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Original Article

Elderly Patients with Laryngeal and Hypopharyngeal Cancer Undergoing Total Pharyngolaryngectomy with a Radial Forearm, Free Flap-reconstructed Phonation Tube☆

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SUMMARY

Background: The radial forearm, free-flap (RFFF)-reconstructed phonation tube was developed for functional restoration of voice after total pharyngolaryngectomy. We aimed to report the efficacy of RFFF phonation tube after pharyngolaryngectomy with radiotherapy (RT) or concurrent chemoradiation therapy (CCRT) with intensity-modulated radiotherapy (IMRT) for elderly.
Materials and methods: Ten patients with laryngeal and hypopharyngeal cancer underwent total pharyngolaryngectomy and one-stage reconstruction with an RFFF-accompanied phonation tube, followed by RT or CCRT. Voice restoration was achieved with the RFFF-reconstructed phonation tube. Functional outcomes of phonation and speech were evaluated and scored.
Results: Percentages of stage III and stage IV patients among all participants were 10% and 90%, respectively. The median follow-up time was 31 months (range, 4–67 months). Almost 9 out of 10 (90%) patients experienced phonation efficacy greater than 80%. The maximal phonation time per breath was 70% longer than 3 sec. The graded as mild of wet voice was 90%. Percentage of mild decreased loudness was 60% and that of low and high pitch was 80%. Of the 10 patients, 40% could count more than 10 and 70% could pronounce more than 1 to 5 words per breath. After RT or CCRT, of patients had moderately good to excellent speech intelligibility.
Conclusion: The RFFF phonation tube that was used after pharyngolaryngectomy with RT or CCRT with IMRT provided acceptable complications and functional restoration of voice for elderly patients.

1. Introduction

Since Theodore Billroth performed the first laryngectomy for cancer in 1873, loss of normal voice has been considered a predominant problem for more than 100 years. To overcome this problem, a randomized trial[1] and the Radiation Therapy Oncology Group (RTOG) 91-11 trial[2] proved similar survival rates between total laryngectomy and organ preservation with radiotherapy (RT) and chemotherapy. However, the recurrent rates of residual and local tumors were higher in the chemotherapy induction group than in the surgical group[1]. In addition, local failure rate was noted to be greater than 20% in the RTOG 91-11 trial[2]. Surgery still plays an important role in radical situations.

To restore the functions of voice, speech, and swallowing, various reconstructive methods for the large defects of head and

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neck surgery, such as those using jejunal flap[3], ileocolic flap[4], or radial forearm free-flap (RFFF), are available[5]. The jejunal flap is a popular choice because it already has a tubal structure and is associated with relatively low rates of fistula formation. However, jejunal interposition requires an additional abdominal surgery, which increases the risk of postoperative morbidity[8,9]. The tubal RFFF has subsequently gained general acceptance with its good defect repair and favorable swallowing outcome[8,9]. Nevertheless, voice quality and functional intelligibility achieved using this method are not as good as it should be for intelligible speech[10], especially when adjuvant RT or concurrent chemoradiation therapy (CCRT) is needed due to the severity of locally advanced disease[11].

Intensity-modulated radiation therapy (IMRT) is highly conformal, with sharp dose gradients from the target volume to neighboring normal tissue, especially compared with conventional RT[12]. Additionally, IMRT is associated with improved quality of life among long-term survivors of head and neck cancer[13]. However, despite recent advances in treatments for head and neck cancer, the treatment paradigms in the elderly population have not been well defined. These patients may not be considered candidates for aggressive multimodality management due to their multiple comorbidities, general debility, poor treatment tolerance, and toxicities.

Here, we report our experience with the RFFF phonation tube (PT) reconstruction technique followed by RT or CCRT with IMRT, focusing on the possibility of preserving functions of phonation and speech in elderly patients, with limited complications.

2. Materials and methods

2.1. Patient selection and data collection

Retrospective patient data were collected with the approval of the Institutional Review Board of Mackay Memorial Hospital. From April 2005 to November 2011, ten patients with locally advanced hypopharyngeal or laryngeal carcinoma underwent total pharyngolaryngectomy and one-stage reconstruction with an RFFF-accompanied PT, followed by RT or CCRT.

2.2. Surgical procedures

All participants were treated by the same team of head and neck surgeons and plastic surgeons[11]. Briefly, the shape and size of the RFFF were designed based on the size of the pharyngeal defect and the expected length of the PT. After the harvest, it was rolled as a connecting tube; one part was connected to the base of the oropharynx, another part was connected to the proximal end of the esophagus, and a third part was sutured near the tracheostoma.

2.3. Radiotherapy

IMRT was performed with a computed tomographic simulation using the Eclipse planning system version 7.3.10 (Varian Medical Systems, Palo Alto, CA, USA). RT was begun as soon as there was adequate healing after surgery. Normally, this was within 4 weeks after the procedure, but in no case RT was started later than 6 weeks postoperatively. Treatment was delivered once daily in five fractions per week over 7 weeks, with all targets being treated simultaneously. The surgical bed containing soft tissue invasion, or regions with extracapsular extension of metastatic neck nodes, received a radiotherapy dose of 64.8–66 grays (Gy). Clinical target volume (CTV)59.4 primarily included high-risk nodal areas. CTV52.8–56 was used for low-risk subclinical disease prophylaxis. Planning target volume (PTV) was created by adding a 3 mm margin to CTV.

Planning for treatment was based on one phase (from skull base to lower neck) using a dose-painting technique.

2.4. Chemotherapy

Patients who received chemotherapy were scheduled to undergo two to three cycles of chemotherapy [containing cisplatin (Abiplatin injection 0.5 mg/mL) 25 mg/m^2/d and 5-fluorouracil (5-FU; fluorouracil injection 50 mg/mL) 750 mg/m^2/d infused continuously for 5 days] concurrently with RT every 3–4 weeks.

2.5. Evaluation of phonation and speech intelligibility

The phonation and speech training was started about 3 weeks postoperatively by a qualified speech language pathologist. Phonation was obtained by covering the tracheostoma with the thumb without occluding the external orifice of the PT, forcing the expiratory airflow through the PT into the neoesophagus. During this study, phonation and speech outcomes were collected postoperatively within 1 month prior to RT or CCRT. Upon completion of RT or CCRT, patients were evaluated every 3 months for the first 2 years.

The phonation outcome data included the ability of voice production, phonation efficacy, maximal phonation time (MPT) per breath, loudness, and grading of wet voice. Phonation efficacy is the success rate of producing voice. For assessing speech outcome, data on number counting per breath, words spoken per breath, and speech intelligibility were collected. Number-counting per breath means how many numbers (from 1 to 10) can be counted in one breath; similarly, words spoken per breath means how many words can be spoken in one breath. These examinations are used to estimate the amount of air streaming through the PT. However, it is more difficult to speak words than to count numbers. The scale used for speech intelligibility evaluation was similar to the one used in our previous work[11]. Briefly, on this scale, 1 = not understandable, 2 = occasionally understandable, 3 = understandable when the topic is limited, 4 = occasionally not understandable, and 5 = understandable. In the current study, speech intelligibility was tested by groups of two to three single-syllable Chinese characters, and was graded by one qualified speech language pathologist and one resident. A total score of 8–10 was considered excellent speech intelligibility, 5–7 moderately good, and 2–4 poor.

2.6. Evaluation for toxicities and treatment results

All patients were evaluated at least once a week during CCRT. Upon completion of radiation, patients were evaluated every 3 months for the first 2 years. At each follow-up visit, a complete evaluation including clinical examination and bimanual palpation of neck was performed. Post-treatment magnetic resonance imaging of the head and neck was done 1 month, 3 months, and 6 months after the completion of RT. Toxicities were defined and graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). The earliest date of detecting grade 3 or worse toxicity was recorded.

2.7. Statistical analysis

Descriptive statistics were calculated to characterize the patients, diseases, and treatment features, as well as toxicities after treatment. The overall survival, disease-free survival, locoregional control, and metastasis-free survival rates were estimated using the Kaplan–Meier product-limit method. Durations were calculated

from the date of pathologic proof of cancer. All analyses were performed using the SPSS, version 12.0 statistical software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Ten men were enrolled in the study. The median age was 65 years (range, 58–76 years). The subsets were laryngeal cancer ($n = 4$, 40%) and hypopharyngeal cancer ($n = 6$, 60%). None experienced close or positive surgical margins. Of all patients, 10% ($n = 1$) had stage III disease, whereas 90% ($n = 9$) had stage IV disease. The median dose of radiation was 66 Gy (range, 64.8–66 Gy) and the median duration of complete RT or CCRT was 7 weeks (range, 7–9 weeks). Patient characteristics are given in Table 1.

3.2. Treatment outcomes and toxicities

The median follow-up time was 31 months (range, 4–67 months). During RT or CCRT, there was no grade 3 acute toxicity for neutropenia. The rate of grade 3 dermatitis was 40% and that of grade 4 mucositis was 20%. None of the patients suffered fistula formation after the completion of treatment, although two (20%) patient experienced leakage of the PT after surgery (Table 2).

Table 1
Patient characteristics.

Variable	Patients who received surgery with radial forearm free flap ($n = 10$)
	n (%)
Age (y)	
Median	65
Range	58–76
Sex	
Male	10 (100)
Subsite	
Laryngeal carcinoma	4 (40)
Hypopharyngeal carcinoma	6 (60)
Pathology	
Squamous cell carcinoma	10 (100)
Resection-margin status	
Negative	10 (100)
Pathology stage	
Tumor stage	
Stage I	0
Stage II	0
Stage III	1 (10)
Stage IVA	8 (80)
Stage IVB	1 (10)
Primary tumor stage	
T1a	0
T1b	0
T2	1 (10)
T3	4 (40)
T4a	5 (50)
T4b	0
Regional lymph node stage	
N0	2 (20)
N1	1 (10)
N2a	0
N2b	0
N2c	6 (60)
N3	1 (10)
Treatment stratagem	
Surgery[a] → RT	3 (30)
Surgery → CCRT	7 (70)
Radiotherapy dose (Gy)	
Median (range)	66 (64.8–66)
Complete weeks	
Median (range)	7 (7–9)

CCRT = concurrent chemoradiation therapy; RT = radiotherapy.
[a] Total pharyngolaryngectomy and one-stage reconstruction with a radial forearm free flap accompanied by a phonation tube.

Table 2
Acute toxicities for laryngeal or hypopharyngeal cancer patients treated with total pharyngolaryngectomy and one-stage reconstruction with RFFF-accompanied phonation tube, followed by radiotherapy or concurrent chemoradiation therapy.

Variable[a]	Patients who received pharyngolaryngectomy with an RFFF phonation tube followed by CCRT $n = 10$ (%)
Mucositis	
Grade 1	5 (50)
Grade 2	1 (10)
Grade 3	2 (20)
Grade 4	2 (20)
Grade 5	0
Dermatitis	
Grade 1	3 (30)
Grade 2	3 (30)
Grade 3	4 (40)
Grade 4	0
Grade 5	0
Leucopenia	
Grade 1	8 (80)
Grade 2	2 (20)
Grade 3	0
Grade 4	0
Grade 5	0
Fistula formation	
No	10 (100)
Yes	0
Leakage of phonation tube	
No	8 (80)
Yes, prior to RT or CCRT	2 (20)

[b]Toxicity of xelostomia (acute): acute toxicity is defined as occurring <90 days after beginning radiotherapy.
CCRT = concurrent chemoradiation therapy; RFFF = radial forearm free flap; RT = radiotherapy.
[a] The grade of toxicity is according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0).

3.3. Phonation outcomes

Table 3 summarizes the phonation and speech outcomes at the last follow-up prior to the writing of this report. The phonation efficacy was 80% or better for almost all patients (9/10, 90%). Seventy percentage of patients experienced MPT more than 3 seconds. Wet voice was graded as mild in 90% of patients. The percentage of mild decreased loudness was 60%. Eighty percent of patients had low or high pitch (Table 3, parts A–E).

3.4. Speech outcomes

For speech outcomes, 40% of patients counted more than 10 consecutive numbers per breath, and 70% of patients pronounced 1 to 5 words per breath. Additionally, 80% of patients had moderately good to excellent speech intelligibility at the last follow-up visit (Table 3, parts F–H).

4. Discussion

According to the RTOG 9501[14] and the European Organisation for Research and Treatment of Cancer (EORTC 22931)[15], these reports confirmed the benefits of multiple modalities for patients having locally advanced head and neck cancer, with intermittent and high risk factors. However, the long-term follow-up data of

Table 3
Phonation and speech outcomes (1 month post operation/last follow-up) for laryngeal or hypopharyngeal cancer patients treated with total pharyngolaryngectomy and one-stage reconstruction with radial, RFFF-accompanied by a phonation tube followed by RT or CCRT.

(A) Evaluation of phonation efficacy at the last follow-up visit after RT or CCRT ($n = 10$).

Phonation efficacy (%)	100	90	80	70	60	50	40	30	20	≥10
n (%)	5 (50%)	1 (10)	3 (30%)	0	0	0	0	1 (10)	0	0

(B) Evaluation of MPT (in seconds) at the last follow-up visit after RT or CCRT ($n = 10$).

MPT	1 s	3 s	5 s	20 s
n (%)	3 (30)	4 (40)	2 (20)	1 (10)

(C) Evaluation of wet voice at the last follow-up visit after RT or CCRT ($n = 10$).

Wet voice	Not available	Mild
Patient number (%)	1 (10)	9 (90)

(D) Evaluation of loudness at the last follow-up visit after RT or CCRT ($n = 10$).

Loudness	Not available	Mild decrease	Moderate decrease	Severe decrease
n (%)	1 (10)	6 (60)	2 (20)	1 (10)

(E) Evaluation of pitch at the last follow-up visit after RT or CCRT ($n = 10$).

Pitch	Not available	Low	High
n (%)	2 (20)	6 (60)	2 (20)

(F) Evaluation of number counting per breath at the last follow-up visit after RT or CCRT ($n = 10$).

Number counting per breath	Not available	1–5	1–10	>10
n (%)	1 (10)	5 (50)	2 (20)	2 (20)

(G) Evaluation of words spoken per breath at the last follow-up visit after RT or CCRT ($n = 10$).

Words spoken per breath	Not available	≥5
n (%)	3 (30)	7 (70)

(H) Evaluation of speech intelligibility at the last follow-up visit after RT or CCRT ($n = 10$) (intelligibility was tested for groups of two to three single-syllable Chinese characters and then was graded by one qualified speech language pathologist and one resident; a total score of 8–10 was considered excellent, 5–7 moderately good, and 2–4 poor).

Speech intelligibility score	Not available	2–4 (poor)	5–7 (moderate)	8–10 (excellent)
n (%)	2 (20)	0	6 (60)	2 (20)

CCRT = concurrent chemoradiation therapy; MPT = maximal phonation time; RFFF = radial forearm free flap; RT = radiotherapy.

RTOG 9501 showed that 13.5% of patients experienced latent effects in the pharynx, larynx, and esophagus[16]. The problems that need to be considered in the case of elderly patients are their multiple comorbidities, general debility, poor treatment tolerance, and toxicities[17].

The failure rate for free flaps was 5–13.5%[18–20] and the mortality rates were 5–20%[20–22]. Additionally, 13–38% of patients experienced pharyngocutaneous fistulas[20,21,23]. Although Wolf et al[1] reported no difference in overall survival rates, the surgery group experienced lower recurrence rates for residual tumors (4%) and local tumors (2%) than the induction chemotherapy group (9% and 12%, $p = 0.042$ and 0.001, respectively). In the RTOG 91-11 trial, the local failure rates for the induction chemotherapy and CCRT groups were 35% and 20%, respectively[2]. In radical settings, proper design of surgery still plays an important role in preserving quality of life.

The loss of normal voice is considered a critical problem of quality of life for locally advanced laryngeal carcinoma after total laryngectomy or laryngectomy combined with postoperative RT. For patients treated with near-total laryngectomy, voice preservation was greater than 77% (in 67 out of 87 patients)[24]. Lewin et al[25] reported that 78% of patients with anterolateral thigh flaps used their tracheoesophageal punctures to speak. In other studies, 30% of patients were able to develop useful tracheoesophageal speech after primary or secondary tracheoesophageal punctures[26]. Characteristics of the skin flap used for voice restoration include a cutaneous lining, low wet voice quality, and no inherent secretion[27,28]. Recently, we found that more than 65% of patients experienced improvement in speech with treatment by the RFFF PT technique[29]. In the current study, 90% patients experienced phonation efficacy greater than 80%.

Although decreased MPT has been reported in near-total laryngectomy patients[30], we noted that 70% of our patients whose MPT achieved longer than 3 seconds. Additionally, 90% of our patients had only mildly wet voices. Only 60% of patients experienced the severely decreased loudness. The percentage of patients able to make both low- and high-frequency pitches was 80% (Table 3). These data supported our previous observation[11]. In our preliminary report, most of our patients were observed to achieve moderately good speech intelligibility[11]. In our current study, 80% of patients had moderate to excellent speech intelligibility. Treatment with the RFFF-accompanied PT followed by RT or CCRT with critical organs sparing decreases the sequelae caused by RT and achieves speech function restoration for elderly patients.

In other studies, grade 3 dermatitis occurred with adjuvant CCRT at a rate of 3–29% for locally advanced head and neck cancer;[14,31,32] the corresponding rate in the current study was 40% (4/10). According to the RTOG 91-11, 97-03, and 99-14 clinical trials of CCRT for locally advanced head and neck cancer, 43% of assessable patients had a severe late toxicity in association with advanced T stage, laryngeal/hypopharyngeal primary site, and neck dissection after CCRT[33]. The occurrence of grade 3 dermatitis in our study participants can be explained by the presence of advanced T stage (T3 and T4, 90%, 9/10) and larynx/hypopharynx primary site. Additionally, relatively small cases caused the higher percentage of sever dermatitis in the current study could not be ruled out. Grade 3 mucositis, induced by chemotherapy, reportedly occurred in 30–60% of patients[14,15,32]. In the current study, 20% of patients experienced grade 4 mucositis even with the use of IMRT technique. The reason for this can partly be attributed to the concurrent chemotherapy. Still now, more than 20% of elderly patients, who are receiving RFFF-accompanied PT followed by RT or CCRT, even using IMRT techniques, have grade 3 dermatitis and mucositis, which indicates that better supportive care is needed for these elderly patients.

Because surgery, radiation, and/or chemotherapy may disrupt lymphatic structure and damage soft tissue, leading to scar tissue formation and fibrosis, and further affect lymphatic function, patients with head and neck cancer may be at high risk for developing secondary lymphedema[34]. IMRT was reported to not only maintain the early improvements in quality of life but also magnify them over time, when compared with three-dimensional conformal RT[13]. In the current study, none of the patients had severe fibrosis. The possible reasons could be limited cases number and management with IMRT. However, further studies are needed to confirm the benefits of the IMRT technique.

There are some limitations to our current study. First, the small case numbers and the retrospective study design make it difficult to draw statistical conclusions. Second, the follow-up time was relatively short so that any potential late effects were addressed insufficiently. Third, the functional phonation and speech restoration by the PT based on RFFF still has room for improvement. Nonetheless, the advantages of one-stage reconstruction, good phonation efficacy, moderate to excellent speech intelligibility, and no prosthesis-related problems provide surgeons with a reference and evidence to justify the radical surgery for locally advanced laryngeal and hypopharyngeal cancer patients.

In conclusion, the phonation efficacy and speech intelligibility attained with RFFF-accompanied PT after pharyngolaryngectomy followed by RT or CCRT in elderly patients are acceptable. The multiple modalities offer a practical reference for elderly laryngeal and hypopharyngeal cancer patients.

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