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ORIGINAL RESEARCH

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Tumor phantom for training and research in transoral surgery

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Abstract

Objective: With the paradigm shift towards minimally invasive surgical techniques such as transoral laser microsurgery and transoral robotic surgery for resection of head and neck malignancies, there is a need to enhance the surgical training of these techniques as well as provide a platform for testing new approaches and technologies. The steeper learning curve associated with minimally invasive surgical techniques may be mitigated with the use of tumor phantoms (TP) placed in cadaver models.

Methods: An injectable TP was developed using an agar-gelatin base, unsalted chicken stock, deionized water, food coloring for visual mimicry, and iohexol for radiographic mimicry. Four percentage glutaraldehyde was used as a cross-linking agent for solidification of the TP. The TP was then injected in various mucosal anatomic sites in four unfixed cadaver heads. Visual, radiographic, and tactile mimicry was assessed via endoscopy, CT scan, and tumor dissection and palpation, respectively.

Results: Tumor phantom injection was successfully achieved in all four cadaver heads. Visually and tactilely, the TP demonstrated similar color change, induration, and firmness of a typical squamous cell carcinoma (SCCa). However, ulceration that is often seen with SCCa could not be replicated. CT mimicry was compared with nine patients with known SCCa. Tumor radiodensity in the nine patients was between 77 and 110 HU (mean 86.3 HU) whereas TP radiodensity was 59 and 127 HU (mean 93.7 HU), with no significant difference between groups (P = .21).

Conclusion: This inexpensive, easy to apply, and unique tumor phantom could be used both to train transoral techniques and as a tool to further investigate new approaches and technologies for transoral surgery.

Level of Evidence: NA.

KEYWORDS

cadaver, surgical training, TLM, TORS, transoral surgery, tumor phantom

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1 | INTRODUCTION

Resection of head and neck cancer has historically involved an open, transcervical or transmandibular, approach. Over the last decade, this paradigm has shifted with the adoption of transoral approaches such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS). Although associated with better oncological outcomes and reduced morbidity[1,2] when compared with open approaches, because of the inside-out nature and lack of haptic feedback, the learning curve to technique mastery is steeper.[3,4]

Cadaver models are often utilized as an effective means of teaching in surgical specialties where learners explore and develop surgical skills and confidence in a low risk setting that can be applied to the operating room[5] In addition to cadaver models, tumor phantoms (TP) have become an effective means to enhance research and training in surgery. TPs have benefitted training and investigation in breast ultrasonic cancer localization,[6] neurosurgical image guidance training,[7] as a lung malignancy deformable airway visualization tool,[8] and as a training tool for laparoscopic rectal surgery.[9]

In this report, we present an inexpensive and easy-to-apply agar-gelatin-based TP in a cadaver model which both visually and radiographically mimics a typical head and neck squamous cell carcinoma (HNSCC). By simulating actual upper aerodigestive tract pathology, this phantom can potentially be used both to improve training in transoral techniques and as a tool to further investigate new approaches and technologies for transoral surgery.

2 | MATERIALS AND METHODS

2.1 | Tumor phantom development and optimization

In developing this TP, we required that it mimic HNSCC physically, visually, and radiographically. Administration had to be easy and non-destructive to the surrounding tissues. Finally, the successful TP had to be inexpensive and easy to make. To this end, various materials were explored in both bovine and porcine models. The resulting solution involved an agar-gelatin base dissolved in a solution of 1:1 unsalted chicken stock and de-ionized water, food coloring for visual mimicry, and iohexol for radiographic mimicry. 4% glutaraldehyde was used as a cross-linking agent for solidification of the TP. The full list of ingredients and mixing instruction is found in Table 1.

A novel dual barrel mixing syringe was modeled in SolidWorks (Dassault Systèmes, Vélizy-Villacoublay, France) and 3D-printed using a Form 2 resin printer (Formlabs, Somerville, Massachusetts) (see Figure 1) to allow for the glutaraldehyde to be mixed with agar-gelatin base during injection, thus allowing in vivo solidification of the mass. This system was necessary as mixing prior to injection would result in early solidification and making timely implantation of the TP difficult. Specifics regarding tumor phantom development, design of the novel mixing syringe, and tumor phantom characteristics are provided in a separate report.[10] CAD drawings of the injector and tumor phantom ingredients can be downloaded from https://engineering.dartmouth.edu/halter-lab/.

2.2 | Cadaver model with tumor phantoms

TPs were applied to four unfixed frozen cadaver heads (Science Care Inc., Phoenix, Arizona) after being allowed to thaw for 24 to 36 hours. None of the cadaver subjects had a prior history of head and neck cancer or a prior history of surgery or radiation to the head and neck. The heads were stabilized utilizing a previously described head-holder system which mimics head position and extension during laryngoscopy procedures.[11] The TP was injected in various anatomic subsites including the tonsillar region, base of tongue, vallecula, pyriform sinus, pharyngeal wall, and oral tongue. A 4.5 in. 17 g epidural needle (Teleflex Medical Research, Triangle Park, North Carolina) was found to provide sufficient length and bore for administering the solution in the target site.

2.3 | Injection technique

Once the mucosa was penetrated, the needle was advanced about 5 mm below the surface. Constant but slow pressure was applied on the injector plunger to prevent clogging of the needle but also to minimize the chance of uncontrolled hydrodissection of the injection in the submucosa. Once a sufficient volume was administered, the needle was withdrawn, still with constant pressure applied to the plunger. Following each injection, the barrel of the needle and syringe adaptor was flushed with

TABLE 1 List of ingredients, supply company, quantity, and mixing instructions for tumor phantom

Ingredients	Measured quantity
Bacteriological Agar (Carolina Biological Supply, Burlington, NC)	0.6 g
Porcine Gelatin (Sigma-Aldrich, St. Louis MO)	2.4 g
DI Water	30 mL
Unsalted Chicken Stock (pacific Foods Inc. Tualatin, OR)	30 mL
Food Coloring (various companies)[a]	4 drops
1:7 Omnipaque-350™ (iohexol) (GE Healthcare, Chicago, IL) to DI water[a]	4.8 mL
4% Glutaraldehyde (Sigma-Aldrich, St. Louis MO)	1 mL
Mixing instructions: 1—Mix the agar, gelatin, water, and chicken stock 2—Heat until boiling and then kept between 45°C and 50°C 3—Add food coloring and iohexol, titrating to need[a], mixing vigorously 4—Maintain solution at 45°C to 50°C until ready to apply 5—4% glutaraldehyde is used a cross-linking agent for solidification of the TP and should be applied at room temperature at the time of TP implantation	

[a]The ratio of food coloring and Omnipaque could be adjusted as needed to affect tumor appearance and enhancement on imaging, respectively.

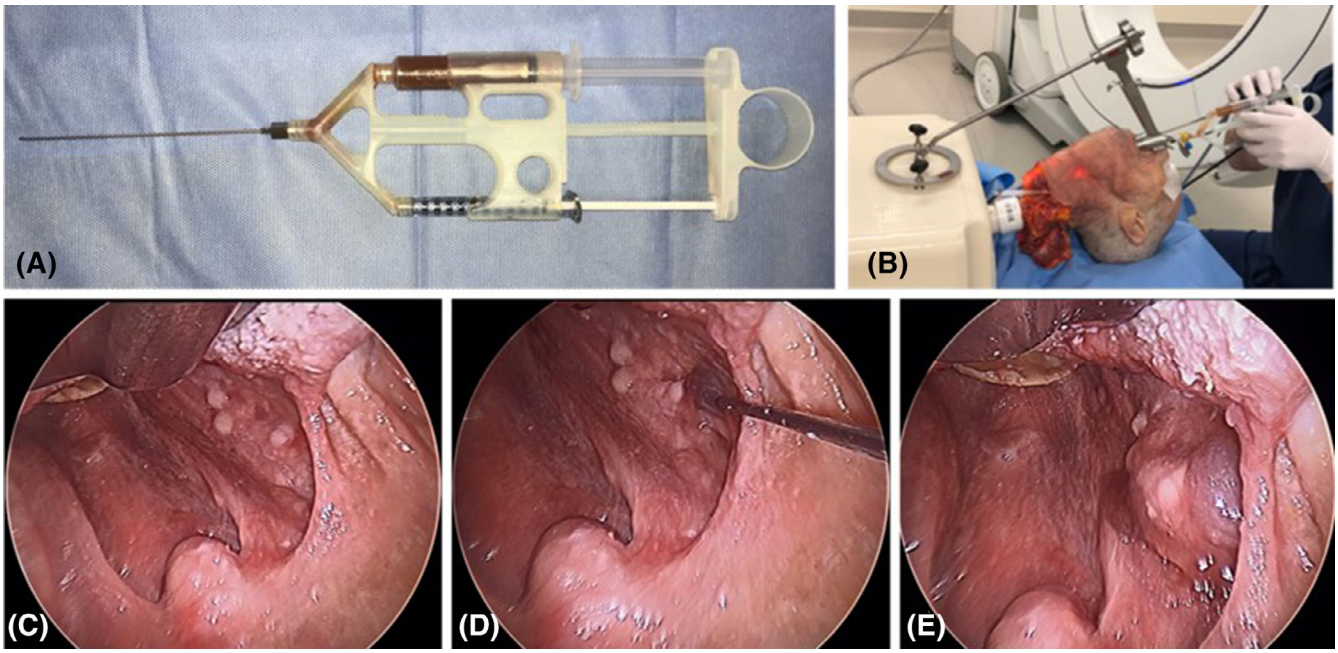

FIGURE 1 A, 3D printed dual barrel mixing syringe. Top syringe is agar mixture as outlined in Table 1 and bottom syringe is 4% glutaraldehyde. B, Suspension laryngoscopy of cadaver head and injection through Lindholm laryngoscope. C-E, Right tonsil prior to injection, C); during injection, D; and post injection, E

water to avoid further solidification and to prepare for the next injection. Endoscopic visualization of the tumor phantoms was performed using a Storz 0° and 30° telescope attached to a Stryker 1088 HD camera.

2.4 | Imaging

TPs were imaged using a 64-detector CT (SOMATOM Definition AS 64-slice, Siemens, Malvern, Pennsylvania) with TP characteristics evaluated in comparison to 9 true malignancies. TPs were then segmented with Mimics (Materialise, Plymouth, Michigan) for volumetric and radiodensity analysis. A binomial blur filter was utilized for ease of localization and segmentation of difficult-to-locate TPs.

Statistical analysis (paired- and two-sample *t* tests, alpha = .05, two-tailed) was performed with MATLAB R2019a (Mathworks, Natick, Massachusetts).

3 | RESULTS

3.1 | Tumor application and visual mimicry

Between 4 and 6 TPs were successfully implanted in each of the 4 cadaver heads (see Figure 1). Solidification of the tumor phantom was within 5 minutes after injection. Examples of the endoscopic appearance of the TP at various anatomic subsites are shown in Figure 2. The most realistic color combination was provided by applying brown and white food coloring in a 1:3 ratio. Visual mimicry of the added tissue volume created by the TP could be appreciated at all injection sites; however, more nuanced features such as ulceration, color heterogeneity, and the papillary appearance of certain tumors could not as easily be mimicked. TP injected into the tonsillar fossa were much better appreciated than those injected into the base of tongue. Radical tonsillectomy and partial glossectomy were performed on 2 TP. TP texture was firm and infiltrative, consistent with a typical HNSCC. Visually after removal, tumor could be delineated from surrounding muscle and soft tissue (Figure 3).

3.2 | Radiographic mimicry

Radiographic mimicry was appreciated at all tumor injection subsites (Figure 4). Iohexol concentration was titrated to achieve radiodensity levels comparable to 9 HNSCC cases. Tumor radiodensity in the nine patients was between 77 and 110 HU (mean 86.3 HU) whereas TP radiodensity was 59 and 127 HU (mean 93.7 HU), with no significant difference between groups ($P = 0.21$).

3.3 | Effect of freeze-thaw on TP characteristics

Volume and radiodensity was evaluated in nine TP in two cadaver heads first at the time of injection and then after one freeze-thaw cycle. No significant change in TP volume was seen (3608 mm^3 vs 4456 mm^3; $P = .37$); however, a significant reduction in radiodensity after one freeze-thaw cycle was measured (105 HU vs 83 HU; $P < .001$). Freeze-thaw did not have a subjective effect on TP appearance and texture.

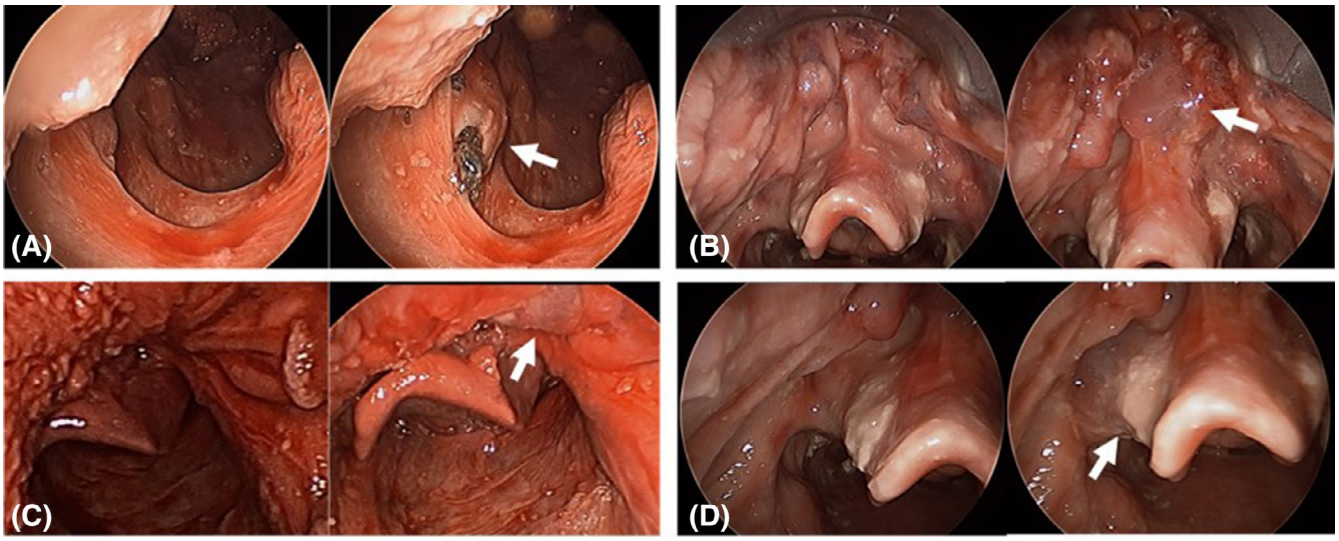

FIGURE 2 Pre and post injection endoscopic images at, A, left tonsil; B, vallecula; C, right lateral base of tongue; D, left pharyngoepiglottic fold. For A,C, blue food coloring was used whereas for B,D, a mixture of brown to white coloring in a 1:3 ratio was used. Note that although tumor fullness can be appreciated, color heterogeneity and ulceration are more difficult to mimic

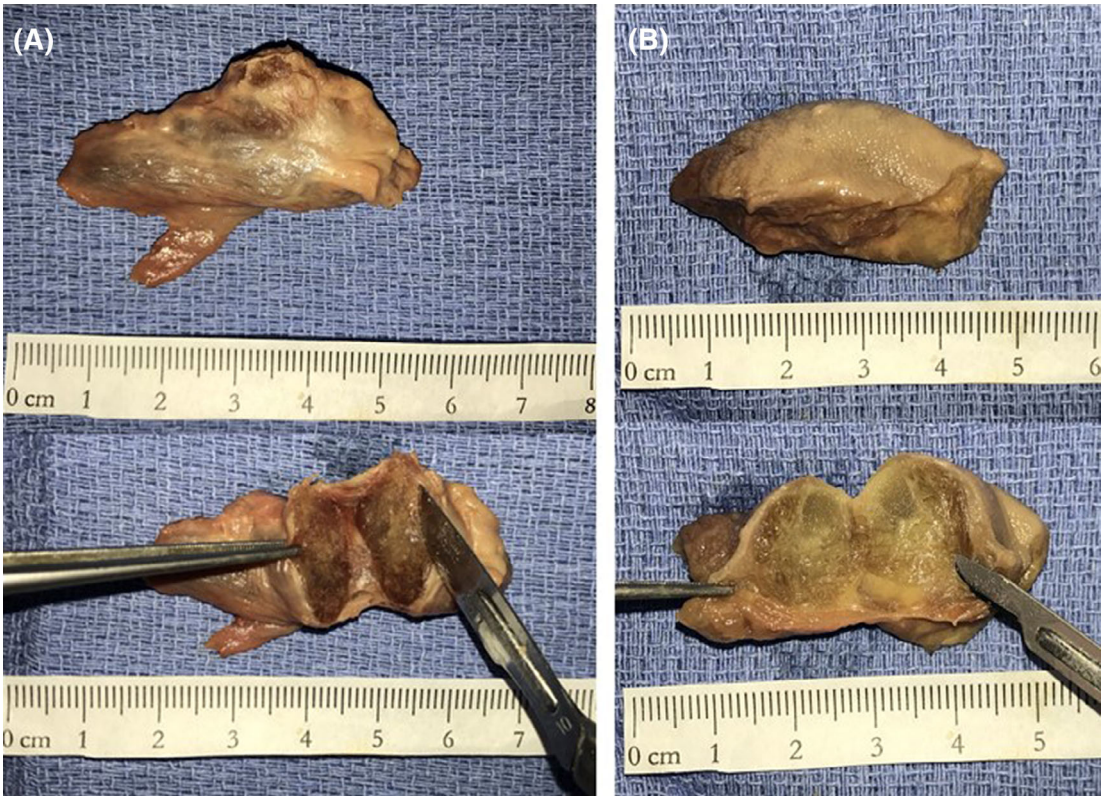

FIGURE 3 A, Radical tonsillectomy and B, partial glossectomy. Top image is specimen right after removal. Lower image is after bisecting TP. Note the ability to easily delineate TP from surrounding soft tissue

4 | DISCUSSION

Cadaver models are routinely used in otolaryngology surgical such as temporal bone surgery[12] transoral robotic surgery,[13] skull base and sinus surgery,[14] and laryngology.[15] Although tumor phantoms have been used successfully in other anatomic subsites, to date, there has been very little reported on tumor phantoms for transoral surgery.

Here we present a novel tumor phantom that can be applied in the cadaver model for teaching and research purposes. Our TP utilizes inexpensive materials that are simple to prepare, easily injectable in a

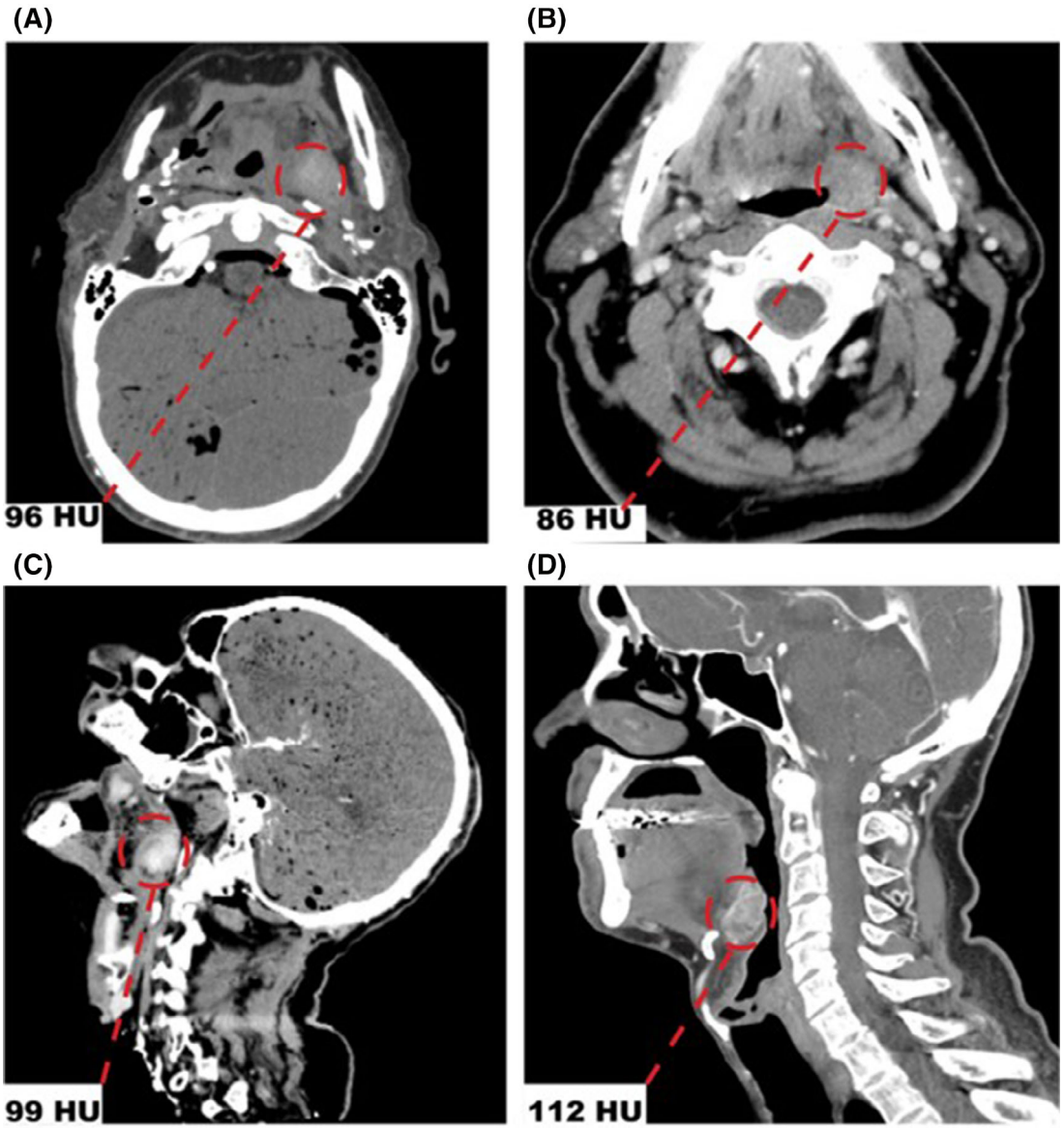

FIGURE 4 CT imaging of cadaver TP (left) and patient (right) for, A,B, tonsil; C,D, tongue base; the tumors in each image are circled with dashed red line and radiodensity is noted

nondestructive manner, and has good radiographic, visual and textural mimicry of typical HNSCCs. The advantage of this approach is that the phantom can be injected into the difficult to access regions of the oropharynx, larynx, and hypopharynx. A previously described phantom by Sobel et al is made of silicon foam which is cut to size but must be imbedded,[16] limiting its utility to anatomic sites that can be easily accessed.

This TP is applicable not only to head and neck malignancy, but to other anatomical sites where non-destructive implantation of tumor phantoms in cadaveric tissue is required. With modification to both agar and glutaraldehyde concentration as well as different food coloring additives, it can be customized to behave physically like other soft tissue tumors. Similarly, the concentration of radiographic contrast can be titrated to mimic typical tumor densities in vivo. Application of this TP is not limited to human cadavers but may also be used in cadaveric porcine and other cadaveric animal models.

We examined the effects of refreezing and thawing on the TP with regards to volume and radiographic density changes. For a training course or experimental setup, logistically the TP may be injected at one setting in a thawed head, head refrozen and then rethawed for the course or experiment itself. We found no significant change in volume, but the radiographic density decreased likely related to the diffusion of contrast material following a freeze-thaw cycle. Visually and physically, TP was not notably different from the pre-freeze state.

There are limitations to this current TP. Although visually a notable change in tissue volume fullness can be appreciated similar to a neoplastic process this TP does not mimic the heterogeneity and ulceration that is seen with most HNSCC. Additionally, we do not have a good way to mimic the vascular and other color changes that occur in and around a tumor. However, in the setting of a training course, this is a minor limitation as the resection would likely be guided more by tumor volume than mucosal

changes. Another limitation is the need to use 4% glutaraldehyde for cross-linking. The glutaraldehyde can be mixed with the main solution prior to injection, however the user will have to be mindful to commence injection immediately after mixing to avoid solidification of the solution in the needle barrel. Although not absolutely required, the dual channel syringe we developed does help to provide a more controlled and timely delivery of solution as it mixes the glutaraldehyde with the main solution at the time of injection. This syringe can be 3D printed from the CAD drawings located on the referenced website.

In summary, the currently presented tumor phantom is first described inexpensive and easy to apply simulation tool that provides excellent physical, visual, and radiographic mimicry of HNSCC. This tool could potentially improve surgical simulation training and aid in testing new surgical approaches and technologies in transoral surgery.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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