their direct laryngoscopy and biopsy.

Locoregional recurrence will be defined as biopsy-proven recurrent squamous cell carcinoma at the original, primary tumor site, or in the neck.

5.2 *Surgery*

Surgery will be performed per standard of care consisting of TORS primary site resection, selective neck dissection, and external carotid artery vessel ligation. The decision to stage the neck dissection and TORS will be determined at the discretion of the head and neck surgeon. Intraoperative continuous monitoring of circulation and respiration will be performed.

5.3 *Radiation Therapy*

Patients who have indications post-operative radiation therapy per NCCN guidelines⁵ will be referred to a radiation oncologist who specializes in the treatment of head and neck cancer within the University of Pennsylvania Health System, with the decision on whether to treat with radiation therapy determined at the discretion of the consulting radiation oncologist.

If the patient meets eligibility criteria for the published AVOID trial which is institutional standard of care for HPV associated OPSCC,¹⁹ then the primary site will be spared, without compromising coverage to the neck volumes. The eligibility for this approach is patients with pT1-T2, negative margins (defined as ≥ 2 mm), no perineural invasion (PNI), and no lymph-vascular space invasion (LVSI).

Simulation for treatment is required. CT-based treatment planning is required. Treatment with either IMRT or PBT is allowed. All fields will be treated every session. Interruptions in therapy should be discussed with the principal investigator but will be instituted at the discretion of the treating radiation oncologist. Dose calculation should be performed using inhomogeneity corrections to account for differences in tissue density across the head and neck region. Patients may miss up to three treatments a week due to illness, travel, etc.

5.4 *Chemotherapy*

Patients who have indications for the use of concurrent chemotherapy in the postoperative setting (ENE or positive margins)⁸² will be referred to a medical oncologist who specializes in the treatment of head and neck cancer within the University of Pennsylvania Health System, with the decision on whether to treat with chemotherapy determined at the discretion of the consulting medical oncologist.

5.5 *Blood Draws*

Research blood draws will be obtained at the following time points:

- 1) Prior to direct laryngoscopy/study intervention on the day of surgery. This will typically be performed in the preoperative area or operating room when obtaining an IV for surgery.
- 2) After direct laryngoscopy/study intervention (but before definitive surgery or radiation). This will typically be performed on the day of the post-laryngoscopy clinic visit to discuss the results of the direct laryngoscopy.

Other blood draws will be obtained according to institutional standard of care.

5.6 *Sample Storage*

Tumor tissue from biopsy and surgery or other collected samples (e.g., blood, serum) may be used or stored for any other future relevant analysis. Specific technical studies in the future could include pathology, immunohistochemical, genetic, genomic, proteomic, or transcriptomic analyses. The tissue may include paraffin blocks or fresh tissue that is frozen.

5.7 *Study Visit Schedule*

An outline of the typical study visit schedule is provided below. There will be no planned additional study visits compared to routine, standard of care (SOC). Clinical research procedures are underlined in the table for clarification purposes.

Visit Number	Visit Procedures
Visit 1	Come to the clinic for a routine (SOC) clinic visit(s). <u>Decide if you want to participate in the study, ask questions, sign the consent form if you do want to participate.</u>
Visit 2	<u>Have a pre-operative research blood draw with blood sample storage on the day of your direct laryngoscopy with biopsy.</u>

	<p>Study Intervention: Participants will be randomly assigned to two groups.</p> <ul style="list-style-type: none"> • <u>Group 1 (Intervention Arm)</u> – Biopsy and injection of lidocaine into tumor while you are under general anesthesia for your direct laryngoscopy. • <u>Group 2 (Control Arm)</u> – Biopsy without injection of lidocaine while you are under general anesthesia for your direct laryngoscopy.
Visit 3	Routine (SOC) clinic visit to discuss the results of your direct laryngoscopy with biopsy and <u>have a research study blood draw with blood sample storage</u> . You will also be asked to take a short survey.
Visit 4	Routine (SOC) treatment with primary surgery or primary radiation <u>with storage of tumor tissue for research</u> . This will allow researchers to study leftover tissue removed during your routine care.
Visit 5	Routine (SOC) follow up for cancer surveillance per National Comprehensive Cancer Network guidelines.

6 Statistical Plan

This study is considered exploratory because, to our knowledge, no prior published data exists on the effects of lidocaine injection on pathologic tumor response, survival, and recurrence in HPV associated OPSCC. The planned sample size for this phase I trial is 30 evaluable subjects split equally between the intervention and control arms. Subjects will need to have a definitive diagnosis of HPV associated OPSCC and undergo surgery (TORS and neck dissection) to be considered evaluable.

The co-primary objectives of this study are to determine safety and if the proportion of patients with pTR-2 in the primary tumor is different in the intervention group compared to the control arm. All enrolled participants, regardless of HPV status or final pathology, will be included in the primary safety analysis. Thus, any adverse events or dose-limiting toxicities observed in participants will contribute to the overall safety assessment of intratumoral lidocaine.

For the pathologic response primary endpoint, H_0 is that there is no difference in the proportions of patients with pTR-2 between the intervention or no intervention (control) groups; H_a is that the intervention arm is associated with a higher proportion of pTR-2. The proportion of pTR-2 will be compared between the intervention and control arms using a one-sided Fisher's exact test with a significance level of 0.05. A 95% confidence interval will be used. We estimate that a sample size of 30 patients is needed to allow us to detect

with 80% power at the one-sided alpha level of 0.05 a major pathologic treatment rate of 30% in the intervention arm compared to 0% in the control arm.

In addition to hypothesis testing for the pathologic response primary outcome, we will use within-between interaction models to account for the effects of the treatment and the interaction between treatment and patient and disease factors including age, sex, disease stage, and adverse pathologic features (e.g. tumor grade, perineural invasion, lymphovascular invasion). We will estimate means and standard deviations for each group and the correlation within subjects to better understand the relationship between repeated measures. We will use mixed-effects models to handle within-subject correlations and between-subject comparisons.

The secondary endpoints include 2-year locoregional control (LCR) rates, progression-free survival (PFS), metastasis-free survival (MFS), and overall survival (OS). PFS will be defined as time from random assignment to disease progression or death from any cause. MFS will be defined as time from random assignment to first evidence of distant metastatic disease or death from any cause. OS will be defined as the time from random assignment and death due to any cause. 95% confidence intervals will be used. LRC rates, PFS, MFS, and OS will be estimated using the Kaplan–Meier method, and log-rank test will be used to compare the two groups using a significance level of 0.05.

Due to distinct biological differences between HPV associated and HPV-negative OPSCC and evidence suggesting that lidocaine's anticancer effects may be more relevant to HPV associated tumors, any HPV-negative tumors will be evaluated separately from HPV associated tumors for primary and secondary efficacy endpoints.

An interim analysis is not planned due to the well-established safety data associated with injectable lidocaine.

7 Safety and Adverse Events

7.1 Definitions

Adverse Event

Adverse events (AE) and Serious Adverse Events (SAE) will use the descriptions and grading scales found in the revised **NCI Common Terminology Criteria for Adverse Events (CTCAE)**. This study will utilize the CTCAE v5.0 for adverse event reporting. All appropriate treatment areas will have access to a copy of the CTCAE v5.0 and adverse events will only be collected up until 30 calendar days after completion of the injection. Any AE's which remain unresolved at 30 days post-injection will be assessed for resolution at subsequent standard of care follow-up visits. Intercurrent illnesses or

injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a Serious Adverse Event (SAE)
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

AEs Not to Include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedures is an AE
- Situations where an untoward medical occurrence did not occur (elective and/or convenience admission to hospital)
- Anticipated day-to-day fluctuation of pre-existing disease(s) or condition(s) present or detectable at the start of the study that do not worsen in grade or severity.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Grade 1 adverse events that are expected and related for radiotherapy and chemotherapy, if indicated (listed in the radiation and chemotherapy protocol/consent).
- Abnormal lab values
- Adverse events in patients receiving chemotherapy or radiation therapy for metastasis and/or additional cancers will not be collected.

7.2 *Expedited Adverse Event Reporting*

Common Toxicity Criteria

Toxicity will be evaluated with the NCI Common Toxicity Criteria (CTCAE) v. 5.0.

Serious Adverse Events

A SAE is defined as any of the following:

- Fatal or life-threatening (real risk of dying) event
- Requires or prolongs hospitalization
- Causes persistent or significant disability/incapacity
- Results in a birth defect or congenital anomaly
- Causes cancer

All hospitalizations or prolongation of existing hospitalization for medical events regardless of phase of study, expected or unexpected attributions are SAE's.

Serious, unexpected drug-related adverse events will be reported to the University of Pennsylvania IRB, and the University of Pennsylvania Cancer Center Data and Safety Monitoring Committee (DSMC) using the expedited reporting guidelines as is required by each board.

The toxicities that develop during the standard chemotherapy portion of this trial will not require reporting in an expedited manner.

7.3 *Lidocaine Safety and Adverse Reactions*

The clinical adverse event profile, pharmacokinetics, pharmacodynamics, and toxicology for injectable lidocaine is well-established and readily available from the manufacturer(s) (<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=76176d50-a987-c9f9-e053-2991aa0aea0f&type=display>). Lidocaine is one of the most commonly used local anesthetics with well-established safety data for its use as an anesthetic but does not have proven safety data for use as a cancer therapy. The most common side effects of lidocaine injection are swelling, bruising, or soreness at the injection site, and temporary rapid heartbeat. Lidocaine overdose can cause central nervous system (CNS) effects such as confusion, seizure, or unconsciousness, respiratory depression and/or respiratory arrest, and cardiovascular effects such as cardiac arrhythmias. Reactions to lidocaine may result from intra-arterial injection of lidocaine with retrograde flow to the cerebral circulation. Less common side effects include damage to nerves resulting in temporary or possibly permanent numbness or tingling and severe and possibly life-threatening allergic reactions.

Monitoring and Management of Adverse Events

Participants will be closely monitored for any adverse events, particularly those potentially related to lidocaine administration. As defined above, the total injected volume of lidocaine will not exceed the established maximum tolerated dose, minimizing the risk to participants. The following precautions and monitoring procedures will also be implemented:

Intraoperative and Postoperative Monitoring:

- In accordance with our standard of care peri-operative management, all participants will undergo continuous electrocardiographic (ECG) monitoring during surgery and immediately postoperatively to detect any arrhythmias or other cardiovascular events.
- Vital signs, including heart rate, blood pressure, and oxygen saturation, will be recorded at regular intervals throughout the procedure and in the recovery period.

- Participants will be monitored in the recovery area for at least 1-hour post-injection, with extended monitoring if signs of toxicity are noted.

Management of Specific Adverse Events:

- **Arrhythmias:** Anti-arrhythmic medications and defibrillators are readily available in the operating room and recovery areas. Any significant arrhythmias will be managed according to our standard clinical protocols, including potential transfer to an intensive care unit if needed.
- **Lidocaine Central Nervous System Toxicity:** CNS toxicity will be managed with supportive measures, including supplemental oxygen, and antiepileptics, per our standard clinical protocols. If required, intravenous lipid emulsion (ILE) therapy, the established treatment for severe local anesthetic systemic toxicity, will be administered. Airway protection, including intubation, will be provided if necessary.
- **Hypersensitivity and Allergic Reactions:** Epinephrine, antihistamines, and corticosteroids will be available in the perioperative period to treat any severe allergic reactions.

This monitoring and management plan will ensure that any adverse reactions are identified and treated promptly, thereby minimizing risks to participants.

7.4 *Dose-Limiting Toxicities and Stopping Rules*

Dose-limiting toxicities (DLTs) will be defined as any of the following adverse events occurring after intratumoral lidocaine injection:

- **Grade 3 or higher cardiac arrhythmia, seizure, or other central nervous system toxicity** attributed to lidocaine, as graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- **Any other Grade 3 or higher adverse event** directly attributed to lidocaine that, in the judgment of the Medical Monitor and Study Sponsor, poses a significant risk to participant safety.

Stopping Rules for Safety

A stopping rule for safety will halt accrual to the study if risks to subjects unexpectedly outweigh the benefits due to unexpected severe adverse events (SAEs). This determination will be made by the DSMC, Medical Monitor, and Study Sponsor. The specific stopping rules are as follows:

- **Cohort-Based Pausing:** If 2 or more participants within a cohort of 5 experience DLTs, the study will be paused. An independent safety review will be conducted by the DSMC and Medical Monitor. The study will only resume if the DSMC concludes it is safe to proceed.

- **Overall Study Pausing:** If **more than 10% of participants across the study experience a DLT or Grade 3 or higher adverse event related to lidocaine**, the study will be paused. The DSMC, Medical Monitor, and Study Sponsor will re-evaluate the safety profile of intratumoral lidocaine injection to determine if modifications to the protocol or dosing are required or if the study should be permanently discontinued.

Reporting and Adjustments

Any unexpected SAEs will be reported to the IRB promptly, and study procedures will be adjusted as necessary to mitigate further risk.

8 Data Handling and Record Keeping

8.1 Records

All patients must have a signed Informed Consent Form. Confirmation of study eligibility will be completed by a participating investigator via the electronic medical record (EPIC) prior to entering the study.

Confidential research charts will be kept in locked cabinets at each participating institution. Subjects will be assigned a study number at the time of study enrollment. This study number and not the subject's name will be used on all case report forms.

HIPAA Compliance:

Prior to direct laryngoscopy and randomization to the intervention vs control, each subject will sign a study informed consent, which also includes consent acknowledging the uses and disclosures of protected health information (PHI) in this study as required by The Health Insurance Portability and Accountability Act (HIPAA). PHI will not be shared with any outside institution except as required by law. Any reporting of the results of this study will be done only with de-identified patient data. Confidentiality will be protected as outlined below.

- Each subject will sign a study informed consent electronically prior to direct laryngoscopy and randomization to the intervention vs control

8.2 Data Collection and Management

All patients must have a signed Informed Consent Form and an On-study (confirmation of eligibility) form filled out and signed by a participating investigator prior to entering the study.

A case report form will be used to standardize data keeping and allow entry to a computerized data base.

- Each subject will be assigned a study number. All research-related material will be labeled with the subject study number and the subject's initials.
- A list of the subject names with the associated subject numbers will be maintained in a locked cabinet and computer by the principal investigator and study coordinator.
- All research subject records will be kept in a study chart or patient binder.
- An electronic, password protected database will be maintained. PHI and patient IDs will be used. Research members outside of those who need to have PHI, will only have the Patient ID (Coded information) to follow UPHS limited data policy.

9 Data and Safety Monitoring Plan

9.1 Overview

The University of Pennsylvania Cancer Center (UPCC) has a formal plan for Data Safety and Monitoring of Clinical Trials. The clinical trial, “A Phase I Randomized Controlled Trial of Intratumoral Lidocaine Injection Before Transoral Robotic Surgery (TORS) and Neck Dissection for HPV associated Oropharyngeal Squamous Cell Carcinoma” is a trial that is subject to oversight of the UPCC through the Data and Safety Monitoring Committee (DSMC). DSMC role is to ensure that the rights and well-being of all subjects are protected and that subjects are treated in full compliance with the study treatment and parameters specified in the protocol. The DSMC is responsible for overseeing the process of monitoring of studies and the conduct of audits. The investigators on this study are responsible for the continuous, close monitoring of subjects enrolled on this trial.

9.2 Study Audits

A DSMC audit of this trial will be performed twice a year for as long as the trial remains open for accrual. The principal investigator will be notified in advance of the selection of their protocol for review. Three randomly selected patients or 10% of the total accrual, whichever is higher will be audited. A written report is provided to the principal investigator following this audit. Any rating less than satisfactory would warrant a repeat full review at the time of the next scheduled audit or sooner, depending upon the extent of the deficiencies found. Substantial protocol deviations will be reported to the Director of the Cancer Center and the Associate Director for Clinical Research for consideration of appropriate administrative action, such as suspending accrual to the protocol.

9.3 Study Monitoring

A Medical Monitor, who is not directly involved in this trial and is not collaborating with the Sponsor-investigator in any other trials, has been selected for this trial. The Medical Monitor for this trial is Noam Cohen, MD, PhD. The Medical Monitor will review adverse events, safety data, and activity data observed in the ongoing clinical trial. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. Meetings with the Medical Monitor will occur biannually or more frequently if necessary. The meetings will take place in person or via telephone. The summary reports of all discussions of adverse events will be submitted to the DSMC on a biannual basis or more frequently if appropriate.

The Principal Investigator or his/her designee of the trial will present to the Medical Monitor all serious adverse events observed in patients, any activity data obtained, and whether those data invoked any stopping criteria in the clinical protocol. Adverse event reporting will follow the NCI guidelines. Results of the data from toxicology or other animal studies that are relevant will be discussed. Other information related to the safety and efficacy of the clinical study will be discussed. This includes information of similar investigational materials used in different studies.

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

10.1 Risks

As part of the research study, subjects will be asked to have blood samples collected in addition to any blood samples that will be drawn as part of the routine clinical care. The risk of having additional blood samples collected is minimal, and includes pain, redness, swelling, and/or bruising where the needle enters the body. Rare instances of fainting, excess bleeding, blood clotting, or infection have happened.

10.2 Benefits

The potential benefits of participating in this study are improved survival and decreased rate of cancer recurrence if subjects are assigned to the group that receives the lidocaine injection. However, these benefits have NOT yet been established in the type of cancer being studied. If subjects are assigned to the group that receives the lidocaine injection, they may also have the benefit of temporarily (i.e. ~2 hours) decreased pain from the biopsy site, as lidocaine is a local anesthetic. The benefits of participating in research using tissue include improving our knowledge of the causes of head and neck disease and other diseases, how to prevent them, how to treat them, and how to cure them. Patients may not get any benefit from being in this research study.

10.3 Risk / Benefit Assessment

The risks of participating in the study are outweighed by the potential benefits of participating in the study.

10.4 Informed Consent Process / HIPAA Authorization

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The potential risks and benefits of participation on the study will be discussed with each subject, with risk-benefit assessment. All subjects will be informed that participation is voluntary, and that treatment on study is investigational. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

This study will be financed through the Department of Otorhinolaryngology – Head & Neck Surgery at the University of Pennsylvania using academic development funds.

11.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and

approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

12 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor (PI). Any investigator involved with this study is obligated to provide the sponsor (PI) with complete test results and all data derived from the study.

13 References

1. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open*. 2021;4(4):e214708. Epub 2021/04/08. doi: 10.1001/jamanetworkopen.2021.4708. PubMed PMID: 33825840; PMCID: PMC8027914.
2. Gooi Z, Chan JY, Fakhry C. The epidemiology of the human papillomavirus related to oropharyngeal head and neck cancer. *Laryngoscope*. 2016;126(4):894-900. doi: 10.1002/lary.25767. PubMed PMID: 26845348.
3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-86. doi: 10.1002/ijc.29210. PubMed PMID: 25220842.
4. Chai RC, Lambie D, Verma M, Punyadeera C. Current trends in the etiology and diagnosis of HPV-related head and neck cancers. *Cancer Med*. 2015;4(4):596-607. doi: 10.1002/cam4.424. PubMed PMID: 25644715; PMCID: PMC4402074.
5. Network NCC. Head and Neck Cancers (Version 2.2023) 2023 [May 28, 2023]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
6. Cramer JD, Burtness B, Ferris RL. Immunotherapy for head and neck cancer: Recent advances and future directions. *Oral Oncol*. 2019;99:104460. doi: 10.1016/j.oraloncology.2019.104460. PubMed PMID: 31683169.
7. Weinstein GS, O'Malley BW, Jr., Cohen MA, Quon H. Transoral robotic surgery for advanced oropharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg*. 2010;136(11):1079-85. doi: 10.1001/archoto.2010.191. PubMed PMID: 21079160.
8. Weinstein GS, Quon H, O'Malley BW, Jr., Kim GG, Cohen MA. Selective neck dissection and deintensified postoperative radiation and chemotherapy for oropharyngeal cancer: a subset analysis of the University of Pennsylvania transoral robotic surgery trial. *The Laryngoscope*. 2010;120(9):1749-55. Epub 2010/08/19. doi: 10.1002/lary.21021. PubMed PMID: 20717944.
9. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. *The New England journal of medicine*. 2010;363(1):24-35. Epub 2010/06/10. doi: 10.1056/NEJMoa0912217. PubMed PMID: 20530316; PMCID: PMC2943767.

10. O'Sullivan B, Huang SH, Siu LL, Waldron J, Zhao H, Perez-Ordonez B, Weinreb I, Kim J, Ringash J, Bayley A, Dawson LA, Hope A, Cho J, Irish J, Gilbert R, Gullane P, Hui A, Liu FF, Chen E, Xu W. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol*. 2013;31(5):543-50. doi: 10.1200/JCO.2012.44.0164. PubMed PMID: 23295795.

11. Cohen MA, Weinstein GS, O'Malley BW, Jr., Feldman M, Quon H. Transoral robotic surgery and human papillomavirus status: Oncologic results. *Head & neck*. 2011;33(4):573-80. Epub 2011/03/23. doi: 10.1002/hed.21500. PubMed PMID: 21425382.

12. Quon H, Cohen MA, Montone KT, Ziobor AF, Wang LP, Weinstein GS, O'Malley BW, Jr. Transoral robotic surgery and adjuvant therapy for oropharyngeal carcinomas and the influence of p16 INK4a on treatment outcomes. *The Laryngoscope*. 2013;123(3):635-40. Epub 2012/05/17. doi: 10.1002/lary.22172. PubMed PMID: 22588642.

13. Carey RM, Brody RM, Shimunov D, Shinn JR, Mady LJ, Rajasekaran K, Cannady SB, Lin A, Lukens JN, Bauml JM, Cohen RB, Basu D, O'Malley BW, Jr., Weinstein GS, Newman JG. Locoregional Recurrence in p16-Positive Oropharyngeal Squamous Cell Carcinoma After TORS. *Laryngoscope*. 2021;131(12):E2865-e73. Epub 2021/06/03. doi: 10.1002/lary.29659. PubMed PMID: 34076275.

14. Brody RM, Shimunov D, Cohen RB, Lin A, Lukens JN, Hartner L, Aggarwal C, Duvvuri U, Montone KT, Jalaly JB, LiVolsi VA, Carey RM, Shanti RM, Rajasekaran K, Chalian AA, Rassekh CH, Cannady SB, Newman JG, O'Malley BW, Weinstein GS, Gimotty PA, Basu D. A benchmark for oncologic outcomes and model for lethal recurrence risk after transoral robotic resection of HPV-related oropharyngeal cancers. *Oral Oncol*. 2022;127:105798. Epub 2022/03/05. doi: 10.1016/j.oraloncology.2022.105798. PubMed PMID: 35245888; PMCID: PMC9288202.

15. Lazarus CL. Effects of chemoradiotherapy on voice and swallowing. *Curr Opin Otolaryngol Head Neck Surg*. 2009;17(3):172-8. doi: 10.1097/MOO.0b013e32832af12f. PubMed PMID: 19337126; PMCID: PMC2745635.

16. Jethwa AR, Khariwala SS. Tobacco-related carcinogenesis in head and neck cancer. *Cancer Metastasis Rev*. 2017;36(3):411-23. Epub 2017/08/13. doi: 10.1007/s10555-017-9689-6. PubMed PMID: 28801840; PMCID: PMC5709040.

17. Suh Y, Amelio I, Guerrero Urbano T, Tavassoli M. Clinical update on cancer: molecular oncology of head and neck cancer. *Cell Death Dis*. 2014;5:e1018. Epub 2014/01/25. doi: 10.1038/cddis.2013.548. PubMed PMID: 24457962; PMCID: PMC4040714.

18. Murphy BA, Ridner S, Wells N, Dietrich M. Quality of life research in head and neck cancer: a review of the current state of the science. *Crit Rev Oncol Hematol*. 2007;62(3):251-67. Epub 2007/04/06. doi: 10.1016/j.critrevonc.2006.07.005. PubMed PMID: 17408963.

19. Swisher-McClure S, Lukens JN, Aggarwal C, Ahn P, Basu D, Bauml JM, Brody R, Chalian A, Cohen RB, Fotouhi-Ghiam A, Geiger G, Gershowitz J, Livolsi V, Mitra N, Montone K, Newman J, Ojerholm E, O'Malley B, Jr., Rajasekaran K, Tan E, Weinstein G, Lin A. A Phase 2 Trial of Alternative Volumes of Oropharyngeal Irradiation for De-intensification (AVOID): Omission of the Resected Primary Tumor Bed After Transoral Robotic Surgery for Human Papilloma Virus-Related Squamous Cell Carcinoma of the Oropharynx. *Int J Radiat Oncol Biol Phys*. 2020;106(4):725-32. doi: 10.1016/j.ijrobp.2019.11.021. PubMed PMID: 31785337.

20. Ferris RL, Flamand Y, Holsinger FC, Weinstein GS, Quon H, Mehra R, Garcia JJ, Hinni ML, Gross ND, Sturgis EM, Duvvuri U, Méndez E, Ridge JA, Magnuson JS, Higgins KA, Patel MR, Smith RB, Karakla DW, Kupferman ME, Malone JP, Judson BL, Richmon J, Boyle JO,

Bayon R, O'Malley BW, Jr., Ozer E, Thomas GR, Koch WM, Bell RB, Saba NF, Li S, Sigurdson ER, Burtness B. A novel surgeon credentialing and quality assurance process using transoral surgery for oropharyngeal cancer in ECOG-ACRIN Cancer Research Group Trial E3311. *Oral Oncol.* 2020;110:104797. Epub 2020/07/18. doi: 10.1016/j.oraloncology.2020.104797. PubMed PMID: 32679405; PMCID: PMC7771718.

21. Ma DJ, Price KA, Moore EJ, Patel SH, Hinni ML, Garcia JJ, Graner DE, Foster NR, Ginos B, Neben-Wittich M, Garces YI, Chintakuntlawar AV, Price DL, Olsen KD, Van Abel KM, Kasperbauer JL, Janus JR, Waddle M, Miller R, Shiraishi S, Foote RL. Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus-Associated Oropharynx Squamous Cell Carcinoma. *J Clin Oncol.* 2019;37(22):1909-18. Epub 2019/06/05. doi: 10.1200/jco.19.00463. PubMed PMID: 31163012; PMCID: PMC7098832.

22. Ferris RL, Flamand Y, Weinstein GS, Li S, Quon H, Mehra R, Garcia JJ, Chung CH, Gillison ML, Duvvuri U, O'malley BW, Ozer E, Thomas GR, Koch W, Kupferman ME, Bell RB, Saba NF, Lango M, Mendez E, Burtness B. Transoral robotic surgical resection followed by randomization to low- or standard-dose IMRT in resectable p16+ locally advanced oropharynx cancer: A trial of the ECOG-ACRIN Cancer Research Group (E3311). *Journal of Clinical Oncology.* 2020;38(15_suppl):6500-. doi: 10.1200/JCO.2020.38.15_suppl.6500.

23. Bachmanov AA, Bosak NP, Lin C, Matsumoto I, Ohmoto M, Reed DR, Nelson TM. Genetics of taste receptors. *Current pharmaceutical design.* 2014;20(16):2669-83. Epub 2013/07/28. doi: 10.2174/13816128113199990566. PubMed PMID: 23886383; PMCID: PMC4764331.

24. Hariri BM, McMahon DB, Chen B, Freund JR, Mansfield CJ, Doghramji LJ, Adappa ND, Palmer JN, Kennedy DW, Reed DR, Jiang P, Lee RJ. Flavones modulate respiratory epithelial innate immunity: Anti-inflammatory effects and activation of the T2R14 receptor. *J Biol Chem.* 2017;292(20):8484-97. Epub 2017/04/05. doi: 10.1074/jbc.M116.771949. PubMed PMID: 28373278; PMCID: PMC5437252.

25. Carey RM, Lee RJ. Taste Receptors in Upper Airway Innate Immunity. *Nutrients.* 2019;11(9). doi: 10.3390/nu11092017. PubMed PMID: 31466230; PMCID: PMC6770031.

26. Clark AA, Dotson CD, Elson AE, Voigt A, Boehm U, Meyerhof W, Steinle NI, Munger SD. TAS2R bitter taste receptors regulate thyroid function. *Faseb j.* 2015;29(1):164-72. Epub 2014/10/25. doi: 10.1096/fj.14-262246. PubMed PMID: 25342133; PMCID: PMC4285546.

27. Kinnamon SC. Taste receptor signalling - from tongues to lungs. *Acta Physiol (Oxf).* 2012;204(2):158-68. Epub 2011/04/13. doi: 10.1111/j.1748-1716.2011.02308.x. PubMed PMID: 21481196; PMCID: PMC3704337.

28. Janssen S, Laermans J, Verhulst PJ, Thijs T, Tack J, Depoortere I. Bitter taste receptors and alpha-gustducin regulate the secretion of ghrelin with functional effects on food intake and gastric emptying. *Proceedings of the National Academy of Sciences of the United States of America.* 2011;108(5):2094-9. Epub 2011/01/20. doi: 10.1073/pnas.1011508108. PubMed PMID: 21245306; PMCID: 3033292.

29. Wu SV, Rozengurt N, Yang M, Young SH, Sinnott-Smith J, Rozengurt E. Expression of bitter taste receptors of the T2R family in the gastrointestinal tract and enteroendocrine STC-1 cells. *Proceedings of the National Academy of Sciences of the United States of America.* 2002;99(4):2392-7. Epub 2002/02/21. doi: 10.1073/pnas.042617699. PubMed PMID: 11854532; PMCID: PMC122375.

30. Choi JH, Lee J, Choi IJ, Kim YW, Ryu KW, Kim J. Genetic Variation in the TAS2R38 Bitter Taste Receptor and Gastric Cancer Risk in Koreans. *Sci Rep.* 2016;6:26904. Epub 2016/06/02. doi: 10.1038/srep26904. PubMed PMID: 27245112; PMCID: PMC4887993.

31. Yamaki M, Saito H, Isono K, Goto T, Shirakawa H, Shoji N, Satoh-Kuriwada S, Sasano T, Okada R, Kudoh K, Motoi F, Unno M, Komai M. Genotyping Analysis of Bitter-Taste Receptor Genes TAS2R38 and TAS2R46 in Japanese Patients with Gastrointestinal Cancers. *Journal of nutritional science and vitaminology.* 2017;63(2):148-54. Epub 2017/05/30. doi: 10.3177/jnsv.63.148. PubMed PMID: 28552880.

32. Carrai M, Steinke V, Vodicka P, Pardini B, Rahner N, Holinski-Feder E, Morak M, Schackert HK, Görgens H, Stemmler S, Betz B, Kloos M, Engel C, Büttner R, Naccarati A, Vodickova L, Novotny J, Stein A, Hemminki K, Propping P, Förstl A, Canzian F, Barale R, Campa D. Association between TAS2R38 gene polymorphisms and colorectal cancer risk: a case-control study in two independent populations of Caucasian origin. *PLoS One.* 2011;6(6):e20464. Epub 2011/06/16. doi: 10.1371/journal.pone.0020464. PubMed PMID: 21674048; PMCID: PMC3107225 Genetisches Zentrum, Munich. This does not alter the authors' adherence to all the PLoS ONE policies on sharing data and materials.

33. Barontini J, Antinucci M, Tofanelli S, Cammalleri M, Dal Monte M, Gemignani F, Vodicka P, Marangoni R, Vodickova L, Kupcinskas J, Vymetalkova V, Förstl A, Canzian F, Stein A, Moreno V, Mastrodonato N, Tavano F, Panza A, Barale R, Landi S, Campa D. Association between polymorphisms of TAS2R16 and susceptibility to colorectal cancer. *BMC gastroenterology.* 2017;17(1):104. Epub 2017/09/17. doi: 10.1186/s12876-017-0659-9. PubMed PMID: 28915899; PMCID: PMC5603047.

34. Choi JH, Kim J. TAS2R38 Bitterness Receptor Genetic Variation and Risk of Gastrointestinal Neoplasm: A Meta-Analysis. *Nutrition and cancer.* 2019;71(4):585-93. Epub 2019/01/22. doi: 10.1080/01635581.2018.1559935. PubMed PMID: 30663393.

35. Schembре SM, Cheng I, Wilkens LR, Albright CL, Marchand le L. Variations in bitter-taste receptor genes, dietary intake, and colorectal adenoma risk. *Nutrition and cancer.* 2013;65(7):982-90. Epub 2013/10/03. doi: 10.1080/01635581.2013.807934. PubMed PMID: 24083639; PMCID: PMC3836614.

36. Choi JH, Lee J, Choi IJ, Kim YW, Ryu KW, Kim J. Variations in TAS1R taste receptor gene family modify food intake and gastric cancer risk in a Korean population. *Molecular nutrition & food research.* 2016;60(11):2433-45. Epub 2016/06/21. doi: 10.1002/mnfr.201600145. PubMed PMID: 27321875.

37. Stern L, Giese N, Hackert T, Strobel O, Schirmacher P, Felix K, Gaida MM. Overcoming chemoresistance in pancreatic cancer cells: role of the bitter taste receptor T2R10. *Journal of Cancer.* 2018;9(4):711-25. Epub 2018/03/21. doi: 10.7150/jca.21803. PubMed PMID: 29556329; PMCID: PMC5858493.

38. Gaida MM, Mayer C, Dapunt U, Stegmaier S, Schirmacher P, Wabnitz GH, Hänsch GM. Expression of the bitter receptor T2R38 in pancreatic cancer: localization in lipid droplets and activation by a bacteria-derived quorum-sensing molecule. *Oncotarget.* 2016;7(11):12623-32. Epub 2016/02/11. doi: 10.18632/oncotarget.7206. PubMed PMID: 26862855; PMCID: PMC4914309.

39. Singh N, Chakraborty R, Bhullar RP, Chelikani P. Differential expression of bitter taste receptors in non-cancerous breast epithelial and breast cancer cells. *Biochemical and biophysical research communications.* 2014;446(2):499-503. Epub 2014/03/13. doi: 10.1016/j.bbrc.2014.02.140. PubMed PMID: 24613843.

40. Choi JH, Lee J, Yang S, Lee EK, Hwangbo Y, Kim J. Genetic variations in TAS2R3 and TAS2R4 bitterness receptors modify papillary carcinoma risk and thyroid function in Korean females. *Sci Rep.* 2018;8(1):15004. Epub 2018/10/12. doi: 10.1038/s41598-018-33338-6. PubMed PMID: 30301923; PMCID: PMC6177438.

41. Salvestrini V, Ciciarello M, Pensato V, Simonetti G, Laginestra MA, Bruno S, Pazzaglia M, De Marchi E, Forte D, Orecchioni S, Martinelli G, Bertolini F, Méndez-Ferrer S, Adinolfi E, Di Virgilio F, Cavo M, Curti A. Denatonium as a Bitter Taste Receptor Agonist Modifies Transcriptomic Profile and Functions of Acute Myeloid Leukemia Cells. *Front Oncol.* 2020;10:1225. Epub 2020/08/15. doi: 10.3389/fonc.2020.01225. PubMed PMID: 32793492; PMCID: PMC7393209.

42. Carey RM, McMahon DB, Miller ZA, Kim T, Rajasekaran K, Gopallawa I, Newman JG, Basu D, Nead KT, White EA, Lee RJ. T2R bitter taste receptors regulate apoptosis and may be associated with survival in head and neck squamous cell carcinoma. *Molecular oncology.* 2021. Epub 2021/10/31. doi: 10.1002/1878-0261.13131. PubMed PMID: 34717036.

43. Carey RM, Kim T, Cohen NA, Lee RJ, Nead KT. Impact of sweet, umami, and bitter taste receptor (TAS1R and TAS2R) genomic and expression alterations in solid tumors on survival. *Sci Rep.* 2022;12(1):8937. Epub 2022/05/28. doi: 10.1038/s41598-022-12788-z. PubMed PMID: 35624283; PMCID: PMC9142493.

44. Shaik FA, Jaggupilli A, Chelikani P. Highly conserved intracellular H208 residue influences agonist selectivity in bitter taste receptor T2R14. *Biochim Biophys Acta Biomembr.* 2019;1861(12):183057. Epub 2019/09/08. doi: 10.1016/j.bbamem.2019.183057. PubMed PMID: 31493373.

45. Medapati MR, Singh N, Bhagirath AY, Duan K, Triggs-Raine B, Batista EL, Jr., Chelikani P. Bitter taste receptor T2R14 detects quorum sensing molecules from cariogenic *Streptococcus mutans* and mediates innate immune responses in gingival epithelial cells. *Faseb j.* 2021;35(3):e21375. Epub 2021/02/10. doi: 10.1096/fj.202000208R. PubMed PMID: 33559200.

46. Meyerhof W, Batram C, Kuhn C, Brockhoff A, Chudoba E, Bufe B, Appendino G, Behrens M. The molecular receptive ranges of human TAS2R bitter taste receptors. *Chem Senses.* 2010;35(2):157-70. Epub 2009/12/22. doi: [bjp092 \[pii\]](https://doi.org/10.1093/chemse/bjp092) 10.1093/chemse/bjp092. PubMed PMID: 20022913.

47. Miller ZA, Mueller A, Kim T, Jolivert JF, Ma RZ, Muthuswami S, Park A, McMahon DB, Nead KT, Carey RM, Lee RJ. Lidocaine induces apoptosis in head and neck squamous cell carcinoma through activation of bitter taste receptor T2R14. *Cell Rep.* 2023;113437. Epub 2023/11/24. doi: 10.1016/j.celrep.2023.113437. PubMed PMID: 37995679.

48. Sun D, Li YC, Zhang XY. Lidocaine Promoted Ferroptosis by Targeting miR-382-5p /SLC7A11 Axis in Ovarian and Breast Cancer. *Front Pharmacol.* 2021;12:681223. Epub 2021/06/15. doi: 10.3389/fphar.2021.681223. PubMed PMID: 34122108; PMCID: PMC8188239.

49. Sun M, Huang S, Gao Y. Lidocaine inhibits the proliferation and metastasis of epithelial ovarian cancer through the Wnt/beta-catenin pathway. *Transl Cancer Res.* 2021;10(7):3479-90. Epub 2022/02/05. doi: 10.21037/tcr-21-1047. PubMed PMID: 35116652; PMCID: PMC8799064.

50. Wall TP, Crowley PD, Sherwin A, Foley AG, Buggy DJ. Effects of Lidocaine and Src Inhibition on Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers (Basel).* 2019;11(10). Epub 2019/09/25. doi: 10.3390/cancers11101414. PubMed PMID: 31546727; PMCID: PMC6826872.

51. Sun H, Sun Y. Lidocaine inhibits proliferation and metastasis of lung cancer cell via regulation of miR-539/EGFR axis. *Artif Cells Nanomed Biotechnol.* 2019;47(1):2866-74. Epub 2019/07/14. doi: 10.1080/21691401.2019.1636807. PubMed PMID: 31299862.

52. Mirshahidi S, Shields TG, de Necochea-Campion R, Yuan X, Janjua A, Williams NL, Mirshahidi HR, Reeves ME, Duerksen-Hughes P, Zuckerman LM. Bupivacaine and Lidocaine Induce Apoptosis in Osteosarcoma Tumor Cells. *Clin Orthop Relat Res.* 2021;479(1):180-94. Epub 2020/10/04. doi: 10.1097/CORR.0000000000001510. PubMed PMID: 33009230; PMCID: PMC7899706 immediate family, has funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article. All ICMJE Conflict of Interest Forms for authors and Clinical Orthopaedics and Related Research(R) editors and board members are on file with the publication and can be viewed on request.

53. Zhu J, Han S. Lidocaine inhibits cervical cancer cell proliferation and induces cell apoptosis by modulating the lncRNA-MEG3/miR-421/BTG1 pathway. *Am J Transl Res.* 2019;11(9):5404-16. Epub 2019/10/22. PubMed PMID: 31632519; PMCID: PMC6789266.

54. Zhang J, Mao W, Dai Y, Qian C, Dong Y, Chen Z, Meng L, Jiang Z, Huang T, Hu J, Luo P, Korner H, Jiang Y, Ying S. Voltage-gated sodium channel Nav1.5 promotes proliferation, migration and invasion of oral squamous cell carcinoma. *Acta Biochim Biophys Sin (Shanghai).* 2019;51(6):562-70. Epub 2019/05/30. doi: 10.1093/abbs/gmz044. PubMed PMID: 31139826.

55. Chiliquinga AJ, Acosta B, Ogonaga-Borja I, Villarruel-Melquiades F, de la Garza J, Gariglio P, Ocádiz-Delgado R, Ramírez A, Sánchez-Pérez Y, García-Cuellar CM, Bañuelos C, Camacho J. Ion Channels as Potential Tools for the Diagnosis, Prognosis, and Treatment of HPV-Associated Cancers. *Cells.* 2023;12(10). Epub 2023/07/06. doi: 10.3390/cells12101376. PubMed PMID: 37408210; PMCID: PMC10217072.

56. Xu X, Dai Y, Feng L, Zhang H, Hu Y, Xu L, Zhu X, Jiang Y. Knockdown of Nav1.5 inhibits cell proliferation, migration and invasion via Wnt/β-catenin signaling pathway in oral squamous cell carcinoma. *Acta Biochim Biophys Sin (Shanghai).* 2020;52(5):527-35. Epub 2020/05/14. doi: 10.1093/abbs/gmaa021. PubMed PMID: 32400862.

57. Bennett ES, Smith BA, Harper JM. Voltage-gated Na⁺ channels confer invasive properties on human prostate cancer cells. *Pflugers Arch.* 2004;447(6):908-14. Epub 2003/12/17. doi: 10.1007/s00424-003-1205-x. PubMed PMID: 14677067.

58. Roger S, Besson P, Le Guennec JY. Involvement of a novel fast inward sodium current in the invasion capacity of a breast cancer cell line. *Biochim Biophys Acta.* 2003;1616(2):107-11. Epub 2003/10/17. doi: 10.1016/j.bbamem.2003.07.001. PubMed PMID: 14561467.

59. Roger S, Potier M, Vandier C, Besson P, Le Guennec JY. Voltage-gated sodium channels: new targets in cancer therapy? *Current pharmaceutical design.* 2006;12(28):3681-95. Epub 2006/11/01. doi: 10.2174/138161206778522047. PubMed PMID: 17073667.

60. Fraser SP, Diss JK, Chioni AM, Mycielska ME, Pan H, Yamaci RF, Pani F, Siwy Z, Krasowska M, Grzywna Z, Brackenbury WJ, Theodorou D, Koyutürk M, Kaya H, Battaloglu E, De Bella MT, Slade MJ, Tolhurst R, Palmieri C, Jiang J, Latchman DS, Coombes RC, Djamgoz MB. Voltage-gated sodium channel expression and potentiation of human breast cancer metastasis. *Clin Cancer Res.* 2005;11(15):5381-9. Epub 2005/08/03. doi: 10.1158/1078-0432.Ccr-05-0327. PubMed PMID: 16061851.

61. Wall TP, Buggy DJ. Perioperative Intravenous Lidocaine and Metastatic Cancer Recurrence - A Narrative Review. *Front Oncol.* 2021;11:688896. Epub 2021/08/20. doi: 10.3389/fonc.2021.688896. PubMed PMID: 34408981; PMCID: PMC8365881.

62. Zhang C, Xie C, Lu Y. Local Anesthetic Lidocaine and Cancer: Insight Into Tumor Progression and Recurrence. *Front Oncol.* 2021;11:669746. Epub 2021/07/13. doi: 10.3389/fonc.2021.669746. PubMed PMID: 34249706; PMCID: PMC8264592.

63. Royds J, Khan AH, Buggy DJ. An Update on Existing Ongoing Prospective Trials Evaluating the Effect of Anesthetic and Analgesic Techniques During Primary Cancer Surgery on Cancer Recurrence or Metastasis. *Int Anesthesiol Clin.* 2016;54(4):e76-83. Epub 2016/09/21. doi: 10.1097/aia.0000000000000123. PubMed PMID: 27648893.

64. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, Ayad S, Mascha EJ, Buggy DJ. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet.* 2019;394(10211):1807-15. Epub 2019/10/28. doi: 10.1016/s0140-6736(19)32313-x. PubMed PMID: 31645288.

65. Cakmakkaya OS, Kolodzie K, Apfel CC, Pace NL. Anaesthetic techniques for risk of malignant tumour recurrence. *Cochrane Database Syst Rev.* 2014(11):Cd008877. Epub 2014/11/08. doi: 10.1002/14651858.CD008877.pub2. PubMed PMID: 25379840.

66. Badwe RA, Parmar V, Nair N, Joshi S, Hawaldar R, Pawar S, Kadayaprath G, Borthakur BB, Rao Thammineedi S, Pandya S, Balasubramanian S, Chitale PV, Neve R, Harris C, Srivastava A, Siddique S, Vanmali VJ, Dewade A, Gaikwad V, Gupta S. Effect of Peritumoral Infiltration of Local Anesthetic Before Surgery on Survival in Early Breast Cancer. *J Clin Oncol.* 2023;41(18):3318-28. Epub 2023/04/07. doi: 10.1200/jco.22.01966. PubMed PMID: 37023374.

67. Tohme S, Simmons RL, Tsung A. Surgery for Cancer: A Trigger for Metastases. *Cancer Res.* 2017;77(7):1548-52. Epub 2017/03/24. doi: 10.1158/0008-5472.CAN-16-1536. PubMed PMID: 28330928; PMCID: PMC5380551.

68. Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. *Cancer Res.* 1989;49(8):1996-2001. Epub 1989/04/15. PubMed PMID: 2702641.

69. Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nat Med.* 1995;1(2):149-53. Epub 1995/02/01. doi: 10.1038/nm0295-149. PubMed PMID: 7585012.

70. Tyzzer EE. Factors in the Production and Growth of tumor Metastases. *J Med Res.* 1913;28(2):309-32.1. Epub 1913/07/01. PubMed PMID: 19972114; PMCID: PMC2099742.

71. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. *Nat Rev Clin Oncol.* 2018;15(4):205-18. Epub 2017/12/29. doi: 10.1038/nrclinonc.2017.194. PubMed PMID: 29283170.

72. Alieva M, van Rheenen J, Broekman MLD. Potential impact of invasive surgical procedures on primary tumor growth and metastasis. *Clin Exp Metastasis.* 2018;35(4):319-31. Epub 2018/05/08. doi: 10.1007/s10585-018-9896-8. PubMed PMID: 29728948; PMCID: PMC6063335.

73. Safran T, Zammit D, Kanevsky J, Khanna M. Efficacy of Local Anesthesia in the Face and Scalp: A Prospective Trial. *Plast Reconstr Surg Glob Open.* 2019;7(5):e2243. Epub 2019/07/25. doi: 10.1097/GOX.0000000000002243. PubMed PMID: 31333967; PMCID: PMC6571352.

74. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny GE, Denkert C, Nekljudova V, Mehta K, Loibl S. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin*

Oncol. 2012;30(15):1796-804. Epub 2012/04/18. doi: 10.1200/jco.2011.38.8595. PubMed PMID: 22508812.

75. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnemoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer CE, Jr., Pazdur R, Ditsch N, Rastogi P, Eiermann W, von Minckwitz G. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-72. Epub 2014/02/18. doi: 10.1016/s0140-6736(13)62422-8. PubMed PMID: 24529560.

76. Weissferdt A, Pataer A, Vaporciyan AA, Correa AM, Sepesi B, Moran CA, Wistuba, II, Roth JA, Shewale JB, Heymach JV, Kalhor N, Cascone T, Hofstetter WL, Lee JJ, Swisher SG. Agreement on Major Pathological Response in NSCLC Patients Receiving Neoadjuvant Chemotherapy. Clin Lung Cancer. 2020;21(4):341-8. Epub 2020/04/14. doi: 10.1016/j.cllc.2019.11.003. PubMed PMID: 32279936; PMCID: PMC7305995.

77. Junker K, Thomas M, Schulmann K, Klinke F, Bosse U, Müller KM. Tumour regression in non-small-cell lung cancer following neoadjuvant therapy. Histological assessment. J Cancer Res Clin Oncol. 1997;123(9):469-77. Epub 1997/01/01. doi: 10.1007/bf01192200. PubMed PMID: 9341895.

78. Uppaluri R, Campbell KM, Egloff AM, Zolkind P, Skidmore ZL, Nussenbaum B, Paniello RC, Rich JT, Jackson R, Pipkorn P, Michel LS, Ley J, Oppelt P, Dunn GP, Barnell EK, Spies NC, Lin T, Li T, Mulder DT, Hanna Y, Cirlan I, Pugh TJ, Mudianto T, Riley R, Zhou L, Jo VY, Stachler MD, Hanna GJ, Kass J, Haddad R, Schoenfeld JD, Gjini E, Lako A, Thorstad W, Gay HA, Daly M, Rodig SJ, Hagemann IS, Kallogjeri D, Piccirillo JF, Chernock RD, Griffith M, Griffith OL, Adkins DR. Neoadjuvant and Adjuvant Pembrolizumab in Resectable Locally Advanced, Human Papillomavirus-Unrelated Head and Neck Cancer: A Multicenter, Phase II Trial. Clin Cancer Res. 2020;26(19):5140-52. Epub 2020/07/16. doi: 10.1158/1078-0432.Ccr-20-1695. PubMed PMID: 32665297; PMCID: PMC7547532.

79. Shibata H, Saito S, Uppaluri R. Immunotherapy for Head and Neck Cancer: A Paradigm Shift From Induction Chemotherapy to Neoadjuvant Immunotherapy. Front Oncol. 2021;11:727433. Epub 2021/09/24. doi: 10.3389/fonc.2021.727433. PubMed PMID: 34552878; PMCID: PMC8451593.

80. Gillison ML, Trott AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, Jordan RCK, Zhao W, Sturgis EM, Burtness B, Ridge JA, Ringash J, Galvin J, Yao M, Koyfman SA, Blakaj DM, Razaq MA, Colevas AD, Beitler JJ, Jones CU, Dunlap NE, Seaward SA, Spencer S, Galloway TJ, Phan J, Dignam JJ, Le QT. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet (London, England). 2019;393(10166):40-50. Epub 2018/11/20. doi: 10.1016/s0140-6736(18)32779-x. PubMed PMID: 30449625; PMCID: PMC6541928.

81. Prevention TNCIsDoC. Clinical Trial Randomization Tool [11 December 2024]. Available from: <https://ctrandomization.cancer.gov>.

82. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK, Lefèvre JL. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy

trials of the EORTC (#22931) and RTOG (# 9501). Head & neck. 2005;27(10):843-50. Epub 2005/09/15. doi: 10.1002/hed.20279. PubMed PMID: 16161069.