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ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Intraoperative Fluorescent Angiography Predicts Pharyngocutaneous Fistula After Salvage Laryngectomy

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ABSTRACT

Background. Technology to assess tissue perfusion is exciting with translational potential, although data supporting its clinical applications have been lagging. Patients who have undergone radiation are at particular risk of poor tissue perfusion and would benefit from this expanding technology. We designed a prospective clinical trial using intraoperative indocyanine green angiography to evaluate for wound-healing complications in patients undergoing salvage laryngectomy after radiation failure.

Patients and Methods. This prospective trial included patients undergoing salvage laryngectomy at a National Cancer Institute-designated tertiary cancer center between 2016 and 2018. After tumor extirpation and prior to reconstruction, 10 mg indocyanine green dye was infused and the fluorescence (F_{HYPO}) and ingress rate of the pharyngeal mucosa recorded. The primary outcome measure was formation of a pharyngocutaneous fistula (PCF).

Results. Patients who developed a PCF had significantly lower F_{HYPO} (87 vs 172, $p < 0.001$) and ingress rates (6.7 vs 15.8, $p = 0.043$) compared with those who did not develop a fistula. There were no fistulas in patients with $F_{\mathrm{HYPO}} > 150$ ($n = 21$) or ingress > 15 ($n = 15$). There was a 50% fistula rate in patients with $F_{\mathrm{HYPO}} \leq 103$ ($n = 10$) and ingress rate ≤ 6 ($n = 6$).

Conclusions. Intraoperative indocyanine green angiography can assess hypoperfusion in patients and predict risk of PCFs after salvage laryngectomy, and can thus intraoperatively risk-stratify patients for postoperative wound-healing complications.

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The Veterans Affairs Larynx Cancer study[1] as well as subsequent work by the Radiation Therapy Oncology Group[2] has shifted the role of primary surgery in the treatment of advanced-stage laryngeal squamous cell carcinoma (LSCC). As a result, radiotherapy (RT) and chemoradiotherapy (CRT) have become the initial therapeutic modality in many patients with the goal of laryngeal preservation in an effort to maintain native speech and swallowing function while also providing similar survival to primary laryngectomy.[1,3,4] Unfortunately, approximately one-third of patients have recurrent or persistent disease after treatment and require salvage laryngectomy.[4–6]

Wound healing after salvage laryngectomy is compromised due to the tissue effects of RT and CRT, which induce a hypoxic, hypocellular, and hypovascular environment.[7] In the setting of salvage laryngectomy, this results in a more challenging wound-healing environment, potentially resulting in development of a pharyngocutaneous fistula (PCF) due to postoperative breakdown of the pharyngeal closure.[8] This occurs in 30–75% of patients,[2,8–13] increases both short- and long-term morbidity, prolongs hospitalization, and is the most common cause of wound-related postoperative mortality in head and neck surgical oncology.[11,13–15]

Several factors influence PCF risk, including disease stage, prior treatment, reconstructive approach, hypothyroidism, and nutritional status.[16–18] To mitigate this risk, surgeons have developed a variety of reconstructive techniques to reduce the risk of fistula.[17,19–32] Unfortunately, there are few recognized intraoperative findings that can predict fistula formation and thus guide surgeons in dynamic reconstructive decision-making. Specifically, surgeons cannot accurately predict tissue quality and perfusion intraoperatively.

Intraoperative laser angiography has the potential to provide real-time intraoperative detection of clinically unapparent ischemia. This technique utilizes intravenous indocyanine green (ICG) dye which is maintained in the intravascular space by binding to plasma proteins. A laser diode array emits a near-infrared wavelength that causes the dye to fluoresce, thus creating a visibly detectable marker for perfusion. Subsequent recording of the fluorescence provides quantitative data regarding tissue perfusion that can be assessed and compared across patients, which can be analyzed in real time. The dye is subsequently metabolized rapidly without any associated hepatic or renal toxicities.

Therefore, we designed a prospective clinical trial to examine the use of intraoperative laser angiography in determining tissue perfusion in order to identify patients undergoing salvage laryngectomy who are at higher risk of PCF formation. We hypothesized that patients who develop PCF have worse perfusion as determined by intraoperative laser angiography compared with patients who do not develop PCF.

PATIENTS AND METHODS

A prospective clinical trial was performed at the University of Michigan between 2016 and 2018. Written informed consent was obtained for all patients. Inclusion criteria limited the study population to adults aged 18 years or older undergoing salvage laryngectomy after radiation therapy (XRT) or CRT for recurrent/persistent laryngeal cancer with planned primary closure of the pharyngeal mucosa. Patients with a known allergy to indocyanine green or iodine/shellfish were excluded. Patients who required a regional or free tissue flap (pharyngeal patch) to reconstruct the pharyngeal mucosa were excluded. The study was approved and monitored by the University of Michigan IRBMED (HUM00087909).

Patients underwent surgical extirpation consisting of laryngectomy with or without neck dissection according to our standard clinical approach.[33] After laryngectomy and before pharyngeal closure, the SPY intraoperative perfusion assessment system was brought into the field. Peripheral intravenous injection of 10 mg indocyanine green was then performed by the anesthesia team, and fluorescence of the native pharyngeal mucosa was recorded using the SPY Elite Fluorescence Imaging System (LifeCell Corp., Branchburg, NJ, USA). Fluorescence was recorded for 120 s. Figure 1 shows representative images of the tissue perfusion and the heat maps generated by the imaging system. All patients included underwent pharyngeal closure using primary closure with an onlay free flap.[3] Patients were followed for at least 4 weeks postoperatively. Fistulas were detected either clinically or with radiologic evidence on esophogram.

Fluorescence analysis can be performed in real time using SPYQ software (LifeCell Corp., Branchburg, NJ, USA). Using the fluorescence contour map generated using the SPYQ software, sites on the pharynx were selected to identify three to five candidate areas for hypoperfusion. A region of interest was defined within each of these candidate areas, and the subsequent fluorescence curves were generated to identify the least perfused. The variables under study were computed from the fluorescence curve. The variables of interest were peak fluorescence (F_{HYPO}), time to peak fluorescence (T), time to half-peak fluorescence ($T_{1/2}$), and rate of ingress as approximated by the slope of the best-fit line. In addition, the peak fluorescence of the region was normalized using a reference point assigned to the middle of the pharyngeal mucosa, which was defined as a separate variable: relative peak fluorescence ($\mathrm{RF}_{\mathrm{HYPO}}$). The primary outcome measure was presence of PCF within 30 days of surgery. Statistical analyses were performed using SPSS version 24 (IBM).

RESULTS

Forty-one patients undergoing salvage laryngectomy [mean (standard deviation, SD) age, 65.7 (7.5) years] were enrolled. Descriptive clinical characteristics are presented in Table 1. All patients received prior radiation therapy, and 18 (58.5%) received chemotherapy. In total, seven patients (17%) developed fistulas, which is consistent with rates reported in literature.[12,13,17] Analysis of the intraoperative laser angiography using ICG dye revealed that patients who developed a fistula had significantly lower F_{HYPO} (87 vs 172, 95% CI of the difference [36–134], $p < 0.001$) and ingress rate (6.7 vs 15.8, 95% CI of the difference [0.3–18], $p = 0.043$) than those who did not. In addition, patients who developed a PCF had a greater T (19.8 vs 15), and greater $T_{1/2}$ (6.3 vs 5).

Receiver operating curves (ROC) were generated for F_{HYPO} and ingress rates for the prediction of fistula, and the areas under the curve were 0.857 (95% CI, 0.723–0.992) and 0.797 (95% CI, 0.616–0.982), respectively (Fig. 2). From these curve coordinates, clinically appropriate cutoffs were identified. For F_{HYPO}, these cutoffs were: less than or equal to 103 [sensitivity/specificity/positive predictive value (PPV)/negative predictive value (NPV), 71.4/85.3/50/93.5%] and greater than 150 (100.0/61.8/35.0/100.0%).

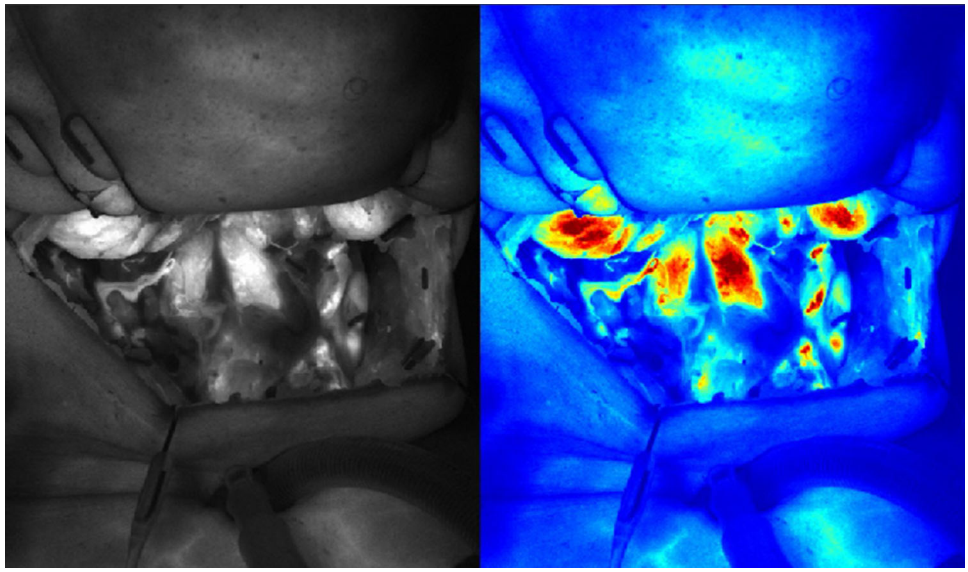

FIG. 1 Representative images of tissue perfusion generated by imaging system and the corresponding heat map used to quantify the fluorescence data

For ingress rate, these cut-offs were: less than or equal to 6 (50.0/91.2/50.0/91.2%) and greater than 15 (100.0/44.1/24.0/100%). These cutoffs were then used to identify and risk-stratify three tiers within the F_{HYPO} and ingress values that delineate high, intermediate, and low rates of fistula formation. The percentage of patients with fistulas in each group is demonstrated in Table 2. More than half of the enrolled patients had F_{HYPO} greater than 150 and therefore fell into the low-risk group, and of these 21 patients, none went on to develop a fistula. Similarly, of the 15 patients with ingress rates of greater than 15, none went on to develop a fistula. Alternatively, within the higher-risk group, 10 patients had F_{HYPO} less than or equal to 103, and half of them went on to develop a fistula, and 6 patients had ingress rates of greater than 150, and half of them went on to develop a fistula as well.

DISCUSSION

A substantial number of patients fail chemoradiation as primary therapy for laryngeal carcinoma, and salvage laryngectomy is required to treat the persistence or recurrence.[26,34] However, salvage laryngectomy bears a significantly higher risk of wound-healing problems as compared with primary laryngectomy, including pharyngocutaneous fistula formation.[22,26] Our prospective study indicates that intraoperative indocyanine green angiography is a potentially powerful tool to intraoperatively predict postlaryngectomy pharyngocutaneous fistula formation. If a patient is identified intraoperatively by indocyanine green angiography as being at high risk of developing a fistula, preventative reconstructive approaches such as vascularized tissue transfers can be personalized to the individual.[26] A fluorescence curve can be generated and analyzed in real time, thus enabling clinical decisions to be made immediately in the operating room based on the perfusion data. The high negative predictive value of this technique can also be used to guide an expedited postoperative course, which is an important consideration to reduce recovery time, improve time to adjuvant therapies, and reduce hospital costs to both the patient and the healthcare system.

While indocyanine green angiography has been previously evaluated for use in general surgery to predict anastomotic complications,[35], in neurosurgery to guide vascular procedures,[35] and in plastic surgery to guide breast and other reconstructive surgeries,[36,37] its usage in the head and neck has been limited. One smaller, retrospective study examined relative perfusion alone as a means to predict fistula formation in salvage laryngectomy.[38] Our study does concur with their results, showing that patients with a lower relative perfusion or RF_{HYPO} (35 vs 55; 95% CI of the difference,[9–32], $p < 0.001$) did have a higher risk of fistula. However, unlike that study, our usage of the software-generated heat map standardizes the data and eliminates the possibility of error from manual selection of data. Additionally, our evaluation of standard values based on the fluorescence curve also allows for additional absolute values that can be used to predict fistula formation.

Future study may focus on higher-risk patients to assess the feasibility of intraoperative modifications such as further pharyngeal resection to remove potentially hypoperfused tissue, different free flap reconstruction options, or earlier postoperative imaging or other assessments for developing complications. Protocols for these and other modifications to intraoperative care in high-risk patients will need to be developed and further assessed in

TABLE 1 Baseline characteristics and mean perfusion metrics of the fistula and nonfistula groups: peak fluorescence (F_{HYPO}), time to peak fluorescence (T), time to half-peak fluorescence ($T_{1/2}$), and rate of ingress

	Fistula (7)	No fistula (34)	p Value
Age (years)	62.8	66.3	0.25
Sex, number (%)			0.08
Female	4 (57.1)	6 (17.6)	
Male	3 (42.9)	28 (82.4)	
Indication, number (%)			0.32
Recurrence	6 (85.7)	32 (94.1)	
Nonfunctional	1 (16.7)	2 (5.9)	
Prior chemotherapy	6 (85.7)	18 (52.9)	0.21
Recurrent T, number (%)			0.45
T1	0	1 (3.1)	
T2	3 (50.0)	11 (34.4)	
T3	3 (50.0)	11 (34.4)	
T4	0	9 (28.1)	
Recurrent N, number (%)			0.42
N0	5 (83.3)	20 (62.5)	
N1	0	7 (21.9)	
N2	1 (16.7)	5 (15.6)	
Recurrent overall stage, number (%)			0.46
1	0	1 (3.1)	
2	2 (33.3)	9 (28.1)	
3	3 (50.0)	9 (28.1)	
4	1 (16.7)	13 (40.6)	
Subsite, number (%)			0.46
Supraglottic	3 (50.0)	9 (28.1)	
Glottic	3 (50.0)	21 (65.6)	
Subglottic	0	2 (6.3)	
Mean perfusion metrics			
Peak fluorescence (F_{HYPO})	87.0	172.0	0.001
Time to peak fluorescence (T)	19.8	15.0	0.15
Time to half-peak fluorescence ($T_{1/2}$)	6.3	5.0	0.25
Ingress	6.7	15.8	0.043
Relative F_{HYPO}	35.0	55.0	0.001

further trials. Patients at higher risk of PCF formation may also warrant modifications in their postoperative care plans as well, while lower-risk patients may be able to be discharged on a more expedited protocol, or even initiate oral intake on an accelerated schedule. Other future studies may evaluate what bearing such interventions and protocols may have on these clinical courses. All in all, PCF risk stratification using intraoperative laser angiography may enable more tailored clinical management for salvage laryngectomy patients, promoting increased intervention and surveillance in those who are most at risk of wound-healing complications and accelerated, abbreviated rehabilitation in those who are not.

For the purposes of establishing a homogeneous study population, this study was limited insofar as it only examined patients who required primary closure of the pharyngeal mucosa. Further validation in a broader cohort of patients will be necessary to understand and validate the impact that risk stratification will have on clinical decision-making.

CONCLUSIONS

Intraoperative indocyanine green angiography effectively quantifies tissue vascularity of the pharyngeal mucosa in patients undergoing salvage laryngectomy. Patients who went on to develop PCFs were found to have significant differences in their intraoperative perfusion metrics—F_{HYPO}, RF_{HYPO}, and ingress rate—relative to those who did not. These results facilitate clinically actionable risk stratification. Modifications to patients' clinical courses—including initiation of oral intake,

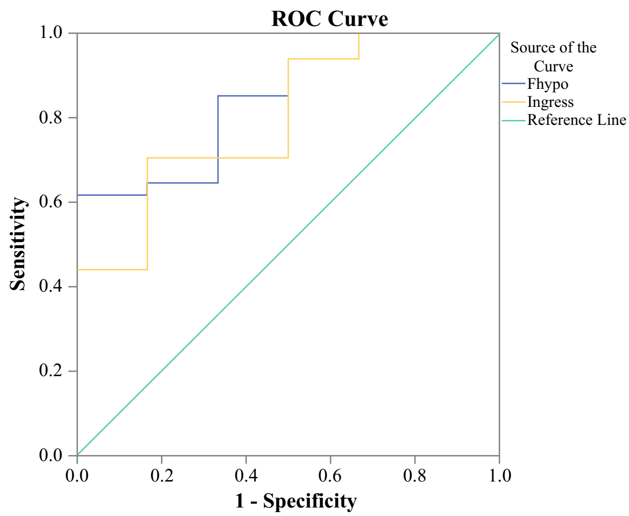

FIG. 2 Receiver operator characteristic curves for F_{HYPO} and ingress rate for the prediction of a fistula. The areas under the curve are 0.857 and 0.797, respectively

TABLE 2 Rate of fistula formation at various cutoff points for F_{HYPO} and ingress rate

	No. (%)	Fistula rate (%)
F_{HYPO}		
≤ 103	10 (24.4)	50
> 103 and ≤ 150	9 (21.2)	11
> 150	21 (51.2)	0
Ingress		
≤ 6	6 (15.0)	50
> 6 and ≤ 15	19 (47.5)	16
> 15	15 (37.5)	0

hospital stay length, reconstructive approach, and postoperative surveillance—may be informed by the use of these data. Thus, indocyanine green angiography may play a role in predicting the risk of wound-healing complications after salvage laryngectomy and may assist in intraoperative and postoperative decision-making.

DISCLOSURES The authors have declared there are no conflict of interest.

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