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ORIGINAL SCIENTIFIC REPORT

Parapharyngeal Metastasis of Papillary Thyroid Carcinoma

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Abstract

Background Nodal involvement of papillary thyroid carcinoma (PTC) commonly occurs in the paratracheal region and the internal jugular chain. Lymph node metastasis in the parapharyngeal space (PPS) is rare. In this report, we describe our experience and surgical outcomes of patients with PPS metastasis of PTC.

Methods Clinical data of patients with PTC who underwent surgery at our institution between January 2006 and December 2013 were retrospectively reviewed, and 22 patients with PPS metastasis were enrolled.

Results There were 2 primary and 20 secondary cases of PPS metastasis. Involvement of the jugular nodes was noted before or at the time of PPS metastasis detection in all cases. A transcervical surgical approach with partial resection of the mandibular angle was performed in 21 patients, while 1 patient underwent extirpation of the PPS metastasis via a transoral approach. Although curative resection was performed in 21 patients, the PPS metastasis was not removable in 1 patient owing to an invaded internal carotid artery at the skull base. Twelve and 6 patients had locoregional and distant recurrence, respectively. Of the 12 patients with locoregional recurrence, isolated locoregional recurrence in the PPS occurred in 1. Eight patients died of distant or locoregional recurrence, with a median survival time of 91.7 months.

Conclusions For patients who experience recurrence after thyroid surgery, the possibility of PPS metastasis should be considered. In this series, all patients with PPS metastasis also had previous unilateral or bilateral cervical metastasis. Despite curative attempt, most patients experienced local or distant recurrence.

Introduction

The parapharyngeal space (PPS) is well described as an inverted pyramid shape, with its base at the skull base and its apex at the greater cornu of the hyoid bone. The medial boundary comprises the superior pharyngeal constrictor muscle; the lateral boundary comprises the fascia overlying the medial pterygoid muscle and the ramus of the mandible; and the posterior boundary comprises the fascia over the vertebral column and the paravertebral muscles. Its three sides are made up of both immobile and distensible boundaries (Fig. 1).

Primary tumors of the PPS are rare, accounting for only 0.5 % of all head and neck neoplasms [1]. Benign tumors reportedly comprise 80 % of PPS neoplasms. Salivary gland neoplasms account for approximately 40 % of PPS neoplasms, followed by neurogenic neoplasms at 30 % [2–7].

Lymph node metastasis is common in patients with papillary thyroid carcinoma (PTC), and has been noted in 20–50 % of patients prior to initial treatment of PTC [8–

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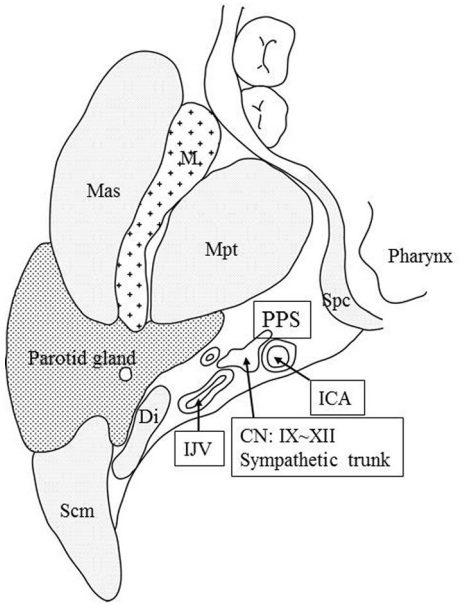

Fig. 1 Anatomy of the parapharyngeal space. *CN IX* glossopharyngeal nerve, *CN X* vagal nerve, *CN XI* accessory nerve, *CN XII* hypoglossal nerve, *Di* digastric muscle, *ICA* internal carotid artery, *IJV* internal jugular vein, *M* mandible bone, *Mas* masseter muscle, *Mpt* medial pterygoid muscle, *PPS* parapharyngeal space, *Scm* sternocleidomastoid muscle, *Spc* superior pharyngeal constrictor muscle

10]. Nodal involvement in PTC commonly occurs in the paratracheal region and the internal jugular chain, but lymph node metastasis to the PPS is rare.

The purpose of this report was to describe our experience and surgical outcomes of patients with PPS metastasis of PTC.

Materials and methods

The medical records of patients with PTC who underwent surgical treatment at Kusatsu General Hospital between January 2006 and December 2013 were retrospectively reviewed. Those with PPS metastasis were enrolled. Data on patient characteristics, tumor characteristics of PPS metastasis, clinical symptoms, and confirmation modality for PPS metastasis were collected. Information about surgical outcomes and complications of PPS metastasis was also compiled.

Our hospital's review board approved this study. Patients' privacy was strictly observed, and written informed consent was obtained.

The PPS was defined as described above. Surgical treatment of PPS metastasis primarily involved a transcervical approach combined with partial resection of the mandibular angle. However, a transoral approach to remove the PPS tumor was selected in cases of disease relapse after transcervical extirpation of the PPS metastasis.

For the transcervical approach combined with partial segmental resection of the mandibular angle, a transverse incision at the level of the hyoid bone was made from the submental region to the infra-auricular region after nasotracheal intubation, which allows bimanual evaluation of the PPS tumor. The skin flap was raised under the platysma muscle layer. The marginal branch of the facial nerve was identified and followed into the level of the parotid gland. The lower border and angle of the mandible were exposed, and the origins of the masseter and internal pterygoid muscles were partially separated from the angle of the mandible. Partial segmental resection of the mandibular angle was completed at a thickness of approximately 15 mm, without damaging the inferior alveolar nerve. The submandibular gland was removed for direct access to the PPS. By removal of the submandibular gland and partial segmental resection of the mandibular angle, it was possible to achieve a wider working space for PPS tumor resection.

Surgical complications were divided into two types as follows: expected and unexpected. Cranial nerve sacrifice secondary to tumor involvement resulted in numerous expected neurologic deficits, leading to permanent damage. Unexpected complications also occurred after PPS surgery, despite cranial nerve preservation. Oral intake was calculated as the time needed to return to normal diet intake.

Postoperative assessments with cross-sectional imaging were performed every 6 months to detect locoregional or distant recurrence. For locoregional recurrence that was surgically resectable, additional surgical treatment was performed.

The Mann–Whitney *U* test or Chi-square test was used to compare variables. Survival curves were constructed using the Kaplan–Meier method, and the medial survival time was calculated. Commercially, available software (Ekuseru-Toukei 2012; SSRI Co., Ltd., Tokyo, Japan) was used for all statistical analyses, and p values of < 0.05 were considered significant.

Results

During the study period, 22 out of 433 surgical patients with PTC had lymph node metastasis in the PPS. This study included 7 men and 15 women, with a mean age at time of PPS surgery of 63.4 years (range 15–82 years). There were 2 primary cases of PPS metastasis and 20 cases of PPS recurrence after PTC surgery. One of the initial cases had a 5-mm primary tumor with intraglandular multiple dissemination in the left thyroid lobe, while the other patient had a 3-cm primary tumor in the upper pole of the right thyroid lobe. Of the recurrent cases, 6 patients had

PPS recurrence after the initial surgery, while 14 had PPS recurrence after several other recurrences. Ten patients had distant metastasis prior to PPS surgery, including lung metastasis in 8 and both lung and bone metastasis in 2. Of the 22 patients, 21 were referred from other institutions for PPS surgery. The mean follow-up duration after surgery for surviving patients was 5.6 ± 2.6 years, as shown in Table 1.

For PPS metastasis, 17 patients were asymptomatic, whereas the other 5 experienced symptoms including fullness in the pharynx in 1 patient, ptosis in 1 patient, and a cervical mass in 3 patients. Of 20 patients without elevated thyroglobulin antibody, increased serum thyroglobulin (Tg) levels at PPS metastasis detection were noticed in 16. Twelve of the 16 patients with increased serum Tg levels (range 34–610 ng/dL) were asymptomatic even though they showed presence of PPS metastasis. Of those 12 asymptomatic patients with increased preoperative serum Tg levels, Tg levels were decreased postoperatively in 9 (range 5–134 ng/dL).

All 22 PPS metastatic lesions were identified by using 2-deoxy-2-[fluorine-18]-D-glucose integrated with computed tomography (PET/CT), magnetic resonance imaging (MRI), or enhanced CT. Twenty-one (95.5 %) of 22 lesions were detected on PET/CT, whereas 4 (18.2 %) were detected on ultrasonography (US) (Table 2).

Table 1 Baseline characteristics of 22 patients with parapharyngeal metastasis of papillary thyroid carcinoma

Characteristic	
Age, mean (range) (years)	63.4 (15–82)
Sex, *n* (%)	
Male	5 (22.7)
Female	17 (77.3)
Treatment, *n* (%)	
Initial	2 (9)
Recurrence	20 (91)
Presentation of primary tumor, *n* (%)	
Well	19 (86.4)
Poorly	3 (13.6)
Extrathyroidal extension, *n* (%)	
Yes	8 (36.4)
No	14 (63.6)
Distant metastasis prior to initial surgery, *n* (%)	
Yes	10 (45.5)
No	12 (54.5)
RAI treatment after initial surgery, *n* (%)	
Yes	10 (45.5)
No	12 (54.5)

RAI radioactive iodine

Table 2 Symptoms and diagnostic imaging for parapharyngeal metastasis

Characteristic	
Symptom, *n* (%)	
Asymptomatic	17 (77.3)
Cervical mass	3 (13.6)
Oropharyngeal mass	1 (4.5)
Ptosis	1 (4.5)
Increased serum Tg levels at PPS metastasis detection, *n* (%)	
Yes	18 (81.8)
No	4 (18.2)
Confirmation modality, *n* (%)	
PET	9 (40.9)
MRI	9 (40.9)
CT	4 (18.2)
US detect, *n* (LN size range, mm)	
Yes	4 (40–65)
No	18 (8–40)
PET detect, *n* (%)	
Yes	21 (95.5)
No	1 (4.5)

CT computed tomography, *LN* lymph node, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *PPS* parapharyngeal space, *Tg* thyroglobulin, *US* ultrasonography

For preoperative diagnosis of PPS metastasis, only 3 patients were diagnosed via fine-needle aspiration (FNA), whereas 19 were diagnosed via intraoperative pathological findings. Of these 19 patients, 15 were diagnosed with other cervical masses via FNA, with the PPS tumor detected on MRI or CT, and 4 were diagnosed with PPS metastasis via abnormal PPS uptake on PET/CT scans, with the PPS tumor detected on MRI or CT.

A transcervical approach with partial segmental resection of the mandibular angle was performed in 21 patients, while 1 patient underwent extirpation of the PPS metastasis via a transoral approach. The mean maximum diameter of the PPS metastasis in all patients was 28 mm (range 8–65 mm). All PPS metastasis presented as solitary tumors. Presentation of the PPS metastasis was well-differentiated carcinoma in 18 and poorly differentiated carcinoma in 4. All except 1 patient had lymph node metastasis in the unilateral PPS, whereas 1 patient had bilateral lymph node metastases. Although curative resection was performed in 21 patients, the PPS metastasis was not removable in 1 patient owing to an invaded internal carotid artery at the skull base. All patients had involvement of the jugular nodes noted before or at the time of PPS metastasis detection (Table 3).

Of the 22 patients with PPS metastasis, 12 had invasive extranodal extension [11]. The mean maximum diameter of

Table 3 Clinical features of 22 patients with parapharyngeal metastasis of papillary thyroid carcinoma

Characteristic	
LN size in PPS, mean (range) (mm)	28 (8–65)
Appearance of PPS tumor, *n* (%)	
Solid	22 (100)
Cystic	0 (0)
Laterality of PPS tumor, *n* (%)	
Right	14 (63.6)
Left	7 (31.8)
Bilateral	1 (4.5)
Presentation of PPS metastasis, *n* (%)	
Well	18 (81.8)
Poorly	4 (18.2)
LN metastasis in lateral cervical region, *n* (%)	
Ipsilateral	8 (36.4)
Bilateral	14 (63.6)

LN lymph node, *PPS* parapharyngeal space

Table 4 Organs invaded by extranodal extension in the parapharyngeal space

	LN invasion + ($n = 12$)
LN size, mean ± SD (mm)	36.2 ± 13
Prevertebral fascia	7
Sympathetic trunk	6 (2)
Glossopharyngeal nerve	5 (1)
Vagal nerve	2 (1)
Facial nerve	1
Accessory nerve	1 (1)
Hypoglossal nerve	1 (1)
Internal carotid artery	2
External carotid artery	2
Internal jugular vein	2

All data are presented as n (complete nerve resection) unless otherwise noted

LN lymph node

the PPS metastasis in patients with invasive extranodal extension was 36.2 ± 13 mm, whereas such diameter in those without extranodal extension ($n = 10$) was 18.5 ± 7 mm. Such a difference in metastatic lymph node size between patients with and without invasive extranodal extension was statistically significant ($p = 0.0015$). As for the organs invaded by the PPS metastasis, the prevertebral fascia was the most frequently invaded, followed by the sympathetic trunk and glossopharyngeal nerve. Of these nerves, the sympathetic trunk was partially resected in 4 and completely resected in 2, while the glossopharyngeal nerve was partially resected in 4 and completely resected in 1. Regarding the cervical arteries, the internal carotid arteries were invaded in 2 patients and the external carotid arteries were invaded in 2 patients. One patient with internal carotid artery invasion was treated by resecting the adventitia with the PPS metastasis, whereas the entire tumor could not be removed in the other patient. The external carotid arteries in both the patients were transected at the proximal side of the PPS metastasis (Table 4).

Of the 10 patients who received radioactive iodine (RAI) treatment after the initial surgery, all were found to have RAI-refractory PPS metastasis. Of the 12 patients who did not receive RAI treatment prior to PPS surgery, only 1 received RAI treatment after PPS surgery. No patient was treated with external beam radiation for PPS metastasis.

Twelve and 6 patients had locoregional and distant recurrence, respectively. Seven patients had locoregional recurrence only, 1 had distant recurrence only, and 5 had both locoregional and distant recurrences (Table 5). Of the 12 patients with locoregional recurrence, locoregional recurrence in the PPS occurred in 1. Of the same 12 patients, 7 underwent additional surgery, while 5 did not undergo additional surgery because of aggressive distant disease ($n = 4$) or poor general condition ($n = 1$). Distant metastasis after PPS surgery occurred in 6 patients, including lung metastasis in 5 and brain metastasis in 1. Eight patients died of distant metastasis ($n = 6$) or locoregional disease ($n = 2$), with a median survival time after PPS surgery of 91.7 months (Fig. 2).

Of 14 cancer survivors, 9 were alive with the disease, and 5 were recurrence-free. Comparison of the duration and number of procedures from initial surgery to PPS surgery, extrathyroidal extension, and differentiation of the primary tumor between recurrence-free patients and patients who died revealed a significant difference in number of procedures (2.0 vs.. 3.75; $p = 0.0093$).

With regard to expected complications, palatal weakness caused by glossopharyngeal nerve involvement occurred in 5 patients, while Horner's syndrome due to sympathetic trunk involvement occurred in 6. As unexpected complications, palatal weakness and tongue

Table 5 Locoregional and distant recurrences after parapharyngeal space surgery

Recurrence type	*n*
Locoregional only	7 (1)
Distant only	1
Both locoregional and distant	5

The number in the parentheses indicates locoregional recurrence in the parapharyngeal space

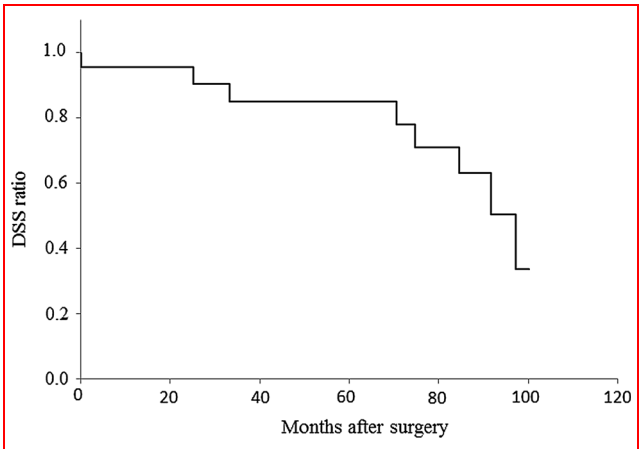

Fig. 2 Disease-specific survival (DSS) rates for patients with papillary thyroid carcinoma and parapharyngeal space (PPS) metastasis. The median survival time after PPS surgery was 91.7 months

weakness occurred in 10 and 1 patient, respectively, but 9 of those cases were temporary palsy (Table 6).

Discussion

In the present study, we found that the possibility of PPS metastasis should be considered in patients who experience recurrence after thyroid surgery. In this series, all patients with PPS metastasis also had previous unilateral or bilateral cervical metastasis. Despite curative attempt, most patients experienced local or distant recurrence.

Lymph node metastasis has been noted in many patients prior to initial treatment of PTC. Nodal involvement commonly occurs in the paratracheal region and the internal jugular chain, but lymph node metastasis to the PPS is rare. Indeed, only a few cases of PPS metastasis have been reported in the literature. In this report, we described our experience and surgical outcomes of 22 patients with PPS metastasis of PTC.

Table 6 Complications of parapharyngeal space surgery

Complication	Expected	Unexpected
Palatal weakness	5 (2)	10 (9)
Horner's syndrome	6 (2)	
Tongue weakness	1	1 (1)
Facial nerve weakness	1	1
Vocal cord paralysis	1	
Limited elevation of shoulders	1	
First bite syndrome		2

All data are presented as n, and the numbers in parentheses indicate temporary palsy

Two types of classification for lymph node metastasis in the PPS have been reported: primary or secondary cases. Primary cases include T1a thyroid carcinoma, whereas secondary cases include recurrences of previously treated thyroid carcinoma [12, 13]. In our series, there were only 2 primary cases of PPS metastasis, whereas 20 patients had PPS recurrence. Both primary cases demonstrated the primary tumor in the upper pole of the thyroid gland.

Rouviere [14] previously described a lymphatic vessel connecting the upper pole of the thyroid gland to the retropharyngeal lymphatic system. This lymphatic trunk was reported in only 20 % of the cases. An anatomical dehiscence behind the fascia of the superior constrictor muscle is allows the parapharyngeal and retropharyngeal spaces to communicate freely with each other. The retropharyngeal lymphatic system was believed to be the cause of PPS metastasis in the initial cases. As for the recurrent cases, the retropharyngeal nodes might include jugular node involvement before or at the time of PPS metastasis. This suggests that neck dissection and/or the metastatic cervical lymph nodes themselves might alter the direction of lymphatic drainage in a retrograde fashion, resulting in the unusual metastasis to the PPS lymph nodes [15, 16]. In our series, all patients with PPS recurrence had involvement of the jugular nodes noted before or at the time of PPS metastasis detection, and 14 patients had PPS recurrence after several other recurrences.

PPS tumors usually present very few symptoms and often are associated with dysphagia, dyspnea, obstructive sleep apnea syndrome, cranial nerve deficits, Horner's syndrome, pain, hoarseness, dysarthria, and trismus. Sometimes, a neck mass also is present. Of the 22 patients with PPS metastasis in this study, only 5 (23 %) exhibited symptoms. Such few clinical symptoms made diagnosis of PPS metastasis difficult. PPS metastasis was detected via US in only 5 patients (23 %) in our series. All PPS metastases were detected by using MRI, enhanced CT, or PET/CT. MRI or enhanced CT of the neck should be considered in thyroidectomy patients with rising serum Tg levels, particularly in those with cervical metastasis in the jugular region [15, 17, 18]. PET/CT might be useful for diagnostic confirmation, especially considering that many of the patients with PPS metastasis in this study were secondary cases with cervical metastasis in the jugular region, and had distant metastasis prior to or after PPS surgery.

The anatomical shape of the PPS has always highlighted the problem of improved exposure for a safer and complete excision. Increased tumor size might pose a great risk for development of cranial nerve deficits, and make surgery more difficult, with increased risk of complications. Approaches for PPS surgery reportedly include the transoral, transcervical, or transcervical-transparotid approach,

with or without several mandibulotomies [19]. Recently, transoral robotic surgery for PPS metastasis has been described [20]. However, the transcervical approach is the most commonly used for PPS surgery. Our surgery involved a transcervical approach combined with partial segmental resection of the mandibular angle. This surgical approach is very simple and improves exposure of the PPS in the internal and upper directions, without the need for mandibular osteotomy. It also allows safe preservation of the marginal branch of the facial nerve and the inferior alveolar nerve, and avoids scaring and facial deformities. However, it is difficult to treat organ invasion at the skull base using this approach.

Dysphagia was the most frequent surgical complication in our series. Fifteen patients (86 %) had palatal weakness postoperatively, 5 of whom had glossopharyngeal nerve invasion by the PPS metastasis. Although most of the patients without glossopharyngeal nerve invasion had palatal weakness temporarily, damage of the glossopharyngeal nerve branching, and swelling of the pharynx resulting from PPS surgery were thought to be the major causes of dysphagia. A transcervical approach with mandibular angle resection was useful for removal of the PPS metastasis in most cases, and major complications, such as continuous dysphagia, were rare without glossopharyngeal nerve invasion.

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