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ORIGINAL RESEARCH

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Salvage transoral videolaryngoscopic surgery for post-irradiation recurrence of hypopharyngeal carcinoma

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Abstract

Background: Transoral salvage surgery has the potential to preserve a patient's quality of life. Therefore, we investigated the outcomes, safety, and risk factors for postoperative complications of salvage transoral videolaryngoscopic surgery (TOVS) for recurrent hypopharyngeal carcinoma after radiotherapy (RT) or chemoradiotherapy (CRT).

Methods: This retrospective analysis enrolled patients with hypopharyngeal cancer who had a history of RT or CRT and underwent TOVS from January 2008 to June 2021. The factors related to postoperative complications, postoperative swallowing functions and survival rates were analyzed.

Results: Seven patients (36.8%) of the 19 patients developed complications. Severe dysphagia was the primary complication, and post-cricoid resection was a complication risk factor. The FOSS score was significantly lower in the salvage treatment group. The survival rates were: 3-year overall survival: 94.4%; disease-specific survival: 94.4%; 5-year overall survival: 62.3%; and disease-specific survival: 86.6%.

Conclusions: Salvage TOVS for hypopharyngeal cancer was feasible, and oncologically and functionally reasonable.

Level of Evidence: 2b.

KEYWORDS
hypopharyngeal carcinoma, radiotherapy, recurrence, salvage surgery, transoral videolaryngoscopic surgery

1 | INTRODUCTION

Diagnosing hypopharyngeal carcinoma early is challenging; consequently, most patients have advanced disease by the time it is detected. Chemoradiotherapy (CRT) is primarily performed as function-preserving therapy,[1] but recurrence is common. The recurrence rate of hypopharyngeal carcinoma after radiation therapy is 40%–60% for advanced tumors.[2] Primarily, salvage surgery is performed for recurrent or residual disease,[3] but studies indicate that radiotherapy (RT) to the head and neck causes tissue fibrosis, prolongs

healing after resection, and causes long-term functional disability.[4,5] Therefore, in addition to being technically difficult, salvage surgery has a high risk of complications, as high as 50%.[6–9] Moreover, despite such radical surgery, the 5-year overall survival rate is low, ranging from 19% to 23%.[10,11] Therefore, recommending an appropriate treatment to patients is challenging owing to the poor prognosis of salvage surgery and the considerable quality of life decrease.

Conversely, transoral resections, such as transoral robotic surgery, transoral laser microsurgery, and transoral video laryngoscopic surgery (TOVS), have become more common for early-stage cancer, and their safety, efficacy, and oncologic and functional outcomes are being assessed.[12–16] Theoretically, transoral post-irradiation salvage surgery has the potential to preserve a patient's quality of life. Therefore, we investigated the outcomes, safety, and risk factors for postoperative complications of salvage TOVS for recurrent hypopharyngeal carcinoma after RT or CRT.

2 | MATERIALS AND METHODS

This retrospective analysis enrolled patients with hypopharyngeal cancer who underwent TOVS at Tokai University Hospital in Kanagawa, Japan, from January 2008 to June 2021. All enrolled patients had a history of RT or CRT and were followed for at least 12 months.

The inclusion criteria for salvage TOVS were: (1) recurrent or residual squamous cell carcinoma (SCC), following definitive radiation with or without chemotherapy, (2) rT1 or rT2 lesion, (3) within half circumferential extension, (4) no lymph node or distant metastasis. The exclusion criteria were (1) invasion to the hyoid bone, thyroid cartilage, and cricoid cartilage on imaging studies, (2) invasion of deep tissue lateral to constrictor muscle or posterior invasion of deep vertebral fascia, (3) a performance status 2 or higher, (4) severe cardio-pulmonary dysfunction and (4) trismus or other impairment that would make oral resection difficult. The medical records of each patient were accessed to obtain information regarding previous tumor site, previous TN classification, previous treatment, total RT dose, duration between presentations, current tumor subsite, current TN classification, complications, preoperative FOSS, postoperative FOSS, onset of dysphagia, nasogastric tube or percutaneous gastrostomy tube dependence, hospitalization, tracheostomy, follow up, and survival outcomes.

The study protocol was approved by the institutional review board (22R194). Given the retrospective nature of the study, the ethics committee waived a written informed consent from the patient.

2.1 | Surgical procedure

The surgical procedure adhered to the TOVS technique reported by Tomifuji et al.[17] The surgical field was expanded using either the FK-WO retractor (Olympus Medical Systems, Tokyo, Japan) or the Weerda distending laryngoscope (Karl Storz, Tuttlingen, Germany). Observations of the surgical field were made using the ENDO EYE® (Olympus Medical Systems, Japan), a videoendoscope equipped with a flexible tip. Electrocautery tips were provided by the Colorado Micro Dissection Needle® (Stryker Japan KK) or a malleable needle electrocautery, KD 600 (Olympus Medical Systems, Japan) was used. Grasping forceps utilized included the LARYNGOFORCERII grasping forceps (STORZ) and the STEINER grasping forceps (STORZ).

The narrow band imaging system[18] and iodine staining technique[19] were employed to confirm the presence of the lesion. The tumor was excised en bloc, leaving a 5–10 mm safety margin. The mucosal defect was covered with fibrin glue and polyglycolic acid sheets (MCFP technique[20]). In cases where total resection was achieved, frozen section pathology was not carried out. Tracheostomy was not performed routinely. The aforementioned procedure was carried out by a proficient surgeon with extensive experience in performing over 30 cases of TOVS (Figure 1).

2.2 | Evaluation of postoperative complications

The patients were grouped based on their postoperative complications: without complications (Clavien-Dindo Classification Grade 1) and with complications (Grades 2 or higher). Then, factors related to postoperative complications were analyzed, including sex, age, tumor (T) stage, history of RT or CRT, radiation dose, operative time, resection area, resection site, pharyngeal constrictor muscle removal (yes/no), cervical esophagectomy (yes/no), and mucosal defect coverage with fibrin glue and polyglycolic acid sheets (MCFP; yes/no). Indicators of the patient's general condition were also assessed, including the body mass index (BMI), albumin and C-reactive protein (CRP) levels, white blood cell (WBC) and platelet counts, platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, CRP/albumin ratio, prognostic nutrition index, prognostic index, and Glasgow prognostic score (GPS). GPS was measured using the serum CRP value and serum Alb value. A CRP >1.0 mg/dL and Alb <3.5 g/dL were given a score of 2, CRP >1.0 mg/dL or albumin <3.5 g/dL were given a score of 1, and CRP ≤1.0 mg/dL and albumin ≥3.5 g/dL were given a score of 0. Dysphagia was evaluated after 6 months postoperatively with the functional outcome swallowing scale (FOSS)[21] to assess swallowing function; a FOSS score of 3 or higher indicated dysphagia. Overall survival (OS) was defined as the time from the start of treatment to the date of death or cutoff, regardless of the cause. Disease-specific survival (DSS) was defined as the time from the beginning of treatment to the date of death or cutoff date from specific cause.

2.3 | Statistical analysis

Survival curves were constructed for overall and disease-specific survival using the Kaplan–Meier method. All statistical tests were performed with GraphPad Prism 8 software (GraphPad Software Inc., San Diego, CA, USA). Associations between factors and outcomes were

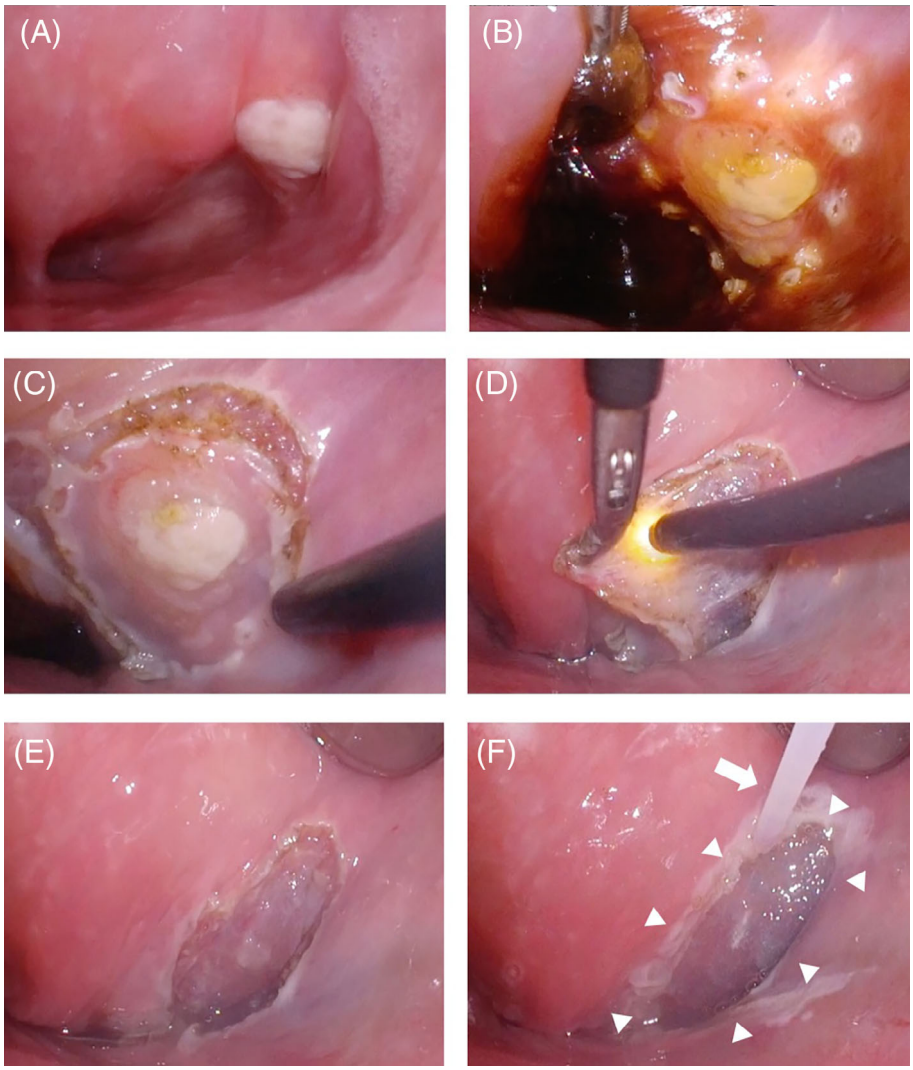

FIGURE 1 Salvage transoral videolaryngoscopic surgery. (A) The tumor is visualized by FK-WO retractor. The tumor is located on the pyriform sinus. (B) Marking around the lesion. (C) Circumferential incision with 5 mm safety margin from the edge of the iodine staining. (D) The tumor is resected by electrocautery. (E) The mucosal defect after resection of the tumor. (F) The mucosal defect was covered with fibrin glue (arrow) and polyglycolic acid sheets (arrowhead).

tested with Pearson's chi-square, Fisher's exact, and Mann–Whitney *U* tests. The Pearson chi-squared test or Fisher's exact test was used to analyze categorical variables. Bonferroni correction was applied for multiple comparisons. Continuous data were compared with the Mann–Whitney *U* tests. Statistical significance was defined as a *p*-value of less than .05.

3 | RESULTS

3.1 | Patient characteristics

During the period of this study, a total of 143 patients with recurrent hypopharyngeal cancer after RT or CRT were observed at our institution. Of these, 19 patients (13.3%) were indicated for salvage TOVS. The median age was 70.8 (range, 44–84) years, with a male-to-female ratio of approximately 9:1. The pyriform sinus was the most common recurrence site ($n = 11$ [57.9%]), followed by the posterior wall ($n = 5$ [26.3%]) and the post-cricoid area ($n = 3$ [15.8%]). At recurrence, 12 patients (63.2%) had stage T1, and 7 (36.8%) had stage T2 tumors. Furthermore, 7 (36.8%) and 12 (63.2%) patients underwent RT and CRT pretreatment, respectively, with a median dose of 65.3 (range, 60–70) Gy (Table 1).

3.2 | Clinical and functional outcomes

Table 2 presents the functional and clinical outcomes of the 19 patients who received salvage TOVS. Seven patients (36.8%) developed complications; dysphagia was the most common, occurring in all seven patients with complications. Three patients had more than one complication, including laryngeal necrosis, severe laryngeal stricture, and thyroid perichondritis. Total laryngotomy was required for the patient with laryngeal necrosis. The median preoperative and postoperative FOSS score were 1 (0–1) and 1 (0–3). The onset of dysphagia in patients with FOSS 3 or higher ranged from 2 to 6 months. Ten patients (52.7%) required temporary nasogastric tube postoperatively, and two patients required permanent PEG. The average of hospitalization was 9.4 days, and no patient required a tracheostomy.

TABLE 1 Patient details.

Patient	Age	Sex	Previous tumor site	Previous TN classification	Previous treatment	Total RT dose (Gy)	Duration between presentations (months)	Current tumor subsite	Current TN classification
1	59	M	CEC	T4N0	CRT	62	62	Pyriform sinus	2
2	72	M	HPC	T2N2b	CRT	66	28	Pyriform sinus	1
3	75	M	LC	T1N0	RT	70	116	Pyriform sinus	2
4	58	M	CEC	T1bN0	RT	66	62	Pyriform sinus	2
5	70	M	CEC	T3N1	CRT	60	21	Posterior wall	2
6	84	F	CEC	T3N3	CRT	60	106	Posterior wall	1
7	67	M	CEC	T4N3	CRT	65	121	Posterior wall	1
8	76	M	HPC	T3N0	RT	66	8	Posterior wall	2
9	67	M	HPC	T4N2b	CRT	70	103	Posterior wall	2
10	74	M	HPC	T2N0	CRT	64	26	Pyriform sinus	1
11	65	M	HPC	T2N2b	CRT	66	7	Pyriform sinus	1
12	77	M	HPC	T3N2b	CRT	66	44	Post-cricoid area	1
13	78	M	HPC	T2N0	RT	64	14	Post-cricoid area	1
14	76	M	LC	T2N0	CRT	67	114	Post-cricoid area	1
15	44	F	HPC	T2N0	RT	66	4	Pyriform sinus	1
16	76	M	HPC	T2N0	RT	66	16	Pyriform sinus	1
17	72	M	HPC	T1N0	RT	66	27	Pyriform sinus	2
18	80	M	CEC	T1N0	CRT	60	14	Pyriform sinus	1
19	76	M	HPC	T2N3b	CRT	70	5	Pyriform sinus	1

Abbreviations: CEC, cervical esophageal cancer; CRT, chemoradiation therapy; HPC, hypopharyngeal cancer; LC, laryngeal cancer; RT, radiation therapy.

3.3 | Risk factors for postoperative complications

Table 3 presents patient characteristics and surgery-related factors associated with postoperative complications. Age, sex, and the T classification at recurrence did not differ between the patients with and without complications. Furthermore, the relationship between actual irradiation (RT or CRT) and complications, radiation dose, and irradiation history did not differ between those with and without complications. Additionally, the operative time, resection area, the removal of the pharyngeal constrictor muscle, and MCFP use did not differ between these two groups. However, significantly more patients with post-cricoid resection had complications than those without resection ($p = .0041$). The results of the multiple comparison test using the Bonferroni correction showed a significant difference between PC and PW ($p = .033$). The complication rate did not statistically differ between patients with and without cervical esophageal mucosal resection, but both patients who underwent the resection had complications.

Table 4 presents the factors representing the patient's systemic status related to postoperative complications. The BMI, albumin and CRP levels, WBC and platelet counts, platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, CRP/albumin ratio, and the prognostic nutrition index did not differ between patients with and without complications. The prognostic nutrition index and GPS also did not differ between the two groups, but all patients with a prognostic index and GPS of 1 developed complications.

3.4 | Survival and oncological outcomes

During the follow-up period, 7 of the 19 patients who underwent salvage TOVS died (36.8%); 2 died of their present illness, and 5 died of other illnesses. (Table 2). OS and DSS were estimated using the Kaplan–Meier method (Figure 2). The median OS was 82 months (95% CI, 45–NA months), and the median DSS was NA (95% CI, NA–NA). The survival rates were: 3-year overall survival: 94.4%; disease-specific survival: 94.4%; 5-year overall survival: 62.3%; and disease-specific survival: 86.6%.

4 | DISCUSSION

Traditionally, extended resection is the recommended treatment for post-irradiation recurrence.[6,7,9] However, the development of transoral robotic surgery has increased the effectiveness of salvage transoral resection. The reports on salvage transoral resection have been mainly for middle pharynx cancers; few have discussed hypopharynx cancers. Hence, the safety and outcomes remain unclear.[17,22–25] Therefore, this study investigated the efficacy, safety, and risk factors

TABLE 2 Postoperative complications and outcome.

Patient	Complications	Preoperative FOSS	Postoperative FOSS	Onset of dysphagia (M)	Temporary NG tube (D)	PEG	Hospitalization (D)	Tracheostomy	Follow up (M)	Status
1		1	1	–	–	–	9	–	154	NED
2		1	1	–	3	–	7	–	117	NED
3		1	1	–	–	–	3	–	134	NED
4		0	0	–	–	–	4	–	82	DOA
5	Dysphagia laryngeal necrosis	1	3	2	–	–	11	–	42	DOA
6	Dysphagia	1	3	3	–	–	5	–	18	NED
7	Dysphagia	1	3	3	–	–	6	–	53	DOA
8		0	0	–	–	–	7	–	87	NED
9		0	0	–	–	–	7	–	45	DOA
10		0	0	–	–	–	6	–	46	NED
11		0	1	–	3	–	8	–	45	DOD
12	Dysphagia	1	3	4	6	–	16	–	14	DOD
13	Dysphagia severe stenosis	0	5	5	5	+	12	–	72	DOA
14	Dysphagia	1	4	4	2	–	11	–	50	NED
15		0	0	–	6	–	11	–	49	NED
16		1	1	–	5	–	10	–	32	NED
17	Dysphagia chondritis of the thyroid cartilage	1	4	6	9	+	18	–	28	NED
18		1	0	–	6	–	12	–	25	NED
19		0	1	–	5	–	16	–	12	NED

Abbreviations: D, day; DOA, death from another disease; DOD, died of disease; FOSS, functional outcome swallowing scale; M, month therapy; NED, no evidence of disease; NGT, nasogastric tube; PEG, percutaneous gastrostomy.

TABLE 3 Surgical factors and complications.

Variables	Complications	No-complications	*p*-value
Number of patients	7	12	
Sex			
Male	6	11	1.000
Female	1	1	
Median age (range)	76.0 (70–84)	75.0 (44–80)	.1714
Tumor classification			
rT1	5	7	.6562
rT2	2	5	
Median total dose of RT (range)	65.0 (60–67)	66.0 (60–70)	.2108
Primary treatment			
RT	2	5	.6562
CRT	5	7	
Operative time (min)	96.4 (40–185)	74.3 (30–180)	.1733
Resection area (cm^2)	6.51 (1–14.4)	4.42 (1.54–10.26)	.4444
Main resection site			
Priform sinus	1	10	**.0041**
Posterior wall	3	2	
Post-cricoid	3	0	
Resection of the PCM			
Yes	1	1	1.000
No	6	11	
Resection of the Ce			
Yes	2	0	.1228
No	5	12	
MCFP			
Yes	3	4	1.000
No	4	8	

Note: Bold indicates statistically significant *P*-values.
Abbreviations: Ce, cervical esophagus; CRT, chemoradiotherapy; MCFP, mucosal defect coverage with fibrin glue and polyglycolic acid sheets; PCM, pharyngeal constrictor muscle; RT, radiotherapy.

TABLE 4 Systemic factors and complications.

Variables	Complications	No-complications	*p*-value
Number of patients	7	12	
Diabetes mellitus			
Yes	1	2	1.000
No	6	10	
BMI	21.2 (18.9–23.6)	21 (12.9–26.2)	.9671
Alb (g/dL)	3.97 (3.3–4.6)	4.24 (3.8–4.7)	.185
CRP (mg/dL)	0.31 (0.09–1.25)	0.12 (0.09–0.22)	.1811
WBC (10^3/μL)	4.9 (3.4–7.2)	4.7 (2.5–8.4)	.7576
Plt (10^4/μL)	20.9 (15.5–32.4)	19.9 (14.4–24.7)	.8854
PLR	227.9 (135.7–362.4)	213.4 (119.8–296.7)	.6504
NLR	4.21 (1.29–9.53)	3.57 (1.57–11.3)	.6504
LMR	3.94 (1.68–7.33)	3.14 (0.03–4.90)	.8369
CAR	0.082 (0.019–0.338)	0.029 (0.018–0.082)	.3845
Prognostic nutrition index	44.7 (38.6–50.6)	47.5 (44.3–51.9)	.1478
Prognostic index			
0	6	12	.3684
1	1	0	
GPS			
0	5	12	.1228
1	2	0	

Abbreviations: Alb, albumin; BMI, body mass index; CAR, CRP to albumin ratio; CRP, C-reactive protein; GPS, Glasgow Prognostic Score; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; Plt, platelets; PLR, platelet to lymphocyte ratio; WBC, white blood cells.

for postoperative complications after salvage TOVS for post-irradiation hypopharyngeal cancer recurrence.

Postoperative complications occurred in 36.8% of patients, and dysphagia was the most common. Tomifuji et al.[17] also reported significantly more patients with dysphagia (FOSS score ≥3) in the salvage treatment group than in the primary treatment group (33.3% vs. 7.5%), indicating that TOVS results in a high incidence of postsurgical dysphagia with greater severity. Patients who have undergone RT or CRT inherently have impaired swallowing function.[26] Moreover, resection in these patients may result in delayed wound healing after irradiation, scar contracture of the mucosa, and pharyngeal stenosis, causing severe dysphagia.

In this study, the pretreatment, operative time, resection area, and pharyngeal constrictor muscle removal did not affect the complication rate. However, the patients in which the resection site was PC had a significantly higher complication rate. On the other hand, Tomifuji et al. reported that, among the primary treatment patients, post-cricoid resection rarely caused dysphagia, but arytenoid resection, pulmonary dysfunction, and extensive defects were dysphagia risk factors.[27] In this study, two of the three patients of PC resection involved the resection of cervical esophagus (Ce). The resection of Ce was not significantly correlated with complications, however, a wide resection spanning PC to Ce could be the cause of severe dysphagia. Therefore, in patients where such extensive resection is anticipated, careful consideration should be given to the indications of TOVS.

Several methods have been reported to prevent postoperative stenosis and dysphagia.[20,28–30] The MCFP technique might prevent dysphagia from postoperative stricture.[20,28,29] For instance, Sakaguchi et al.[28] reported no postoperative stricture after endoscopic mucosal resection of esophageal cancer using this technique. However, in this study, the MCFP technique did not affect the complication rate, implying that this method alone is insufficient to avoid complications. Ohki et al.[30] developed a method to prevent stenosis by transplanting autologous oral mucosa cell sheets into the defect after esophageal endoscopic mucosal resection (ESD) to regenerate the epithelium at an early

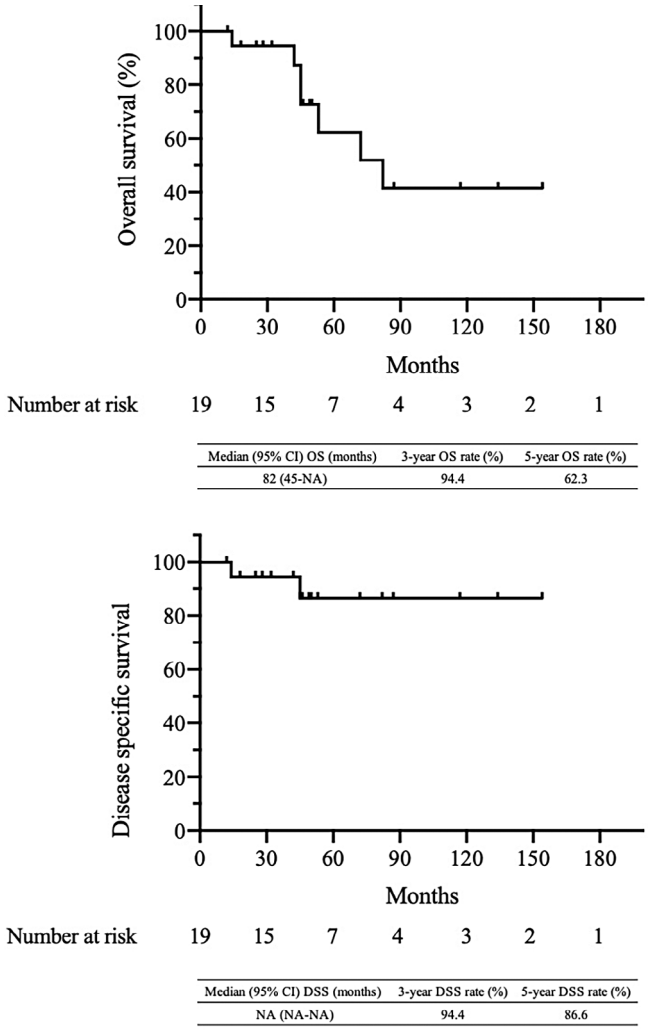

FIGURE 2 Overall and disease-specific survival rates after salvage surgery. The survival rates were: 3-year overall survival: 94.4%; disease-specific survival: 94.4%; 5-year overall survival: 62.3%; and disease-specific survival: 86.6%.

stage, reporting that effectively promotes re-epithelialization of the esophagus after ESD. The widespread use of these new methods may prevent complications; thus, we expect more studies in the future.

This study also analyzed systemic factors reportedly associated with postoperative complications, such as the BMI,[31] platelet/lymphocyte ratio,[32] neutrophil/lymphocyte ratio,[33] lymphocyte/monocyte ratio,[34] CRP/albumin ratio,[35] prognostic nutrition index,[36] prognostic index,[37] and GPS.[38] None were associated with postoperative complications, but both patients with a GPS of 1 had complications. Hiramatsu et al.[38] found that patients with GPS 1 and 2 were significantly more likely to have postoperative complications than patients with GPS 0 in various surgeries. Although there were no significant differences in this study, these inflammatory and nutritional factors should be considered preoperatively, and if the risk of complications is high, the treatment should be more carefully considered to avoid postoperative complications.

In this study, the overall survival and disease-specific survival 5 years after salvage TOVS were 62.3% and 86.6%, respectively; both survival rates after 3 years were 94.4%. Previous studies have reported 3-year overall and disease-specific survival rates of 67%–100% and 80%–100%, respectively, after salvage transoral resection for hypopharyngeal carcinoma,[17,25,39] similar to our results. In contrast, Suzuki et al. reported a 2-year overall survival rate of 50%, and Taguchi et al. reported a 5-year overall survival rate of 56.7% for conventional treatment for hypopharyngeal carcinoma.[40] Although the patient population for conventional treatment includes many advanced cancers and should be interpreted with caution, our results indicate that transorally resectable lesions are oncologically controllable.

Note that early recurrent lesions are rare, and only 13% of recurrent patients in our study were indicated. Our favorable outcomes may have resulted from very careful selection and treatment by an experienced and skilled group of surgeons. Therefore, the indication for salvage TOVS should be treated with great caution.

This study is limited by the small number of cases. Additionally, it is a single-center, retrospective study. Furthermore, very few patients have early-stage, transorally resectable lesions, making it challenging to conduct a case study at a single institution. Therefore, a multicenter collaborative study is needed in the future.

5 | CONCLUSIONS

Salvage TOVS for hypopharyngeal carcinoma with prior RT or CRT was feasible, and oncologically and functionally reasonable. Severe dysphagia was the primary complication, and post-cricoid resection was a complication risk factor. Our results suggest that salvage TOVS, which preserves quality of life compared to conventional methods, may be an option for the treatment of recurrent early stage hypopharyngeal carcinoma.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data has been presented in this manuscript.

PATIENT CONSENT

The institutional review board waived the informed consent requirement owing to the study's retrospective nature.

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