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HEAD AND NECK

Treatment outcomes for one-stage concurrent surgical resection and reconstruction of synchronous esophageal and head and neck squamous cell carcinoma

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Abstract

Purpose It is not uncommon to see the synchronous presentation of esophageal squamous carcinoma (ESCC) and head and neck cancer (HNC), and most patients were treated with staged interventions. This study retrospectively reported the outcomes of patients with synchronous ESCC and HNC treated with one-stage concurrent surgical resection and reconstruction.

Methods We identified 17 consecutive patients with synchronous ESCC and HNC undergoing primary concurrent surgical resections between 2011 and 2017 at our hospital. All patients had received esophageal screenings prior to treatment.

Results The HNC patients in this study had the following subsite involvements: oral cavity ($n=5$), oropharynx ($n=4$), larynx ($n=1$), hypopharynx ($n=9$), and thyroid gland ($n=1$). Eighty percent of the HNC subsites (16/20) were treated in advanced stages, while most ESCCs were treated at early stages. The mean follow-up time was 3.2 ± 1.6 years. Surgery-associated morbidity and mortality were 94.1% and 0%, respectively, and the most common complication was anastomotic leakage. The two-year overall survival, 2-year loco-regional recurrence-free survival, and 2-year distant metastasis-free survival were 86.7%, 85.6%, and 78.7%, respectively. No significant difference was found between overall survival and HNC subsite or anastomotic leakage. Four patients (23.5%) developed secondary primary malignancies (SPMs) within a mean follow-up period of 2.9 years (standard deviation 1.6 years).

Conclusion Although one-stage concurrent surgical resection and reconstruction of synchronous ESCC and HNC were highly invasive and complicated, survival was promising. Isolated distant metastasis remained the most common failure pattern. Vigilant follow-up strategy is mandatory to detect secondary primary malignancies (SPMs), especially within the first 3 years following initial treatment.

Keywords Simultaneous · Synchronous · Esophageal squamous cell carcinoma · Head and neck cancer · Concurrent surgical resection · Second primary malignancy · Survival · Complications

Abbreviations

ESCC	Esophageal squamous cell carcinoma
HNC	Head and neck cancer

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SPM(s)	Second primary malignancy(ies)
HPV	Human papilloma virus
ALDH	Acetaldehyde dehydrogenase
EGDS	Esophagogastroduodenoscopy
NAD-CRT	Neoadjuvant chemoradiotherapy
AJCC	American Joint Committee on Cancer
CT	Computed tomography
MR	Magnetic resonance
PET-CT	Positron emission tomography computed tomography
FJT	Free jejunal transfer
ALT	Anterolateral thigh
GTPU	Gastric-tube pull-up
OS	Overall survival
LRFS	Local regional failure free survival
DMFS	Distant metastasis-free survival
SD	Standard deviation
HPC	Hypopharyngeal cancer
TIL	Tumor-infiltrating lymphocyte
MMPs	Metalloproteinases
VEGFR-1	Vascular endothelial growth factor receptor 1

Introduction

Head and neck cancer (HNC) is the sixth most common cancer [1], with 686,000 new cases and 376,000 related deaths reported each year worldwide [2]. It is two-to-four times more common in men than women due to its strong association with lifestyle and environmental factors [1]. Unlike HNC populations in the West, East-Asians have a relatively low prevalence of HNCs associated with human papilloma virus (HPV) [3, 4], and in this population, viral status has not been found to accurately predict survival or field cancerization [4, 5].

In Asian populations, there is a higher prevalence of the acetaldehyde dehydrogenase (ALDH) 2 × 2 allele [6, 7]. Patients with inactive ALDH2*2 are more susceptible to the dose-dependent carcinogenic effects of alcohol and are more likely to develop of multiple neoplasms in the upper aerodigestive tract [8–10]. In addition, epidemiologic studies suggest that genetically susceptible HNC patients have a significantly higher prevalence of esophageal squamous cell carcinoma (ESCC), with prevalence varying by subsite, from high to low, the hypopharynx, larynx, oropharynx, and oral cavity [11].

Esophagogastroduodenoscopy (EGDS) is becoming more widely used to evaluate patients with newly diagnosed HNC, and with its increased use has come an increase in detection of synchronous esophageal cancer in HNC patients [11, 12]. Treatment of patients with both diseases is complicated and requires sound clinical judgment tailored to each patient's needs [13–16]. For potentially curable patients, one strategy is the use of neoadjuvant chemoradiotherapy (NAD-CRT) [17]. Patients with operable ESCC have been found to have better survival rates when, prior to surgery, they receive NAD-CRT with complete pathologic response, compared to those who receive primary esophagectomy alone [17]. However, with regard to this strategy's effect on HNC survival, there is no consensus [18]. Another strategy is to apply concurrent CRT for multiple radio-sensitive cancers, including esophageal cancer, oro/hypopharyngeal cancer, and laryngeal cancer, to preserve the organ [16, 19]. Concurrent CRT has, however, been associated with significant impaired performance status and several treatment-associated toxicities [13, 15, 16, 19]. In addition, its use on advanced-stage ESCC and HNC has been associated with poor loco-regional control [20, 21]. There are few therapeutic options for post-CRT patients with residual or recurrent disease [22–25], and salvage treatments have been associated with high treatment-related morbidity and mortality, mostly due to the poor health of patients adversely affected by irradiation [22–25]. Considering the above-mentioned difficulties, one-stage surgical resection and reconstruction might be a better option for patients with synchronous ESCC and HNC [13–15].

To find out, we perform a retrospective follow-up study to investigate survival, peri-operative morbidities, and post-treatment functional status of patients with synchronous ESCC and HNC treated with one-stage concurrent surgical resection and reconstruction. We also explored the order in which the cancers occurred and patterns of treatment failure.

Materials and methods

Patients' characteristics

We identified 43 patients diagnosed with HNC and ESCC from our hospital's Cancer Registry between January in 2011 and December in 2017. Patients were excluded from this study if they had distant metastasis at diagnosis ($n = 2$), had a pathologic diagnosis other than squamous cell carcinoma ($n = 1$), had refused esophagogastroduodenoscopy (EGDS) ($n = 2$), had metachronous occurrences ($n = 15$), had unresectable tumors or tumors with low surgical curability based on 7th edition of American Joint Committee on Cancer (AJCC) T and N classifications ($n = 2$), or were lost to follow-up after diagnosis ($n = 4$) (Supplementary Fig. 1). After exclusion, seventeen patients were left to be included in our analysis. All the patients had received computed tomography (CT) or magnetic resonance (MR) imaging, chest CT scan, esophageal ultrasonography, abdominal sonography, and whole-body bone scan for cancer staging. Positron emission tomography computed tomography (PET-CT) was used with those

who had locally advanced cancers and with those in whom distant metastasis was highly suspected. Metastatic lymph nodes were defined as regional primary nodes if they were found in the drainage area and defined as distant if they were found outside the region of both neoplasms. This study was approved by the institutional review board of National Cheng Kung University Hospital and was conducted in accordance with the Declaration of Helsinki. Written consent was waived, because the study was a retrospective review of patients with concurrent HNCs and ESCCs who had previously undergone concurrent surgery.

Starting in 2011, patients with newly diagnosed HNC routinely received narrow-band imaging EGDS in our hospital using a high-resolution magnifying endoscope to evaluate upper aerodigestive tract. All cancers are staged according to definitions established in AJCC 7th edition. Patients are followed up every 1–3 months for 2 years after surgery and every 3 months thereafter.

Surgical treatments

Surgical interventions were performed by cooperating surgical teams consisting of head and neck surgical oncologists, microsurgical reconstructive surgeons, and chest surgeons. Patients were placed in left lateral decubitus position. Video-assisted thoracoscopic surgery was performed for dissection of area around the esophagus, mediastinal lymph nodes, and for the ligation of thoracic ducts. Head and neck surgeons performed neck dissections and wide excision of HNCs. Following recommendations proposed by Chang et al. [26], our reconstructive surgeons harvested free tissue transfers to bridge defects in cases in which the highest nick reached the lower mandible (Fig. 1). Depending on the presence of skin defect and surgeon's preference, either a free jejunal flap transfer (JFT) or anterolateral thigh (ALT) flap was used. Additional free tissue was harvested if the patient was found to have an additional defect. A chest surgeon completed the

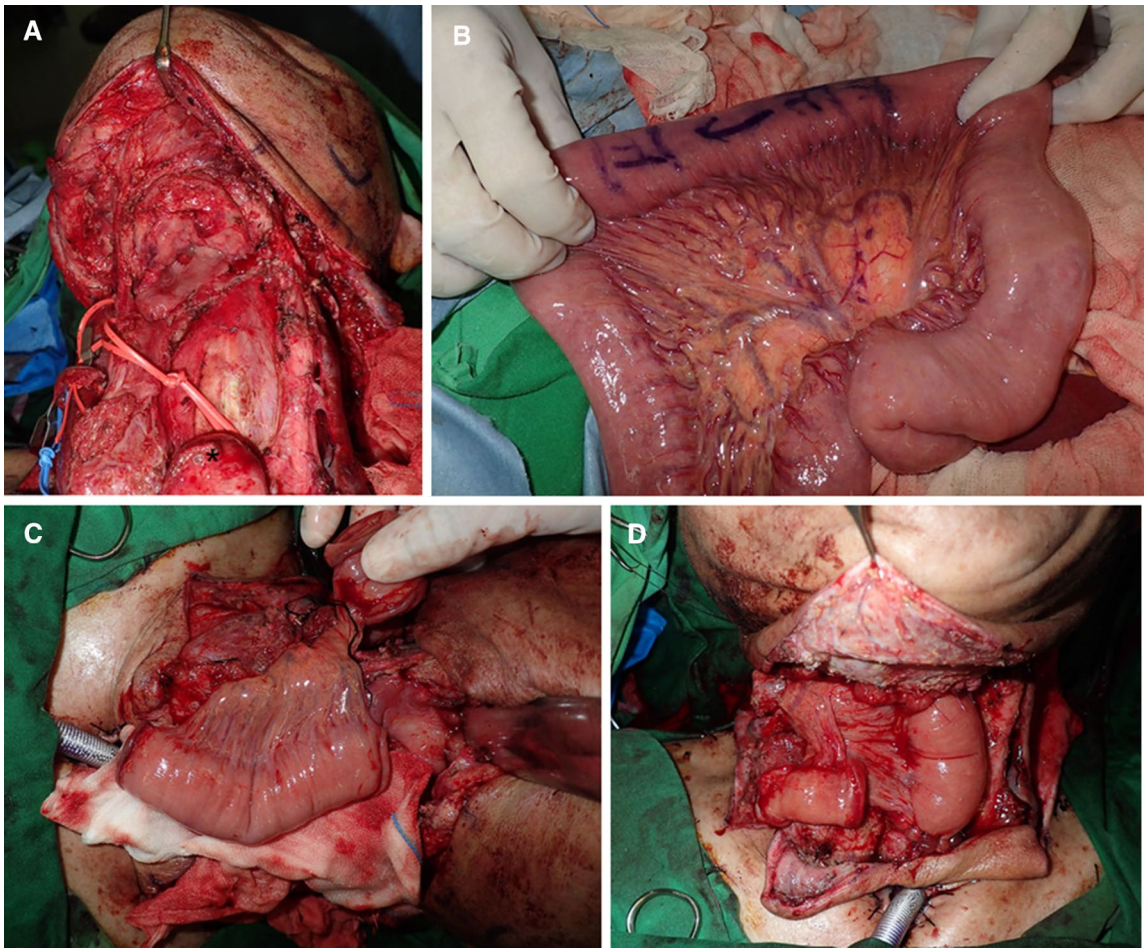

Fig. 1 A male patient with hypopharyngeal cancer and esophageal squamous cell carcinoma undergoing one-stage laryngo-pharyngo-esophagectomy. **a** The narrowed gastric tube was placed in the dissected neck (asterisk). **b** Free jejunal flap selection to bridge gastric tube and oropharyngeal remnant. **c** Designation of sentinel flap to monitor transferred vascularized free jejunal flap. **d** Photograph of completed end-to-end hand sewn anastomosis prior to wound closure

esophagectomy and jejunostomy after performing midline laparotomy. The gastric tube (GT) was pulled up via the posterior mediastinum. For patients who needed bridging flaps, reconstructive surgeons completed microvascular anastomoses.

After surgery, all patients were transferred to an intensive-care unit for immobilization and nutrition support; empirical antibiotics were administered for at least 14 days. Patients tried oral intake if there was no evidence of anastomosis leakage or if the leakage was well controlled.

Chemoradiotherapy, radiotherapy, and post-treatment complications

Whether chemotherapy or (chemo)radiotherapy would be used was determined by consensus of medical and radiation oncologists. Some patients received one-cycle induction chemotherapy of TP(F) (docetaxel 60 mg/m^2 on day 1, and cisplatin 60 mg/m^2 on day 1 with or without 5-fluorouracil 600 mg/m^2 on day 1–2). Post-treatment (chemo) radiotherapy involved concurrent administration of radiation (60–66 Gy to the high-risk region and 50–56 Gy to low-risk region) and weekly cisplatin/every 3 week PF for patients at risk. As for ESCCs, we apply chemotherapy alone if the treated esophageal malignancies were of advanced stages or of pathologically positive lymph nodes. Additional radiotherapy was administered for patients whose radiographs suggested suspicious lymphadenopathy during the follow-up period but not immediately applied postoperatively to avoid damage of the gastric tube and the serious complications such as aerodigestive tract fistula. If the adjuvant radiation was administered, its dosage was 45 Gy/25 fractions. Post-treatment complications are listed in Table 3.

Rehabilitation program

At our hospital, these patients take part in a swallowing and speech rehabilitation program starting 10–14 days after esophagram. The program is led by an experienced clinician. Therapy tailored to individual patient need involves both private and group sessions once a week until the patient demonstrates adequate function or the patient drops out of the program. Maintenance therapy is conducted month-to-month.

Statistical analysis

Survival was determined using Kaplan–Meier method and any difference between two curves was analyzed by the log-rank test. The clinical endpoints included 2-year overall survival, 2-year loco-regional free survival, 2-year distant metastasis-free survival, and 2nd primary malignancy-free survival. Overall survival (OS) was defined as the time that had elapsed between diagnosis and the date of death from any cause during 2 years after surgery if patients were still alive at the end of the study period (August 31, 2018). Other endpoints were calculated starting on the date of pathology-based diagnosis. The first recurrence status was defined as the first failure pattern. All statistical operations were performed using SPSS software ver. 22.0 (SPSS, Chicago, IL, USA). A p value of less than 0.05 was considered significant.

Results

Demographic data and clinical characteristics

Patient characteristics are summarized in Table 1. This study included 17 patients (all male) with a mean age of 53.4 years (standard deviation [SD] 6.7 years; range 39–69 years). The 17 patients had a total of 31 HNCs, including oral cavity ($n=8$), oropharynx ($n=10$), larynx ($n=2$), hypopharynx ($n=10$), and thyroid ($n=1$). Twelve of the seventeen ESCCs (70.6%) were located at the mid-esophagus. Sixteen of the seventeen ESCCs (94.1%) were early stage lesions. Most patients underwent video-assisted thoracoscopic esophagectomy followed by gastric-tube reconstruction (Table 1). Five of the seventeen patients (29.4%) had been treated for HNCs previously before surgical resection (Table 1). Three of these patients underwent definitive chemoradiotherapy for oropharynx (complete remission) and one for hypopharynx (persistent disease). One 54-year-old patient with index gingival cancer (Case 9, Table 1) had received three consecutive ablative surgeries for his HNCs prior to his definite surgery. Five patients had two HNCs, three patients had three HNCs, and one patient had four HNCs. Seven out of thirty-one HNCs (22.6%) had developed before their index ESCCs, whereas four HNCs (12.9%) were detected after ESCC treatment (Table 2).

Simultaneous surgical resection

Eleven of the seventeen male patients were actively consuming alcohol (64.7%) (Table 2). Subsites of index HNC were mostly hypopharynx ($n=9$, 45%), followed by gingiva ($n=3$, 15%), tongue base ($n=2$, 10%), and oral tongue ($n=2$, 10%). Three patients received bridging chemotherapy before surgery. Most of the patients with ESCC and hypopharyngeal cancer were treated with total laryngo-pharyngo-esophagectomy followed by gastric-tube reconstruction. One patient, a 51-year-old male (Case 1, Table 1), underwent right colon interposition reconstruction surgery, because he had a previous subtotal gastrectomy. Four patients (23.5%) required additional

Table 1 Details of patients undergoing concurrent surgical resections

Cases	Age	Previous HNCs subsites, staging (order of malignancy, AJCC stage, and treatment)	Locations of index HNCs (order of malignancy, AJCC staging)	Procedures for index HNCs	ESCC location	ESCC AJCC staging
1	51M	N/A	HPC (1, T2N2cM0, stage IVA)	TLP, Bil. ND, permanent tracheostoma	L/3	pT1bN0M0, stage IB
2	55M	N/A	HPC (1, T1N2bM0, stage IVA)	TLP, Bil. ND, permanent tracheostoma	M/3	pT1aN0M0, stage IB
3	57M	Tongue base (1, cT1N1M0, stage III, CRT)[a]	tongue (2, T1N0M0, stage I)	TWE, Uni. ND	M/3	pT1bN0M0, stage IB
4	69M	Oropharynx (1, cT1N0M0, stage I, RT)[a]	HPC (2, T3N0M0, stage III)	TLP, Bil. ND, permanent tracheostoma	M/3	pT1aN0M0, stage IA
5	59M	N/A	HPC (1, T4N2cM0,stage IVA); soft palate (1, T2N2cM0,stage IVA)	TWE; TLP, Bil. ND, permanent tracheostoma	M/3	pT2N0M0, stage IIB
6	45M	N/A	tongue base (1, T2N2aM0,stage IVA)	TWE, Bil. ND, ALT reconstruction	M/3	pT1aN0M0, stage IA
7	56M	Hypopharynx (1, cT3N2cM0, IVA, CRT)[b]	tongue (2, T2N0M0,stage II)	TLP, TWE, Uni. ND	M/3	pT1bN0M0, stage IB
8	47M	Tonsil(1, cT2N2M0, stage IVA, CRT)[a]	Gingival (2, T4aN0M0, stage IVA)	TWE, Uni. ND, ALT reconstruction	L/3	pT3N0M0, stage IIB
9	54M	Tongue (1, T2N0M0, stage II, TWE+ reconstruction); soft palate (2, T1N0M0, stage I, TWE); tongue (2, T1N0M0, TWE)	Gingiva (3, T4aN0M0, stage IVA)	TWE, Uni. ND, ALT reconstruction	U/3	pT1bN0M0, stage IB
10	52M	N/A	Gingival (1, T1N0M0, stage I)	TWE, Uni. ND, tracheostomy	M/3	pT1bN1M0, stage IIB
11	51M	N/A	HPC (1, T4aN2cM0, stage IVA)	Bridging CT+TLP, Bil. ND, permanent tracheostoma	M/3	ypT1aN0M0, stage IA
12	53	N/A	Tonsil (1, T2N2cM0, stage IVA); HPC (1, T2N2cM0, stage IVA)	TWE; PLP, Bil. ND, tracheostomy	C	pT2N1M0, stage IIB
13	53M	N/A	HPC (1, T2N2bM0, stage IVA)	TLP, Bil. ND, permanent tracheostoma	M/3	pT1bN1M0, stage IIB
14	53M	N/A	HPC (1, T4aN2cM0, stage IVA)	TLP, Bil. ND, permanent tracheostoma	M/3	pT1aN0, stage IB
15	50M	N/A	Tongue base (1, T4aN2cM0, stage IVA); PTC (1, T1N1aM0,stage IVA)	bridging CT+TWE, TL, Bil. ND, permanent tracheostoma	M/3	ypT2N2M0, stage IIIA
16	39M	N/A	HPC (1, T3N2cM0, IVA)	TLP, Bil. ND, permanent tracheostoma	L/3	pT2N1M0, stage IIB
17	64M	N/A	SGC (1, T3N1M0, III)	Bridging CT+TLP, Bil. ND, permanent tracheostoma	M/3	ypT1bN0, stage IB

Table 1 (continued)

Esophagectomy procedures	Reconstructed substitute	Temporary tracheostomy	First recurrence status	Locations of secondary primary malignancy (treatment)	Final disease status	Feeding tube-dependent (reason)
VATS esophagectomy	Right colon	0			NED	0
VATS esophagectomy	Gastric tube	0			NED	0
VATS esophagectomy	Gastric tube	1	2nd primary	Oropharynx (TWE)	NED	0
VATS esophagectomy	Gastric tube + free jejunal flap	0	Local recurrence		DOD	0
VATS esophagectomy	Gastric tube + free jejunal flap	0	2nd primary	Hard palate (TWE)	NED	1
VATS esophagectomy	Gastric tube	0	Regional recurrence		AWD	1 (salvage treatment)
VATS esophagectomy	Gastric tube	0			NED	0
VATS esophagectomy	Gastric tube	1	2nd primary	Larynx (TWE,TORS)	DOD	0
VATS esophagectomy	Gastric tube	0	Distant metastasis		NED	1, s/p esophageal dilatation
VATS esophagectomy	Gastric tube	0	2nd primary	Tonsil (CRT)	NED	0
VATS esophagectomy	Gastric tube + ALT	0			NED	0, s/p esophageal dilatation
VATS esophagectomy	Gastric tube	1	Distant metastasis		DOD	1 (salvage treatment)
VATS esophagectomy	Gastric tube	0			NED	0
VATS esophagectomy	Gastric tube	0			NED	1, s/p esophageal dilatation
VATS esophagectomy	Gastric tube + ALT	0			NED	0
VATS esophagectomy	Gastric tube	0			NED	0
VATS esophagectomy	Gastric tube	1			NED	1 (radiotherapy-related toxicity)

HNC head neck cancer, *ESCC* esophageal squamous cell carcinoma; *AJCC* American Joint College of Cancer, *CRT* chemoradiotherapy, *TWE* tumor wide excision, *CT* chemotherapy, *HPC* hypopharyngeal cancer, *TC* papillary thyroid carcinoma, *SGC* supraglottic cancer, *TLP* total laryngopharyngectomy, *ND* neck dissection, *ALT* antero-lateral thigh, *VATS* video-assisted thoracic surgery, *TORS* transoral robotic surgery, *NED* no evidence of disease, *DOD* die of disease, *AWD* alive with disease

[a]Complete remission

[b]Partial remission

Table 2 Demographic features of patients with synchronous HNCs and ESCC

Clinical factors	Number of patients (%) or mean ± SD
Age (year)	53.4 ± 6.7
Gender	
Male	17 (100)
Alcohol	
Yes	11 (64.7)
No	6 (35.3)
Length of stay (day)	33.2 ± 12
Location of HNCs	
Oral cavity	5 (25)
Oropharynx	4 (20)
Larynx	1 (5)
Hypopharynx	9 (45)
Thyroid	1 (5)
Location of ESCC	
Cervical	1
Upper-esophagus	1
Mid-esophagus	12
Lower-esophagus	3
HNC and ESCC stages	
Early vs early	3 (17.6)
Advanced vs early	13 (76.5)
Advance vs advanced	1 (5.9)
Reconstruction of neo-pharynx	
Colon	1 (5.9)
GT	12 (70.6)
GT+ALT	2 (11.8)
GT+FJT	2 (11.8)
Comorbidities	
Hepatitis	4 (23.5)
Pulmonary tuberculosis	1 (5.9)
Previous abdominal surgery	2 (11.8)
Previous solid cancer history	5 (29.4)
Secondary primary malignancies	
HNC	4 (23.5)

HNC head–neck cancer, *ESCC* esophageal squamous cell carcinoma, *SD* standard deviation, *GT* gastric tube, *ALT* anterolateral thigh, *FJT* free jejunal transfer

free flaps (two JFTs and two ALTs) to bridge the pull-up gastric-tube end and proximal remnant (Table 2). Three of these patients required additional ALTs for the reconstruction of HNC defects (Table 1).

The mean overall length of stay was 33.2 days ([SD 12], ranging from 15 to 61 days) (Table 2). The number of complications ($n \geq 2$ vs. $n < 2$) was not significantly associated with prolonged admission ($p = 0.93$). Most patients underwent adjuvant chemoradiotherapy without event.

Table 3 Peri-operative Complications, $N = 16$

Anastomotic leakage	8
Pneumonia/empyema	4
Tracheal necrosis/tracheostoma stenosis	2
Hepatic failure/acute hepatitis	3
Symptomatic hypocalcemia	2
Surgical site infections	2
Vocal fold paralysis	2
Chylothorax/chylous leak	2
Sepsis	1
Wernick encephalopathy	1
Subcutaneous emphysema	1
Stroke	1
Pharyngo-cutaneous fistula	1
Small bowel ischemia	1
Total	31

Peri- and post-treatment complications

As can be seen in Table 3, there were a total of 31 complications in sixteen patients. Nine patients (52.9%) had two complications or more. The most common complication was anastomosis leakage ($n = 8$, 47.1%) exclusively over the upper side of gastric tube, successfully managed with continuous negative-pressure vacuum system without surgical intervention. Two patients developed surgical site infections, requiring local treatment and computed tomography-guided aspiration. Four patients (23.5%) developed pulmonary complications. Of these four patients, three (one with gingiva, one with tongue base, and one hypopharyngeal cancer receiving partial laryngopharyngectomy) developed aspiration pneumonia (Table 3). Of note, one 51-year-old malnourished male (Case 1, Table 1) developed Wernicke encephalopathy, had a cerebral vascular accident, had a catheter-related blood stream infection, and chylothorax, all successfully managed. One patient (Case 15**,** Table 1) survived lethal small bowel ischemia resulting from internal herniation 13 months following definite surgery. Two patients had tracheal necrosis and required stoma-plasty later for tracheostomal stenosis (Table 3). There was no flap loss, 30-day readmission, or in-hospital mortality.

Tubal dependence after surgical resection

The most concerning morbidities associated with the concurrent resections which we performed were swallowing and speech disabilities. By the end of the study, six patients remained dependent on their feeding tubes. Two were categorized as having had level 2 dependencies (i.e., tube dependence, minimal attempts of food or liquid), assessed

using the Functional Oral Intake Scale (Table 1) [27]. Four were categorized as having had level 3 dependencies (i.e., tube dependence with consistent oral intake of food or liquid). Two of the level 3 tube-dependent patients had received salvage treatments (1 regional recurrence, 1 distant metastasis); one of them had ongoing acute radiation toxicities, and the other had surgically treated advanced gingival cancer (Table 1). Three of the level 3 tube-dependent patients had developed reconstructed-conduit strictures, with only one patient becoming capable tube independence after neo-pharyngoesophageal dilatation. The other two remained tube-dependent for both food and liquid (Table 1) [27].

Survival and oncologic outcomes

The follow-up period of time ranged from 0.7 to 5.4 years (3.2 [1.6] years). The two-year overall survival, 2-year loco-regional free survival, and 2-year distant metastasis-free survival were 86.7%, 85.6%, and 78.7%, respectively (Fig. 2a, b). Five patients did not remain disease-free during the follow-up. Of those five, one had local disease, one had regional disease, and three had distant disease. Among the three with distant disease, one 54-year-old male (Case 9, Table 1), who had been treated for quadruple oral cancers, developed solitary lung metastasis. His metastasis was treated with wedge resection and was still surviving at end of the follow-up period. We found no significant difference in overall survival regardless of index HNC subsite or occurrence of anastomotic leakage. However, the result should be interpreted with caution due to the limited case numbers.

Four patients (23.5%) developed secondary primary malignancies (SPMs) in the remnants of their upper aerodigestive tracts (two in the oropharynx, one in the oral cavity, and one in the larynx). Estimated 2-year and 5-year SPM-free survivals were 85.9% and 65.5%, respectively (Fig. 2b). Average time from diagnosis to development of SPMs was 2.9 years (SD, 1.6 years). We did not find any significant associations between HNCs located in hypopharynx and anastomotic leakage and SPM-free survival in our Kaplan–Meier analysis (log-rank test, $p = 0.91$ & 0.18, respectively).

Discussion

This study found one-stage concurrent surgical resection and reconstruction to be a reliable and safe treatment of synchronous HNC and ESCC. Although the procedures are highly invasive, surgical outcomes were promising. We also report the chronology of these cancers and highlight the occurrence of second primary malignancies in patients undergoing definitive surgery.

Because in East Asia, there is a high prevalence of ALDH2 polymorphisms [6, 7], multiple upper aerodigestive carcinomas are not uncommon as EGDS is commonly used as a part of HNC cancer staging [11, 12]. One epidemiologic study has reported that patients with hypopharyngeal cancer

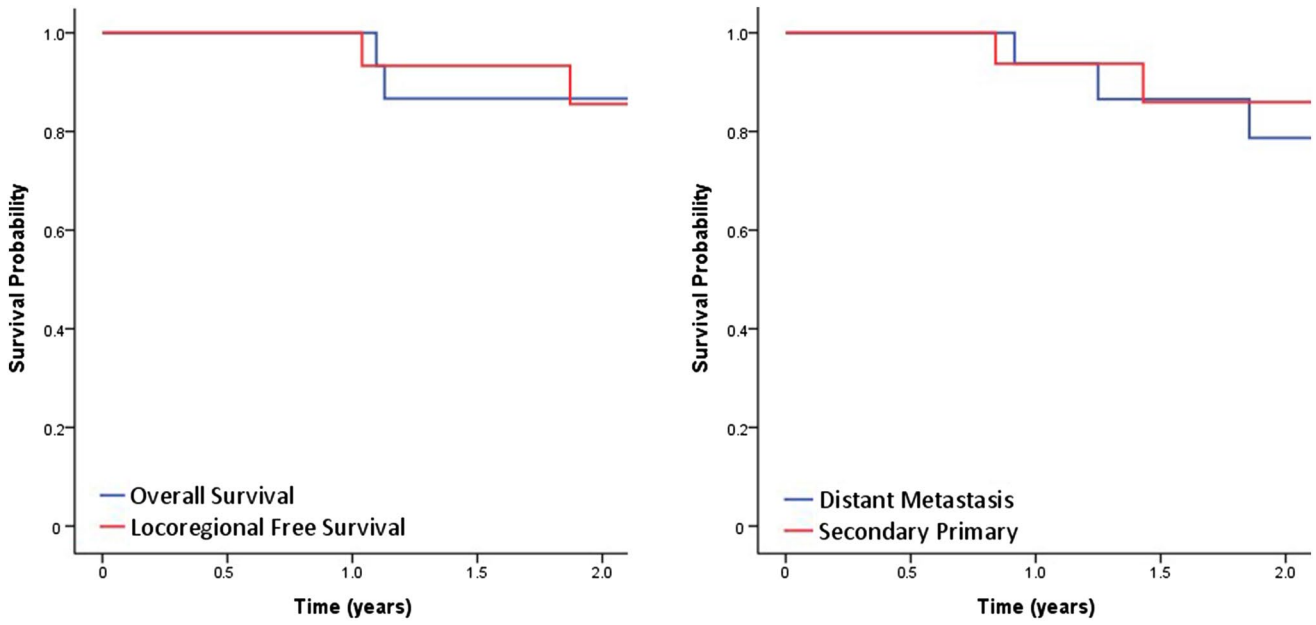

Fig. 2 Estimated survivals of 17 patients receiving concurrent surgical resections. Kaplan–Meier analyses of **a** 2-year overall survival and 2-year loco-regional free survival. **b** 2-year distant metastasis-free survival and 2-year second primary malignancy-free survival

to be most susceptible to develop synchronous ESCCs, found in as much as 27.2% of those patients [28]. For oral malignancies, genetic polymorphisms also greatly influence the association between peri-odontopathogenic bacteria and the consumption alcohol consumption, one of several known carcinogens [29]. Our surgical department started performing one-stage wide-field cancer ablations for synchronous ESCC and HNC for several reasons. The first reason was that we wanted the patient to be able swallow as soon as possible after surgery, because a visceral conduit is more pliable and versatile than free myocutaneous flap or pedicle flap [30]. The use of gastric-tube pull up (GTPU) to reconstruct defect makes it possible for most patients to consume an oral diet without restrictions, though regurgitation and reduced eating capacities have occasionally been encountered. Another reason we started performing one-stage wide-field cancer ablations was that patients with synchronous ESCC and HNC are susceptible to field cancerization in remnant tissues [4, 5, 9]. In a retrospective study of endoscopic therapy for early staged ESCC, Altorki et al. reported the incidences of multifocal occurrences ranged from 30 to 45% even in T1 disease [31]. Still another reason for this surgical strategy is that effects of previous multimodalities (i.e., surgery and/or irradiations) for persistent or recurrent cancers usually make salvage therapies difficult [22–25]. Although salvage surgery is theoretically the best option for prolonging survival [22], its efficacy remains limited for resectable patients failing to respond to (chemo) radiotherapy, especially if the persistent disease is due to resistant tumor biology [22–25]. Finally, further adjuvant therapy is not recommended for at-risk patients unable to tolerate multiple irradiations within a short period of time [22–25].

Eight of our seventeen patients (47.1%) had anastomosis leakages, an incidence higher than reported by other studies. Kamiyama et al. [32] reviewed 40 naïve hypopharyngeal cancer or esophageal cancer cases treated with TLPE and GTPU reconstruction alone, and found that 10% of cases developed anastomotic leakages. The high leakage rates in our study may have been related use of bridged free flaps (i.e., free anterolateral thigh flap or jejunal flap) to release tension of the gastric tube. This reconstructive method requires the formation of additional surgical anastomosis, increasing the risk of more leakage sites [26].

Another reason for the high incidence of anastomosis leakage is that the use of one-stage total laryngopharyngoesophagectomy with standard mediastinum lymph-node dissections has been associated with increased incidence of severe leakage as well as tracheal necrosis [33]. To overcome the treatment-associated leakage, Sekido et al. [34] have suggested a "supercharge technique" involving the augmentation of arterial blood flow in the neo-pharynx and neo-esophagus. Other studies have tried different suturing techniques (e.g., stapling or Gambee suture) for anastomosis or omental flaps to protect anastomotic site [35]. Morita et al. [36] recently suggested that leakage could be prevented by performing additional venous microvascular anastomosis (short gastric vein and appropriate cervical vein) of the distal end of reconstructed pedicle-conduit and additional local muscular flap coverage the anastomotic site. We plan to use aforementioned strategies to prevent leakage in the future.

Our study found a slightly lower incidence of tracheal necrosis compared to the incidences reported in previous literature [32–36], possibly because pre-tracheal lymph nodes were not routinely dissected in our patients and the vascular supply to the trachea was mostly preserved [36]. We also tried to minimize the time that the trachea and esophagus were detached intra-operatively aiming to reduce tracheal necrosis [36]. Furthermore, most of our patients did not receive irradiation before surgery, so that we could avoid radiotherapy-associated microvasculature disruption or the subsequent delay in wound healing.

Overall survival in this study was comparable to rates reported by other studies. Distant metastasis remained discouraging (3/17, 17.6%). Although it is difficult to determine the origin of distant metastasis, there is a great need to try to predict its occurrence and tailor diagnostic approaches to reduce this risk. In a study investigating 96 locally advanced hypopharyngeal cancer specimens, Ono et al. [37] found a lower incidence of metastasis in patients whose specimens had higher CD8+ tumor-infiltrating lymphocyte (TIL) densities, not CD4+ TIL or FOXP3+ TIL densities. In addition, one recent meta-analysis of 22 observational studies of ESCCs also found an association between better disease-free survival and increased CD8+ TIL densities [38]. Distant metastasis could possibly be suppressed by increases in intra-tumoral CD8+ TILs which have been found to be regulated by cancer-associated fibroblasts through down-regulation of interleukin-6 [37–39].

Matrix metalloproteinases (MMPs) can regulate molecular communications between tumor and stroma. Wang et al. found a positive correlation between MMP-9 and advanced-stage disease and lymph-node metastasis in patients with HNC and ESCC [40]. In their study of 40 synchronous cancer patients, MMP-3 and MMP-9 were both found to be associated with increased incidence of distant metastasis [40]. The authors concluded that findings of concomitant increases in serum MMP-3 and 9 better predicted survivals than predictions based on traditional AJCC TNM classifications [40]. One mechanism that may underlie the association between MMP and distant metastasis is the existence of vascular endothelial growth factor receptor 1 (VEGFR-1) positive bone marrow-derived hematopoietic progenitor cells expressing VLA-4 [41]. MMP-9, which is produced by VEGFR-1+ hematopoietic progenitor cells, directs metastasis with its release of Kit-ligand and its alteration of pre-metastatic microenvironments, a process enhanced by

VLA-4 signaling [41]. Distant metastasis might be predicted by imaging. Yao et al. found that image findings of advanced AJCC T classification, AJCC N classification, and maximum standardized uptake value of the lymph node at diagnosis could be used to as independent predictors of metastasis and poor survival [42]. Thus, imaging and histopathologic findings could possibly better integrate to help identify patients at risk for distant metastasis.

Most importantly, nearly a quarter of the patients in this study developed SPMs, a significantly higher incidence rate than those previously reported for isolated HNC patients [43–45]. Several population-based epidemiologic studies have reported that head and neck cancer carries the highest excess risk for SPMs in the upper aerodigestive tract (i.e., head and neck, esophagus, and lung), predominantly in the hypopharynx and oropharynx [5, 43, 44]. Although SPM risk began declining for oropharyngeal cancer after the 1990s in the Western world, it has remained high among non HPV-associated HNCs patients, especially in those with heavy consumption of tobacco and/or alcohol [5, 44]. The interaction between active alcoholism and ALDH polymorphisms is known to be highly tumorigenic and clonogenic, which may explain the reason for our higher incidence of SPM in our cancer-surviving patients [10, 45]. Thus, abstinence from alcohol may play an important role in improving survival in patients with these polymorphisms, particularly in Asia. Mayne et al. found that continued use of alcohol among patients had a significant effect on cancer survival and alcohol-related morbidity [46]. However, in the real world, only 29.7–54.3% of cancer patients reduce their consumption of alcohol after diagnosis, and those odds decrease substantially over time [47, 48]. These findings suggest that more effort is needed to eliminate the use of known carcinogens (including alcohol) in these patients and to find effective preventive agent to help retard ALDH2*2 mutation-related carcinogenic processes [49, 50].

This study has some limitations. One limitation is that it is a retrospective follow-up study of a relatively small numbers of patients. Another limitation is that most of the ESCCs were early stage diseases, making it impossible to weigh the impact of ESCC cancer stage on survival of HNC patients. The overall survival of this cohort may depend on the dominant and large tumor either over head and neck cancer or esophageal cancer. Still, another limitation is related to the impact of one-cycle bridging chemotherapy. While standard NAD-CT is known to improve outcomes in advanced-stage HNCs and ESCCs patients with major histologic response [51], a better understanding of the impact of bridging CT on outcomes in this patient group is needed. Still another is that because most analyses of synchronous cancers from head and neck and esophagus are derived from East-Asia patients, further investigations are needed to test its efficacy in other ethnic groups [52]. Furthermore, the results of this study may be confounded by loss of data of patients who were lost to follow-up after diagnosis. Another limitation of this study is the short follow-up period.

In conclusion, one-stage surgical resection and reconstruction for synchronous HNC and ESCC provided favorable survival in the era of esophageal screening in HNC patients. Although the procedures are highly invasive and complicated, the outcomes can be promising with attention paid to meticulous care tailored to the individual patient. The development of distant metastasis and secondary primary malignancy remain the most common failure patterns. Future research might want to focus on vigilant post-treatment surveillance for the detection of SPMs and implementation of strict preventive measures (e.g., alcohol abstinence or preventive agent prescription for halting ALDH2*2 mutation-related carcinogenetic processes).

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Compliance with ethical standards

Conflict of interest None of the authors declare any conflict of interest, financial, or otherwise.

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