Ann Surg Oncol (2019) 26:3711–3717
https://doi.org/10.1245/s10434-019-07476-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Thyroid and Parathyroid Functions After Pharyngo-Laryngo-Esophagectomy for Cervical Esophageal Cancer

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ABSTRACT

Background. Cervical esophageal cancer (CEC) patients whose larynx function cannot be preserved often undergo chemoradiotherapy, whereas those with residual or recurrent lesions undergo a pharyngo-laryngo-esophagectomy (PLE); however, some need to undergo a pharyngolaryngectomy with total esophagectomy (PLTE) for synchronous or metachronous esophageal cancer. We retrospectively evaluated the relationship between preoperative irradiation (or the extent of esophageal resection) and postoperative endocrine complications in CEC, including hypothyroidism and hypoparathyroidism.

Methods. The cancers of 35 (5.4%) of 678 esophageal cancer patients with esophagectomy treated in 2000–2017 were CECs. We also analyzed the 17 cases of CEC patients who underwent PLE with thyroid lobectomy—11 with irradiation before PLE and 6 without irradiation. Seven patients underwent a PLTE.

Results. Hypothyroidism and hypoparathyroidism occurred in 14 and 12 patients, respectively. The hypothyroidism rate was significantly higher in patients with irradiation versus those without irradiation (100% vs. 50%; $p = 0.010$), and the hypoparathyroidism rate was significantly higher in the PLTE versus non-PLTE patients (100% vs. 50%; $p = 0.026$). The mean levothyroxine dosage was 1.60 μg/kg/day in the PLE patients post-irradiation.

Conclusions. Irradiation appears to be a risk factor for hypothyroidism after PLE with thyroid lobectomy, while PLTE might have some effect on hypoparathyroidism. Due to vocal function loss, PLE patients may experience symptoms from endocrine complications. Levothyroxine treatment soon after PLE for post-irradiation patients and patients requiring as-needed calcium or vitamin D supplementation based on biochemical hypocalcemia for PLE (especially PLTE), may be effective in preventing symptomatic endocrine complications.

Cervical esophageal cancer (CEC) is rare, accounting for < 5% of all esophageal cancers,[1,2] and is often diagnosed as advanced cancer invading adjacent structures.[3] The optimal primary treatment for CEC, including chemoradiotherapy (CRT) and surgery, is controversial.[4–6] The Guidelines for the Diagnosis and Treatment of Carcinoma of the Esophagus edited by the Japan Esophageal Society state that the surgical procedure should be determined carefully because of the loss of vocal function that accompanies a pharyngo-laryngo-esophagectomy (PLE).[3] In the US National Comprehensive Cancer Network (NCCN)[7] and European Society for Medical Oncology (ESMO) clinical practice guidelines[8] definitive CRT is recommended for patients with CEC, while palliative surgery can be considered for patients with localized recurrent or untreatable stricture after definitive CRT.[7]

Esophageal cancer is frequently associated with synchronous or metachronous multiple cancer.[3] In some cases, patients need to undergo a PLE and an esophagectomy at the same time, i.e. a pharyngolaryngectomy with total esophagectomy (PLTE), for synchronous cancer located in

First Received: 7 November 2018;
Published Online: 11 June 2019

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the cervical or thoracic esophagus. In other cases, a PLE may be appropriate for CEC patients who have a history of esophagectomy for thoracic esophageal cancer.

There are some characteristic complications associated with PLE. When a PLE is planned for an individual with CEC, a lobectomy or total thyroidectomy is usually necessary.[9,10] Endocrine complications, including hypothyroidism and hypoparathyroidism, comprise the majority of specific complications of PLE in CEC patients; however, a standard management strategy for endocrine complications in CEC patients with PLE has not yet been established. Although it is well known that irradiation to the thyroid for a malignant lymphoma,[11] and the performance of a thyroid lobectomy for a thyroid neoplasm,[12] are risk factors for hypothyroidism, very little is known about the relationship between preoperative irradiation and hypothyroidism after a PLE with a thyroid lobectomy for CEC. There are also few data regarding the relationship between a PLTE with a thyroid lobectomy for CEC and postoperative hypoparathyroidism, although it was reported that hypoparathyroidism occurred frequently in patients who had undergone a PLTE.[10] We hypothesized that (1) for CEC patients undergoing a PLE with a thyroid lobectomy, CRT would have some effect on the rate of postoperative hypothyroidism; and (2) PLTE may also have some effect on the postoperative hypoparathyroidism rate. We conducted the present study to test these hypotheses.

METHODS

Patients

This was a retrospective study of CEC patients who underwent a PLE at Keio University Hospital (Tokyo, Japan) during the nearly 18-year period from January 2000 to October 2017. We reviewed the medical records of these patients after approval by the Ethics Committee of Keio University School of Medicine. During that period, 678 patients underwent an esophagectomy for esophageal cancer, of whom 35 (5.2%) had CEC. We excluded CEC patients who underwent an esophagectomy with larynx preservation ($n = 15$). Furthermore, we also excluded from our analysis of endocrine complications CEC patients who underwent a PLE with a total thyroidectomy ($n = 3$) because patients who have undergone a total thyroidectomy will surely have postoperative hypothyroidism. The final study population was 17 patients, all of whom underwent a PLE with a thyroid lobectomy for CEC.

Assessment Parameters

To evaluate the association between endocrine complications and CRT, we compared the group of patients treated with CRT before their PLE (the CRT group) with the non-CRT group of patients who underwent a PLE without CRT. We also evaluated the relationship between endocrine complications and PLTE by classifying patients into the following two groups: (1) PLTE patients who underwent a PLE and a total esophagectomy at the same time, along with PLE patients with a history of esophagectomy (PLTE group); and (2) PLE patients who did not undergo an esophagectomy (non-PLTE group).

We defined hypothyroidism as a plasma thyroid-stimulating hormone (TSH) level > 10 μIU/ml[13] without levothyroxine (LT4) supplementation. Our group of patients with subclinical hypothyroidism (i.e. normal free T3 and free T4 serum levels with the upper limit of normal $<$ TSH < 10 μIU/ml)[13] did not include those with hypothyroidism. Moreover, these patients did not start to take LT4 in this series. The LT4 dosage after surgery was defined as the dosage necessary to achieve euthyroidism.

Each patient's serum calcium and albumin were measured after surgery (usually once every few days), and hypocalcemia was diagnosed when a low serum calcium level corrected for the serum albumin concentration was identified. Patients who were diagnosed as hypocalcemia were prescribed calcium or vitamin D supplements, which were gradually tapered off in accordance with the patient's albumin-corrected calcium level and clinical symptoms of hypocalcemia. We defined postoperative hypoparathyroidism as the patient's need to continue any calcium and/or vitamin D supplementation, or showing an albumin-corrected calcium level ≤ 8.0 mg/dl[14–16] at 3 months after surgery.

Statistical Analyses

Statistical analyses were conducted using STATA software, version 15 (StataCorp LLC, College Station, TX, USA). Pearson's Chi-square test was used for the comparison of categorical variables, and the Student's *t* test and Mann–Whitney *U*-test were used to compare continuous variables. A p value < 0.05 was considered significant.

RESULTS

Complications After Pharyngo-Laryngo-Esophagectomy

Table 1 summarizes the complications that occurred in the 17 CEC patients who underwent a PLE with a thyroid lobectomy. There were characteristic complications

TABLE 1 Complications after PLE with thyroid lobectomy (n = 17) at our institute

Complication	N (%)
Hypothyroidism	14 (82)
Hypoparathyroidism	12 (71)
Wound infection	3 (18)
Anastomotic leakage	2 (12)
Bleeding from the carotid artery	1 (6)
Abdominal bleeding	1 (6)
Venous thrombosis at the microvascular anastomosis	1 (6)
Tracheal necrosis	1 (6)
Tracheoesophageal fistula	1 (6)
Pneumonia	1 (6)

PLE pharyngo-laryngo-esophagectomy

associated with PLE compared with esophagectomy, i.e. hypothyroidism, hypoparathyroidism, bleeding from the carotid artery, venous thrombosis at the microvascular anastomosis, and tracheal necrosis. Among the various complications, endocrine complications occurred frequently; 14 (82%) and 12 patients (71%) had hypothyroidism and hypoparathyroidism, respectively.

Association between Chemoradiotherapy and Endocrine Complications

The 17 patients who underwent PLE with thyroid lobectomy for CEC included 12 men and 5 women, with a mean age of 62.6 years—11 in the CRT group (a mean radiation dose of 58.5 Gy) and 6 in the non-CRT group. In the CRT group, four patients (36%) were treated with intensity-modulated radiotherapy or volumetric-modulated arc therapy. As shown in Table 2, the demographics of the CRT and non-CRT patients were similar. There were no significant differences between the groups in age, sex, body mass index (BMI), rate of PLTE, reconstruction after PLE, or extent of thyroid resection.

The comparison of endocrine outcomes between the CRT and non-CRT groups is shown in Table 3. None of the patients in the present series had a thyroid or parathyroid function abnormality before being treated for CEC. Hypothyroidism following CRT was observed in 2 of the 11 CRT patients (18%), and the LT4 doses of these two patients were increased after a PLE for a postoperative decline in thyroid function.

The incidence of postoperative hypothyroidism was significantly higher in the CRT group compared with the non-CRT group (100% vs. 50%; p = 0.010). The LT4 dosage, to stabilize thyroid function after surgery, was also significantly higher in the CRT group compared with the non-CRT group (mean 89 μg/day vs. 42 μg/day; p = 0.043). All 11 patients who underwent a PLE with thyroid lobectomy following CRT needed LT4 supplementation; the mean (standard deviation) weight-based LT4 dosage for replacement was 1.60 (0.72) μg/kg/day. The timing of LT4 supplementation varied from within 1 week to > 1 month after surgery, and thus the TSH levels at 1 month post-surgery did not differ significantly between the CRT and non-CRT groups. The incidence of postoperative hypoparathyroidism was 64% in the CRT group and 83% in the non-CRT group (a non-significant difference).

Association between Pharyngolaryngectomy with Total Esophagectomy and Endocrine Complications

To determine whether PLTE affects the occurrence of postoperative endocrine complications, we next compared the PLTE group (n = 7) with the non-PLTE group (n = 10). The demographic characteristics of the PLTE and non-PLTE patients are presented in Table 4. There were no significant differences between the PLTE and non-PLTE groups with regard to age, sex, BMI, or rate of CRT before PLE. At our hospital, we usually used a free jejunal autograft for reconstruction after PLE regardless of whether or not the patient had a history of esophagectomy, and usually used the gastric pull-up for patients who underwent a PLE and total esophagectomy at the same time. Therefore, the rate of use of a free jejunal autograft for reconstruction after PLE was significantly higher in the non-PLTE group compared with the PLTE group (100% vs. 29%; p = 0.001).

Table 5 summarizes the comparison of endocrine outcomes between the PLTE and non-PLTE groups. There was no significant difference in the occurrence of postoperative hypothyroidism between these groups (86% vs. 80%). The rate of postoperative hypoparathyroidism was significantly higher in the PLTE patients compared with the non-PLTE patients (100% vs. 50%; p = 0.026).

DISCUSSION

Our retrospective analyses revealed that the incidence of postoperative hypothyroidism was 100% among the 11 patients treated with CRT before PLE. The reported incidences of hypothyroidism as a result of irradiation to the thyroid (40–45 Gy), and irradiation including the thyroid (20–40 Gy), were 44% and 47%, respectively.[11,17] On the other hand, Nishimura et al. reported a 16% incidence of hypothyroidism as a result of definitive CRT (60 Gy) for esophageal cancer; 11% of the tumors in their series were located in the cervical esophagus.[18] In our present series, a

TABLE 2 Demographic and operative characteristics of CEC patients with or without CRT

	Total [n = 17]	Non-CRT [n = 6]	CRT [n = 11]	p value
Age, years [mean ± SD]	62.6 ± 9.3	64.5 ± 3.7	61.6 ± 11.3	0.56
Sex				0.39
Male	12 (71)	5 (83)	7 (64)	
Female	5 (29)	1 (17)	4 (36)	
BMI, kg/m^2 [mean ± SD]	20.7 ± 3.2	21.5 ± 4.4	20.4 ± 2.5	0.52
PLTE	7 (41)	2 (33)	5 (45)	0.63
PLE performed with EG	5 (30)	2 (33)	3 (27)	0.79
PLE for patients with a history of EG	2 (12)	0 (0)	2 (18)	0.27
Reconstruction after PLE				0.79
Free jejunal autograft	12 (71)	4 (67)	8 (73)	
Gastric pull-up	5 (29)	2 (33)	3 (27)	
Extent of thyroid resection				0.40
Right lobectomy	9 (53)	4 (67)	5 (45)	
Left lobectomy	8 (47)	2 (33)	6 (55)	

Data are expressed as n (%) unless otherwise specified

BMI body mass index, *CEC* cervical esophageal cancer, *CRT* chemoradiotherapy, *EG* esophagectomy, *PLE* pharyngo-laryngo-esophagectomy, *PLTE* pharyngolaryngectomy with total esophagectomy, *SD* standard deviation

TABLE 3 Endocrine outcomes of the CRT and non-CRT groups

	Total [n = 17]	Non-CRT [n = 6]	CRT [n = 11]	p value
Thyroid function				
Hypothyroidism before CRT	–	–	0 (0)	–
Preoperative hypothyroidism	2 (12)	0 (0)	2 (18)	0.27
Postoperative hypothyroidism	14 (82)	3 (50)	11 (100)	0.010*
TSH level 1 month after PLE, μIU/ml [median (IQR)]	6.9 (4.6–45.1)	4.4 (0.9–64.6)	9.8 (5.7–52.4)	0.21
LT4 dosage, μg/day [mean (min, max)]	72 (0, 150)	42 (0, 100)	89 (25, 150)	0.043*
Parathyroid function				
Preoperative hypoparathyroidism	0 (0)	0 (0)	0 (0)	–
Postoperative hypoparathyroidism	12 (71)	5 (83)	7 (64)	0.40

Data are expressed as n (%) unless otherwise specified

CRT chemoradiotherapy, *IQR* interquartile range, *LT4* levothyroxine, *max* maximum, *min* minimum, *PLE* pharyngo-laryngo-esophagectomy, *TSH* thyroid-stimulating hormone

*$p < 0.05$

thyroid lobectomy was performed with PLE; thyroid lobectomy for thyroid neoplasms is associated with a 6–49% incidence of postoperative hypothyroidism,[12,19–21]

It is known that preoperative thyroiditis is related to hypothyroidism after lobectomy.[22] In fact, there were many reports that positive antithyroid peroxidase antibody (one of the thyroid antibodies) was a relevant preoperative indicator of hypothyroidism after lobectomy.[19] Irradiation can induce thyroiditis, and the potential capacity of thyroid hormone production might decrease after CRT, even if the thyroid hormone level is normal after CRT. For lack of standby capacity of thyroid hormone production in the CRT group, the perioperative increment of hypothyroidism was higher in the CRT group (82%) compared with the non-CRT group (50%).

Kojima et al. studied the thyroid function of 21 patients with hypopharyngeal cancer or laryngeal cancer who had undergone surgeries (including total laryngectomy) and postoperative adjuvant irradiation (40–50 Gy).[23] In their series, thyroid lobectomy was performed during surgery in 18 patients, and 13 patients (72%) had clinical hypothyroidism (TSH ≥ 10 μIU/ml). The higher hypothyroidism

TABLE 4 Demographic and operative characteristics of patients with and without PLTE

	Non-PLTE [n = 10]	PLTE [n = 7]	p value
Age, years [mean ± SD]	61.5 ± 11.0	64.3 ± 6.7	0.56
Sex			0.25
Male	6 (60)	6 (86)	
Female	4 (40)	1 (13)	
BMI, kg/m^2 [mean ± SD]	21.8 ± 3.4	19.2 ± 2.2	0.092
CRT before PLE	6 (60)	5 (71)	0.63
Reconstruction after PLE			0.001*
Free jejunal autograft	11 (100)	2 (29)	
Gastric pull-up	0 (0)	5 (71)	

Data are expressed as n (%) unless otherwise specified

BMI body mass index, *CRT* chemoradiotherapy, *PLE* pharyngo-laryngo-esophagectomy, *PLTE* pharyngolaryngectomy with total esophagectomy, *SD* standard deviation

*$p < 0.05$

TABLE 5 Endocrine outcomes in the PLTE and non-PLTE groups

	Non-PLTE [n = 10]	PLTE [n = 7]	p value
Thyroid function			
Preoperative hypothyroidism	2 (20)	0 (0)	0.21
Postoperative hypothyroidism	8 (80)	6 (86)	0.76
Parathyroid function			
Preoperative hypoparathyroidism	0 (0)	0 (0)	–
Postoperative hypoparathyroidism	5 (50)	7 (100)	0.026*

Data are expressed as n (%)

PLTE pharyngolaryngectomy with total esophagectomy

*$p < 0.05$

rate in our study compared with the above results may be attributable to the effect of irradiation on the thyroid, which is near the cervical esophagus as opposed to the hypopharynx, and to differences in the irradiation dose.

Patients who undergo a total thyroidectomy take LT4 after surgery. The average LT4 dose required to normalize TSH is approximately 1.6–1.8 μg/kg/day.[24,25] The administration of LT4 soon after a PLE with a thyroid lobectomy following CRT may be effective in stabilizing a patient's thyroid hormone level in the postoperative period, since, in our series, these patients all had postoperative clinical hypothyroidism. One of our patients treated with CRT followed by a PLE, without LT4 after surgery, had a peak TSH level > 100 μIU/ml and required time for normalization of the TSH level. In light of the results of the present analyses, we began administering an initial 1.6 μg/kg daily dose of LT4 after surgery to similar patients.

It has been reported that hypoparathyroidism after thyroid surgery can be prevented by saving more than two to three parathyroids.[16,26–28] The location of the superior parathyroid is commonly at the superior pole of the thyroid, whereas the location of the lower parathyroid varies, although it is usually at the back of, or below, the lower thyroid, including the mediastinum.[29] Postoperative hypoparathyroidism is usually caused due to devascularization or excision of the parathyroid glands.[30] When a PLE with a thyroid lobectomy is performed for CEC, at least the superior parathyroid preserved at the remnant thyroid lobe side is saved. In the present study, the rate of hypoparathyroidism was higher in CEC patients who underwent a PLTE compared with those who underwent a PLE, suggesting that an intrathoracic esophagectomy and lymphadenectomy have the potential to incidentally excise lower parathyroids.

There are few data in the literature regarding hypoparathyroidism after PLTEs with thyroid lobectomy or partial thyroidectomy. In a series of 25 patients who underwent PLTE with partial thyroidectomy for esophageal, pyriform sinus, retrocricoid, or laryngeal carcinomas, Martins and Tincani reported that the incidence of postoperative hypoparathyroidism was 44%.[10] In our series, most patients with hypoparathyroidism received calcium or vitamin D supplementation before the occurrence of clinical signs or symptoms of hypocalcemia. The definition of hypoparathyroidism was not stated in the report by Martins and Tincani, and, in their series, hypoparathyroidism was

treated only in the presence of clinical signs or symptoms of hypocalcemia. Although, for these reasons, the rates of hypoparathyroidism cannot be compared between the study by Martins and Tincani and the present study, both studies demonstrated that hypoparathyroidism is a complication of PLTE that should receive careful attention. When a PLE (especially a PLTE) with a thyroid lobectomy is performed, clinicians should be aware of the potential for postoperative biochemical hypocalcemia. When necessary, sufficient calcium or vitamin D supplementation soon after a PLE also appears to be important for the prevention of symptomatic hypocalcemia.

Despite our encouraging results, there are some limitations to our study. This retrospective, single-center study may have confounding and selection biases, and the small patient population from a single center may have affected our conclusions. Prospective trials of larger numbers of patients are needed to validate our findings.

CONCLUSIONS

Our updated analyses suggest that irradiation may be a risk factor for postoperative hypothyroidism after a PLE with thyroid lobectomy. We also observed that hypoparathyroidism often occurred after PLEs with thyroid lobectomies, and that a PLTE may have some effect on postoperative hypoparathyroidism. Because of the loss of vocal function, patients who have undergone a PLE often encounter difficulties reporting symptoms[31] that are typically associated with endocrine complications, and healthcare providers sometimes miss the first signs of symptoms. The administration of LT4 soon after a patient has undergone a PLE with CRT and as-needed calcium or vitamin D supplementation based on biochemical hypocalcemia, may be effective in preventing symptomatic endocrine complications in patients with CEC.

DISCLOSURES Yoshiyuki Saito, Hirofumi Kawakubo, Hiroshi Takami, Junya Aoyama, Shuhei Mayanagi, Tomoyuki Irino, Kazumasa Fukuda, Koichi Suda, Rieko Nakamura, Norihito Wada, and Yuko Kitagawa report no conflicts of interest relating to this work.

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