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ORIGINAL ARTICLE

Risk factors for pneumonia after endoscopic laryngopharyngeal surgery in cases with prior esophageal cancer treatment

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Abstract

Background and Study Aims: Endoscopic laryngopharyngeal surgery is an effective treatment for superficial laryngopharyngeal cancer, particularly in cases with prior esophageal cancer treatment. Despite its frequent application, reports on the risk factors for postoperative complications are limited. This study aimed to identify the risk factors for pneumonia after endoscopic laryngopharyngeal surgery and to examine the variations in pneumonia incidence among the types of prior esophageal cancer treatment.

Methods: Patients who had a history of esophageal cancer treatment and subsequently underwent endoscopic laryngopharyngeal surgery for superficial pharyngolaryngeal cancer were retrospectively analyzed. We examined the association between postoperative pneumonia and several factors, including number of lesions; diameter of the resected lesion; and type of previous esophageal cancer treatment, such as endoscopic submucosal dissection, chemoradiotherapy, and esophagectomy.

Results: The study included 79 patients who had a mean age of 67.4 years. Postoperative pneumonia occurred in 16.4%. Multivariate analysis showed that the pneumonia incidence significantly increased in cases with multiple lesions (OR 4.794, 95% CI 1.133–20.288, $p = 0.033$) and larger diameter of the resected lesion (OR 7.047, 95% CI 1.791–27.730, $p = 0.005$). Importantly, compared with other treatments, prior esophagectomy for esophageal cancer did not increase the pneumonia incidence.

Conclusions: Multiple lesions and larger lesion diameter were the significant predictors of postoperative pneumonia. Moreover, endoscopic laryngopharyngeal surgery can be safely performed even in patients who have previously undergone esophageal cancer surgery, although careful monitoring remains necessary.

KEYWORDS
endoscopic laryngopharyngeal surgery, endoscopic treatment, esophagectomy, laryngopharyngeal cancer, pneumonia

1 | INTRODUCTION

Esophageal cancer ranks sixth globally in mortality, with significant sex differences in incidence and mortality rates.[1] In Asia, squamous cell carcinoma predominates and is often secondary to prolonged exposure to carcinogens in the upper aerodigestive tract (i.e., field cancerization).[2–5] This exposure was reported to lead to multiple primary cancers, particularly head and neck cancers, in 14% to 35% of patients with esophageal cancer.[6–8] Advances in endoscopic technologies, such as narrow band imaging (NBI) and magnification, have facilitated detection of superficial pharyngolaryngeal cancer in the early stage, which can be treated endoscopically.[9,10]

Endoscopic laryngopharyngeal surgery (ELPS), which was developed in September 2004 by Omori et al., is a treatment option for superficial laryngopharyngeal cancer.[11] This procedure uses a curved laryngoscope for laryngeal expansion and involves oral insertion of forceps to perform submucosal dissection under endoscopic guidance. Although less invasive, compared with traditional surgeries that involve external incisions, ELPS is associated with potential complications, such as postoperative bleeding, swallowing disorders, and pneumonia. Specifically, pneumonia was reported to occur frequently as a complication after ELPS, with an incidence rate of approximately 7%. In elderly patients aged ≥65 years, the reported incidence was approximately 10%.[12]

At our institution, patients with esophageal cancer are initially treated with endoscopic submucosal dissection (ESD), chemoradiotherapy (CRT), or esophagectomy, depending on the clinical stage. Following these treatments, patients are routinely monitored by endoscopy every 6 months. During the long-term follow-up after esophageal cancer treatment, superficial pharyngolaryngeal cancers are frequently identified and are treated by ELPS. To our best knowledge, reports on the risk factors for pneumonia after ELPS had been limited. Identifying these risk factors is crucial for safe performance of the procedure. Moreover, esophageal cancer surgery is known to possibly impair swallowing function, leading to increased incidence of aspiration pneumonia.[13–15] Therefore, the incidence of pneumonia after ELPS might be relatively high in patients who have undergone esophageal cancer surgery, although this remains to be clarified.

In this study, we aimed to identify the risk factors for pneumonia after ELPS in patients who have undergone prior esophageal cancer treatment, with particular focus on the incidence of pneumonia after ELPS in those who had previously undergone esophageal cancer surgery.

2 | METHODS

2.1 | Patients

A retrospective analysis was conducted on patients who received prior treatment for esophageal cancer and subsequently underwent ELPS for superficial pharyngolaryngeal cancer from October 2015 to June 2021 at our institution. The initial treatment for esophageal cancer included ESD, CRT, or surgical intervention. The evaluations prior to ELPS focused on superficial pharyngolaryngeal cancer confined to the submucosal layer and involved upper gastrointestinal endoscopy with NBI and magnification, CT scan, and blood tests. In addition, we assessed the preoperative patient characteristics, such as age, sex, BMI, smoking history, diabetes, and history of cervical radiation and the methods of esophageal cancer treatment. The intraoperative findings included lesion localization, macroscopic type, predicted depth, number of lesions, and operation time. The pathological assessments included the maximum diameter of lesion length and depth.

2.2 | Surgical procedure

All ELPS procedures were performed, as previously reported.[11] A curved laryngoscope was used to elevate the larynx and secure a working space, followed by lesion identification by standard observation, NBI, magnification, and iodine staining. A 1.2% iodine solution outlined the lesion boundary, and coagulation mode marks were placed 1–2 mm outside this boundary. Thereafter, adrenaline in saline solution was injected into the subepithelial layer of the pharyngolarynx, followed by creation of an incision around the marks and removal of the lesion under appropriate traction. Finally, the site was checked for bleeding and laryngeal edema, and measures, such as hemostasis, were applied as necessary.

2.3 | Definition of complications

Postoperative pneumonia was defined as the occurrence of fever, increased white blood cell count, and elevated C-reactive protein level within 1 week after surgery and was classified as Clavien–Dindo grade 2 or higher. In addition, the definition included the presence of new infiltrates on X-ray or CT scan or the presence of clinical signs of pneumonia.[16] Swallowing disorder was defined as oral intake impairment that required treatment, such as tube feeding. Postoperative bleeding was defined in cases requiring emergency endoscopic hemostasis after surgery.

2.4 | Statistical analysis

To determine the predictors of pneumonia after ELPS, both univariate and multivariate logistic regression analyses were carried out. For univariate analysis, categorical variables were evaluated using chi-square test, whereas continuous variables were examined using the Mann–Whitney U test. A p value of <0.05 was considered to indicate statistical significance. Variables that achieved a p value of <0.2 in the univariate analysis were then included in a logistic regression model for further multivariate analysis. The cutoff values for the evaluated risk factors, including surgical duration, lesion resection length, and Brinkmann Index, were

determined using receiver operating characteristic curves, by selecting the point that was closest to the top left corner (0,1), where the balance between sensitivity and specificity was optimal. All statistical calculations were performed using SPSS software version 29 (IBM; Armonk, NY, USA).

3 | RESULTS

3.1 | Patient characteristics

This study enrolled 79 patients with 84 lesions; the mean age was 67.4 years, with 75 men (94.9%) and four women (5.0%). The mean BMI was 20.5, and the mean Brinkman Index was 578. A medical history of diabetes was found in six cases (7.5%). The type of prior treatment for esophageal cancer was ESD in 25 cases (31.6%), CRT in 21 cases (26.5%), surgical intervention in 47 cases (59.4%), and multiple modalities in 14 cases (17.7%). Among the 79 patients, the number of lesions was one in 65 patients (77.3%), two in 10 patients (11.9%), three in three patients (3.5%), and four in one patient (1.1%). The most common tumor site was the pyriform sinus of the hypopharynx, accounting for 61 lesions (64%). The maximum estimated tumor depth before surgery was epithelium (EP) in 61 cases (77.2%) and subepithelium (SEP) in 18 cases (22.7%), with type 0–IIb lesions being the most common in 63 cases (75%). The patient background characteristics are summarized in Table 1.

TABLE 1 Patient characteristics.

Patient characteristics	
Total number of cases	79
Total number of lesions	84
Age (year) mean ± SD	67.4 ± 6.6
Sex	
Male	75 (94.9%)
Female	4 (5.0%)
BMI (kg/m²)	20.5 ± 2.5
Brinkman Index, mean ± SD	578 ± 438
Diabetes	6 (7.5%)
History of esophageal cancer treatment	
ESD	25 (31.6%)
CRT	21 (26.5%)
Esophagectomy	47 (59.4%)
Multiple treatment	14 (17.7%)
Number of lesions	
1	65 (77.3%)
2	10 (11.9%)
3	3 (3.5%)
4	1 (1.1%)
Location	
Larynex	
Epiglottis	5 (5.9%)
Plica aryepiglottic	2 (2.3%)
Middle pharynx	
Anterior wall	2 (2.3%)
Lateral wall	3 (3.5%)
Posterior wall	2 (2.3%)
Hypopharynx	
Pyriform sinus	61 (72.6%)
Pharyngoesophageal junction	2 (2.3%)
Posterior wall	7 (8.3%)
Maximum estimated depth of tumor	
EP	61 (77.2%)
SEP	18 (22.7%)
Macroscopic classification	
0-I	1 (1.1%)
0-IIa	17 (20.2%)
0-IIb	63 (75%)
0-IIc	3 (3.5%)

Abbreviations: BMI, body mass index; CRT, chemoradiotherapy; EP, epithelium; ESD, endoscopic submucosal dissection; SD, standard deviation; SEP, subepithelium.

3.2 | Perioperative outcomes

The mean procedure time was 44 min, and bleeding was minimal in almost all cases. The mean time to resume oral intake postoperatively was 3.1 days. The postoperative complications included pneumonia in 13 cases (16.4%), swallowing disorder in two cases (2.5%), and postoperative bleeding in two cases (2.5%). Pathological examination revealed dysplasia in two cases, with depth of EP in 17 cases (20.2%) and SEP in 65 cases (77.3%). The mean maximum diameter of the resected lesion was 22.3 mm. There were no in-hospital deaths postoperatively. The perioperative outcomes of ELPS are detailed in Table 2.

3.3 | Comparison of patients with pneumonia and those without pneumonia

Age, BMI, Brinkmann Index, history of diabetes, number of pyriform sinus lesions, preoperative diagnosis of subepithelial infiltration, presence of type 0–IIb lesions, procedure time, presence of multiple lesions, postoperative subepithelial infiltration, and maximum lesion length were compared between patients with pneumonia and those who had no pneumonia. As shown in Table 3, patients with pneumonia ($n = 13$) and those who had no pneumonia ($n = 66$) had significant differences in the presence of multiple lesions ($p = 0.009$) and maximum lesion diameter ($p = 0.002$).

3.4 | Risk factors for postoperative pneumonia

Univariate analysis identified the presence of multiple lesions (OR 6.214, 95% CI 1.664–23.201, $p = 0.007$) and maximum lesion diameter

of ≥27 mm (OR 8.357, 95% CI 2.238–31.202, $p=0.002$) as the significant risk factors for postoperative pneumonia. On multivariate analysis, the presence of multiple lesions (OR 4.794, 95% CI 1.133–20.288, $p=0.033$) and maximum lesion diameter of ≥27 mm (OR 7.047, 95% CI 1.791–27.730, $p=0.005$) remained independent prognostic factors. Furthermore, univariate logistic regression analysis revealed that previous esophagectomy as treatment for esophageal cancer was not a significant risk factor for pneumonia after ELPS (OR 0.523, 95% CI 0.158–1.733, $p=0.289$). These results are summarized in Table 4.

TABLE 2 Perioperative outcomes.

Perioperative outcomes	
Operation time (min), mean ± SD	44.0 ± 23.1
Timing of oral intake (POD), mean ± SD	3.1 ± 3.1
Complications	
Pneumonia	13 (16.4%)
Swallowing dysfunction	2 (2.5%)
Postoperative bleeding	2 (2.5%)
Depth of tumor	
Atypical epithelia	2 (2.3%)
EP	17 (20.2%)
SEP	65 (77.3%)
Maximum diameter of lesion (mm), mean ± SD	22.3 ± 10.8

Abbreviations: EP, epithelium; POD, postoperative day; SD, standard deviation; SEP, subepithelium.

3.5 | Characteristics of esophageal cancer treatment

The presence or absence of pneumonia was compared based on factors related to the initial treatment for esophageal cancer, including esophagectomy, ESD, and CRT. For esophagectomy cases, comparisons included the anastomotic site, lymph node dissection field, use of thoracoscopy, reconstruction route, reconstructed organ, number of lymph nodes dissected, presence of recurrent laryngeal nerve paralysis, and the duration from esophagectomy to ELPS. In ESD cases, tumor location and the interval between ESD and ELPS were analyzed. For CRT cases, the presence or absence of neck irradiation and the interval between CRT and ELPS were compared. No statistically significant differences were observed in the occurrence of pneumonia for any of these factors. These results are summarized in Table 5.

3.6 | Logistic regression model for postoperative pneumonia after ELPS in patients with prior esophagectomy

In cases where esophagectomy was performed as the initial treatment, both univariate and multivariate analyses identified maximum diameter of lesion ≥27 mm as a significant risk factor for pneumonia, while no statistical significance was observed for other factors, as shown in Table 6.

TABLE 3 Comparison of patients with pneumonia and those without pneumonia after ELPS.

	Pneumonia (+) ($n=13$)	Pneumonia (−) ($n=66$)	p value
Age, (year), mean ± SD	69.9 ± 6.4	66.9 ± 6.6	0.154
BMI (kg/m²)	20.1 ± 1.8	20.6 ± 2.6	0.213
Brinkman Index ≧600	9 (69.2%)/4 (30.7%)	32 (48.4%)/34 (51.5%)	0.171
Diabetes	1 (7.6%)/12 (92.3%)	5 (7.5%)/61 (92.4%)	1.000
Location of pyriform sinus	10 (76.9%)/3 (23.0%)	47 (71.2%)/19 (28.7%)	1.000
Estimated submucosal invasion	2 (15.3%)/11 (84.6%)	16 (24.2%)/50 (75.7%)	0.721
Macroscopic classification: 0-IIb	9 (69.2%)/4 (30.7%)	48 (72.7%)/18 (27.2%)	0.748
Operative time, mean ± SD	48.6 ± 19.9	43.1 ± 23.9	0.391
Multiple lesions	6 (46.1%)/7 (53.8%)	8 (12.1%)/58 (87.8%)	0.009
Pathological submucosal invasion	11 (84.6%)/2 (15.3%)	45 (68.1%)/21 (31.8%)	0.326
Maximum diameter of lesion (mm), mean ± SD	30.5 ± 6.9	20.8 ± 10.0	0.002

Abbreviations: BMI, body mass index; CRT, chemoradiotherapy; ESD, endoscopic submucosal dissection; SD, standard deviation.

TABLE 4 Logistic regression model for postoperative pneumonia after ELPS.

	Univariate			Multivariate		
Factors	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age (year) ≥ 67	2.778	0.700–11.021	0.146	6.100	0.791–47.044	0.083
BMI (kg/m²) ≥ 20.3	0.394	0.110–1.406	0.151	0.295	0.052–1.668	0.167
Brinkman ≥ 600	2.391	0.669–8.537	0.180	3.350	0.541–20.740	0.194
Diabetes	1.017	0.109–9.497	0.998			
History of esophagectomy for esophageal cancer	0.523	0.158–1.733	0.289			
History of other treatment[a] for esophageal cancer	2.118	0.593–7.562	0.248			
Location of pyriform sinus	1.348	0.334–5.442	0.675			
Estimated submucosal invasion	0.568	0.114–2.838	0.491			
Macroscopic classification: 0-IIb	0.844	0.231–3.085	0.797			
Operative time ≥ 37 min	2.540	0.711–9.074	0.151	0.314	0.043–2.305	0.255
Multiple lesions	6.214	1.664–23.201	0.007	13.189	1.417–122.71	0.023
Pathological submucosal invasion	2.567	0.522–12.626	0.246			
Maximum diameter of lesion ≧27 mm	8.357	2.238–31.202	0.002	12.357	2.192–69.657	0.004

Abbreviation: BMI, body mass index.

[a]Other treatment includes ESD or CRT for esophageal cancer.

4 | DISCUSSION

In this study, we found that the occurrence of pneumonia after ELPS was not associated with a history of esophagectomy but had a high probability in pharyngolaryngeal cancer cases with multiple lesions and larger lesion diameter. To our best knowledge, this was the first study to demonstrate that although esophagectomy can decrease swallowing function, it had no negative impact on the occurrence of pneumonia after ELPS. The prognosis after ELPS is generally favorable. Regular endoscopy monitoring after esophageal cancer treatment facilitates early detection and safe treatment of pharyngolaryngeal cancer and significantly benefits a patients' quality of life and prognosis.[17]

There had been few previous reports on the risk factors for pneumonia following ELPS. In one study from France, Aubry et al. indicated that advanced age > 65 years, tumor stage, and location were the significant risk factors for pneumonia after transoral robotic surgery for pharyngolaryngeal cancer.[16] Conversely, in a research on ELPS in Japan, Kishimoto et al. found no correlation between the size or location of the resection and the incidence of pneumonia after ELPS, but they showed that age, especially ≥65 years, tended to be associated with a relatively high incidence of pneumonia.[12] In this study, the significant risk factors for pneumonia after ELPS were the presence of multiple lesions and the diameter of the resected lesion but not age, and the incidence of pneumonia following ELPS was higher in this study compared to previous reports.[12] The different results may be attributed to the fact that our study focused on patients who were previously treated for esophageal cancer. Despite the frequent overlap between head and neck cancer and esophageal cancer, previous reports have not mentioned a history or prior treatment for esophageal cancer.[6–8] Therefore, we considered prior esophageal cancer treatment in our study. The novelty of this present study was that it was the first to consider previous esophageal cancer treatment as a risk factor for pneumonia after ELPS. Another strength of this research, compared with previous reports, was the evaluation of a larger number of perioperative variables as potential risk factors for pneumonia.

This study speculated that as lesions enlarge or multiply, the extent of resection would increase and can lead to more extensive tissue scarring. Weakening of the swallowing function may, in turn, increase the risk of developing pneumonia. Interestingly, we found no significant difference in the risk of pneumonia among the different types of esophageal cancer treatments, such as ESD, CRT, and esophagectomy. Furthermore, in the detailed analysis of each treatment, no correlation was observed between the presence of pneumonia and factors such as the anastomotic site, lymph node dissection field, reconstructed organ or route, use of thoracoscopy, number of lymph nodes dissected, or presence of recurrent laryngeal nerve paralysis in patients who underwent esophagectomy. Similarly, no correlation was found between tumor location and pneumonia incidence in ESD cases, or between the presence or absence of neck irradiation and pneumonia in CRT cases. Additionally, for any initial treatment, the interval between esophageal cancer treatment and ELPS was not associated with the occurrence of pneumonia. One explanation could be the comprehensive preoperative care. All patients who underwent ELPS received preoperative oral care from our dental and oral surgery departments. This regimen focused on maintaining a clean oral environment, which likely played a vital role in preventing

TABLE 5 Characteristics of esophageal cancer treatment.

Characteristics of esophageal cancer treatment		Pneumonia (+)	Pneumonia (−)	*p* value
Esophagectomy	Anastomosis cervical	5 (10.6%)	40 (85.1%)	0.107
	Intrathoracic	1 (2.1%)	1 (2.1%)	
	LN dissection			
	3 fields	6 (12.7%)	34 (72.3%)	0.273
	2 fields	0	7 (14.8%)	
	Thoracotomy			
	VATS	6 (12.7%)	33 (70.2%)	0.235
	OPEN	0	8 (17.0%)	
	Reconstructed route			
	Posterior mediastinal	6 (12.7%)	37 (78.7%)	0.424
	Retrosternal	0	2 (4.2%)	0.580
	Antesternal	0	2 (4.2%)	0.580
	Reconstructed organ			
	Gastric reconstruction	6 (12.7%)	40 (85.1%)	0.699
	Colon reconstruction	0	1 (2.1%)	
	Number of lymph node dissected, mean ± SD	63.3 ± 16.6	55.9 ± 17.8	0.351
	Recurrent laryngeal nerve palsy	2 (4.2%)	11 (23.4%)	0.739
	The time interval between esophagectomy and ELPS (month), mean ± SD	63 ± 45.1	44.6 ± 44.2	0.357
ESD	Tumor location			
	Ut	3 (12%)	5 (20%)	0.278
	Mt.	2 (8%)	8 (32%)	0.702
	Lt	5 (20%)	12 (48%)	0.356
	The time interval between ESD and ELPS (month), mean ± SD	64.5 ± 38.6	52.3 ± 52.2	0.605
CRT	Radiation field With neck field irradiation	2 (9.5%)	9 (42.8%)	0.916
	The time interval between CRT and ELPS (month), mean ± SD	70.2 ± 45.1	65.4 ± 54.4	0.871

Abbreviations: CRT, chemoradiotherapy; ESD, endoscopic submucosal dissection; SD, standard deviation; VATS, video-assisted thoracic surgery.

pneumonia. Particularly for cases with multiple lesions or large resection diameters, interventions such as enhanced postoperative rehabilitation and meticulous monitoring are considered necessary. Moreover, appropriate risk stratification might be achieved during patient selection.

This study had several limitations. First, the retrospective and single-center design that was limited to a Japanese population and a small number of experts might have introduced an element of selection bias. Second, this study involved only 79 cases; accumulation of a larger number of cases is necessary in the future. Third, there were changes in the indications for ELPS, preoperative preparation, management of postoperative complications during the 6-year study period. Fourth, this study lacks a detailed evaluation of weight loss, changes in nutritional indices, muscle mass reduction, quality of life, dysphagia scores, and pulmonary function following esophageal cancer treatment. In the current cohort, there were few cases of long-term pneumonia. However, information on long-term swallowing function is crucial, and we plan to accumulate more data in this area in the future. A multicenter prospective study is necessary to assess the external validity of our findings.

TABLE 6 Logistic regression model for postoperative pneumonia after ELPS in patients with prior esophagectomy.

	Univariate			Multivariate		
Factors	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age (year) ≥ 67	2.556	0.420–15.553	0.309			
Diabetes	3.900	0.297–51.196	0.300			
Brinkman ≥ 600	3.125	0.512–19.089	0.217			
Cervical anastomosis	0.125	0.007–2.326	0.163	0.127	0.002–6.817	0.310
Recurrent laryngeal nerve palsy	1.364	0.218–8.523	0.740			
Estimated submucosal invasion	0.711	0.073–6.889	0.769			
Macroscopic classification: 0-IIb	0.733	0.117–4.583	0.740			
Operative time≧37 min	2.824	0.463–17.210	0.260			
The time interval between esophagectomy and ELPS≦1 year	0.431	0.046–4.069	0.462			
Multiple lesions	4.125	0.698–24.386	0.118	1.467	0.171–12.555	0.726
Pathological submucosal invasion	0.929	0.150–5.733	0.936			
Maximum diameter of lesion ≧27 mm	20.625	2.106–201.99	0.009	18.465	1.599–213.23	0.019

Abbreviation: BMI, body mass index.

5 | CONCLUSIONS

In patients who had received prior esophageal cancer treatment and subsequently underwent ELPS for pharyngolaryngeal cancer, the presence of multiple lesions and larger lesion resection diameter significantly predicted the occurrence of postoperative pneumonia. Furthermore, the type of esophageal cancer treatment, particularly surgery, did not increase the risk of pneumonia after ELPS. Therefore, ELPS can be safely performed in patients who had previously undergone esophageal cancer surgery. Nevertheless, careful monitoring for postoperative pneumonia is necessary for patients with multiple lesions or large lesion diameters.

AUTHOR CONTRIBUTIONS

Atsushi Nakao: Conceptualization; investigation; writing – original draft. **Hirofumi Kawakubo:** Methodology; project administration; supervision; writing – original draft; writing – review and editing. **Masashi Takeuchi:** Methodology; project administration; supervision; writing – original draft; writing – review and editing. **Satoru Matsuda:** Methodology; project administration; supervision. **Kazumasa Fukuda:** Methodology; project administration; supervision. **Yuko Kitagawa:** Methodology; project administration; supervision.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The datasets generated and analyzed in this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the ethics committee of Keio University School of Medicine (approval number: 20150044) and was performed according to the Declaration of Helsinki principles.

Informed consent: The opt-out method to obtain patient consent was utilized.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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