

Original Article

Parotid metastases from thyroid carcinomas

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Abstract: Parotid metastases (PMs) that originate from thyroid carcinomas (TCs) are extremely rare, and many questions about their diagnosis and management remain unanswered. Of the 15,780 patients with TC that we had prospectively recorded in our institutional databases between 1996 and 2015, we retrospectively retrieved only three patients (0.019%) with PM. Patient characteristics, histological findings on initial thyroidectomy and parotidectomy specimens, treatments, and times of recurrence and death were reviewed. In addition, we searched PubMed, Embase, and ISI Web of Science databases (1996-2015) for articles published in the English language using the key words “parotid” and “thyroid”, and reviewed almost all reports that described PM that were derived from TC. These rare cases of thyroid carcinoma presenting as metastasis in the parotid gland highlight the importance of maintaining close communication between clinicians, radiologists, and histopathologists to ensure that such rare cases are not missed.

Keywords: Thyroid carcinoma, parotid metastasis, histologic subtype, treatment

Introduction

A mass in the parotid region usually indicates a tumor of salivary gland origin. In addition to its own primary neoplastic transformation, the parotid gland may act as a target for metastatic or invasive forms of malignant tumors from other regions. Most parotid gland tumors are benign, but, about 10% of the cases are malignant, of which, 20% are metastases from either somatic or lymphatic origin [1-3]. It is fairly common for the parotid gland to be invaded by metastases from squamous cell carcinoma and melanomas from the head and neck region, but parotid metastases (PM) originating from thyroid carcinoma (TC) are extremely rare. A majority of publications in the literature are case reports [4-13]. Here, we report three cases of PM that originated from TC. To our knowledge, this is one of the largest case series. As only relatively few cases have been reported in the literature, diagnosis and management of patients with PM of TC origin is unclear. The aim of this study was to analyze the patients' clinical characteristics, histological findings, treatments, and outcomes, in order to better understand this rare disease.

Clinical history

Patient 1

A 61-year-old man was diagnosed with papillary thyroid carcinoma (PTC) in the right thyroid lobe with regional lymph node metastasis 28 years ago. He was treated with right thyroidectomy and regional lymph node dissection. He had two local recurrences in the thyroid isthmus and left thyroid lobe with regional lymph nodes in the 12th and 17th year after the initial treatment. Twenty-seven years after the initial treatment, the patient presented with a slow-growing, painful right parotid mass. A head and neck examination revealed a significant mobile, firm, 3.0 cm submucosal mass in the right parotid. No external parotid mass was noted, and these findings were considered to be consistent with a parotid tumor. Computed tomography (CT) showed a 3.0×1.5 cm heterogeneous density in the right parotid region, and metastatic malignant tumors in both lungs. Fine needle aspiration biopsy (FNAB) guided by ultrasonography of the right parotid mass revealed tumors with large necrotic areas, that originated from the salivary gland; these tend to be malignant.

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Enlarged right parotid tumor resection and regional lymph node dissection was performed. The final diagnosis was metastatic papillary carcinoma of the thyroid. Subsequently, the patient was treated with radioactive iodine. The diagnosis of skeletal metastatic thyroid carcinoma was made by a radioactive iodine scan five months later, and a pulmonary evolution appeared, but he was still alive 3.5 years after the enlarged right parotid tumor resection.

Patient 2

A 71-year-old woman was diagnosed with follicular thyroid carcinoma (FTC) in the left thyroid lobe without regional lymph node metastasis 25 years ago. She was treated with left lobar subtotal thyroidectomy and ipsilateral central compartment node dissection, and received postoperative thyroid hormone suppressive therapy. Twenty-five years after the initial treatment, the patient presented with a slow-growing, painless left parotid mass. On physical examination, a firm, immobile, 2.0×2.0 cm swelling in front of the left ear was detected, along with multiple enlarged lymph nodes at the neck, that were firm, immobile, with unclear borders, and about 0.5~2.0 cm in size. The postoperative scar could be seen in the neck, and no facial palsy was detected. The CT showed a 2.5×1.3 cm heterogeneous density in the left parotid region, metastatic malignant tumors in both lungs, and the margin of the left residual thyroid was not clear. FNAB guided by ultrasonography of the left parotid mass revealed that it was a salivary gland tumor in origin that typically tends to be malignant. A left superficial parotidectomy, a left residual thyroidectomy, a right thyroidectomy and a left modified radical neck dissection were performed. Histologically, the left parotid lesion showed metastatic follicular carcinoma of the thyroid, and local recurrences in the left residual thyroid and neck lymph nodes were present. Subsequently, the patient was treated with radioactive iodine, but a pulmonary evolution appeared, and she was still alive 8 years after the left superficial parotidectomy.

Patient 3

A 54-year-old man was diagnosed with medullary thyroid carcinoma (MTC) in the left thyroid lobe with regional lymph node metastasis 4 years ago. He was treated with a left thyroidec-

tomy and an ipsilateral lymph node dissection. He did not receive postoperative thyroid hormone suppressive therapy, but was comfortable. He had distant metastases in the left hip joint 6 months after treatment. Subsequently, he received radiotherapy (left ilium bone: DT 30 Gy/10 F, right chest wall: DT 30 Gy/12 F) and radioactive strontium treatment. However, the disease was not controlled very well. Three months later, the patient presented with a rapid-growing, painless mass on the left side of the neck. FNAB guided by ultrasonography of the mass on the left side of the neck revealed metastasis of poorly differentiated thyroid carcinoma with necrosis. Enlarged left neck tumor resection and regional lymph node dissection was performed. The final diagnosis was metastatic medullary carcinoma of the thyroid with vascular invasion, but no lymphatic metastasis. Subsequently, he underwent radioactive strontium treatment, to control bone metastases, but the disease was still not well-controlled. 1.5 years after the diagnosis of parotid metastasis, the patient presented with a rapid-growing, painful mass near the left ear. FNAB guided by ultrasonography of the mass revealed metastasis of poorly differentiated thyroid carcinoma with necrosis. CT showed a gigantic heterogeneous density in the left parotid region and metastatic lymphadenopathy. The patient appeared with symptoms of cachexia, and his family members refused further treatments. The patient died of the disease 39 months after the diagnosis of parotid metastasis.

Materials and methods

The prospectively-maintained institutional database at Zhejiang Cancer Hospital was retrospectively searched for patients with PM of TC origin in the period between 1996.01 and 2015.12. Three patients with PM derived from TC were identified, and a histological confirmation of the thyroid origin of PM was performed on all the patients. Medical records were reviewed and the following data were reported: the demographic data, presenting symptoms, pathology findings, types of treatment, and clinical outcomes (**Table 1**). Features of the pathological types of TC and prior history of TC were specifically recorded (**Table 1**). All pathologic specimens were reviewed by a single experienced pathologist using current WHO criteria and the Union for International Cancer Control classification. All diagnoses were made

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Table 1. Summary of prior reported cases of parotid metastases thyroid carcinoma

Series (references)	Age (years)/ sex	Clinical presentation	Prior history of TC	Treatment of parotid metastasis	The location of parotid metastasis	Pathological types	Survival
Seifert et al. [4]	NA	NA	NA	NA	NA	MTC(1); NA(2)	NA
Markitziu et al. [5]	69/Female	The left side of her face was swollen and a marked laterally expanded parotid gland was palpated.	Bilateral follicular variant of PTC without lymph node metastasis 2 years ago, treated with subtotal thyroidectomy.	Irradiation and chemotherapy	Left parotid	PTC	No recurrence in 18 months.
Kini et al. [6]	65/Female	A firm, mobile, 7*5*3 cm swelling at the angle of the mandible.	Classical PTC 31 years ago, treated with unilateral thyroidectomy.	Surgery	Left parotid	PTC	Lost follow-up after parotid surgery.
Mathew et al. [7]	45/Female	A firm, 8*6 cm nodular swelling of the parotid gland with infiltration of the overlying skin and features of a lower motor neurontype of facial palsy on the right side.	None. Right PTC with lymph node metastasis was found in the metastatic workup, and treated with total thyroidectomy and right-sided modified radical neck dissection.	Surgery	Right parotid	PTC	Lost follow-up 7 days after parotid surgery.
Malhotra et al. [8]	70/Female	A right parotid swelling.	None. Left follicular variant (diffuse subtype) of PTC was found in the metastatic workup, and treated with a near total thyroidectomy.	Surgery + Radioactive iodine	Right parotid	PTC	Right parotid swelling, right chest wall and left scapular swelling recurred following surgery.
Alzaraa et al. [9]	78/Female	A smooth, soft lesion in the tail of the left parotid gland, and the patient had tinnitus but no other complaints.	None.	Radioactive iodine	Left parotid	FTC	No recurrence in 2 years.
Stanley et al. [10]	19/Female	A 1.5 cm, firm, mobile right facial mass.	Multifocal MTC was diagnosed 5 years ago, treated with total thyroidectomy and central paratracheal neck dissection. She was found to be positive for the germline RET protooncogene mutation.	Surgery	Right parotid	MTC	No recurrence in 1 years.
Conway et al. [11]	61/Male	Right facial paralysis was noted along with focal swelling and tenderness below the right auricle.	None. MTC was found in the metastatic workup, but without any further processing.	Surgery	Right parotid	MTC	Clinically stable and relatively asymptomatic in 13 months.
Petros et al. [12]	68/Male	A right parotid mass.	MTC was diagnosed 10 years ago and treated with total thyroidectomy and paratracheal neck dissection.	Surgery	Right parotid	MTC	No recurrence in 2 years.
Juan et al. [13]	30/Male	A right parotid mass.	None. Left PTC was found in the metastatic workup, and treated with total thyroidectomy and central and bilateral lymph node dissection.	Surgery	Right parotid	PTC	NA
Cao et al. (our study)	61/Male	A right submandibular mass.	Right PTC with regional lymph node metastasis 28 years ago, treated with right thyroidectomy and regional lymph node dissection, Local recurrences 12 and 17 years after the 1st surgery.	Surgery + Radioactive iodine	Right parotid	PTC	Recurred in 5 months in the skeletal, and a pulmonary evolution appeared. Alive at 3.5 months.
	71/Female	A painless left parotid mass.	Left FTC without regional lymph node metastasis 25 years ago, treated with left lobar subtotal thyroidectomy and ipsilateral central compartment node dissection.	Surgery + Radioactive iodine	Left parotid	FTC	A pulmonary evolution appeared after parotid surgery, Alive at 8 years.
	54/Male	A painful mass after the left ear.	Left thyroid MTC with regional lymph node metastasis 4 years ago, treated with left thyroidectomy and ipsilateral lymph nodes dissection, developed bone metastasis 6 months after the surgery, and then he received radiotherapy and radioactive strontium.	Surgery	Left parotid	MTC	Died in 39 months.

(NA) not available, (PTC) papillary thyroid carcinoma, (FTC) follicular thyroid carcinoma, (MTC) medullary thyroid carcinoma.

based on morphologic features and confirmed by immunohistochemistry (IHC). The lesions were fixed in 10% formalin and embedded in paraffin, and 4- μ m-thick slices were prepared for hematoxylin and eosin (HE) staining and IHC, and observed under an optical microscope. The IHC stains were performed on an automated immunostainer (Leica, Bondmax, Germany). The following primary antibodies were used for our study: thyroglobulin (TG) (1:400) (clone 1D4; Leica), thyroid transcription factor-1 (TTF-1) (1:200) (clone SPT24; Leica), and calcitonin (1:100) (clone EPR68(2); Abcam). All tissue sections underwent heat-induced antigen retrieval. This study was performed with the approval of the Ethics Committee of Zhejiang Cancer Hospital, and all the patients signed informed patient consents, and agreed to publish these case reports and any additional related information. Follow-ups were conducted in August 2016. We also searched PubMed, Embase, and ISI Web of Science databases for articles published in the English language using the key words "parotid", and "thyroid", and we reviewed almost all reports describing PM from a TC source.

Results

We report three patients with PM that originated from TC. These included one woman and two men between 54 to 71 years of age at the time of diagnosis of PM. Patients presented with nonspecific symptoms such as facial paralysis. All of them had a prior history of TC (one PTC, one FTC, and one MTC), and the pathological types of TC were defined based on the current WHO criteria. PM originating from PTC showed cell nuclear clearing, enlargement and occasional grooves. IHC staining showed that these cells were strongly positive for TG and TTF-1, and negative for calcitonin. PM originating from FTC showed cells arranged in a follicular structure, with a consistent nuclear size. IHC staining showed that these cells were positive for TG and TTF-1 and negative for calcitonin. PM originating from MTC showed cells arranged in a solid and/or follicular structure, with an amphophilic cytoplasm. IHC staining showed that the cells were positive for calcitonin and TTF-1, and negative for TG (**Figure 1**). The patients were treated primarily with ipsilateral thyroidectomy and lymph node dissection. The PM occurred 4 to 28 years after the first treat-

ment. Out of the three parotid metastases in our series, two occurred in the left parotid, and one occurred in the right parotid. A gross total resection of PM and radioactive treatment was performed in all the patients. Only one patient died of the disease 39 months after his first presentation of PM due to the recurrence of PM and various complications.

Discussion

Metastases to salivary glands account for 3.2%-10% of all salivary gland tumors [3, 5, 6, 13-17]. Two general types of metastases should be distinguished in metastatic salivary gland tumors: regional metastases (head and neck) and distant metastases [4]. The occurrence of parotid metastasis from a primary site in the head and neck is not common, with the exception of melanoma of the scalp, ears, or nose, and anaplastic squamous cell carcinoma of the ear and external ears [18]. It is more common for the parotid gland to be involved as a part of a generalized metastatic disease rather than an isolated metastasis [18]. This gland contains some lymph nodes and lymph follicles connected with a rich interwoven network of lymph vessels. Lymph may directly enter the gland, without involvement of the paraglandular lymph nodes, or maybe secondarily deposited from the paraglandular lymph nodes, or through retrograde extension from massive metastases in the neck [6]. Furthermore, secondary spread to the parotid gland clinically and/or pathologically, manifests itself as a primary salivary gland tumor, and may mislead clinicians, pathologists and radiologists [6]. In addition to direct invasion by tumors in the vicinity, the parotid gland may also be involved as the site of hematogenous and lymphatic metastasis. Metastasis from primary sites below the head and neck are exceptions rather than the rule, and are usually derived from carcinomas in the lung, breast, colon, kidney, and prostate [3, 16, 18, 19]. Thyroid carcinoma is the most common endocrine malignancy that has a variable tendency to metastasize to other parts of the body, according to histologic subtypes. However, for each of the subtypes, metastasis to the parotid gland is decidedly unusual. In fact, a detailed search of the English language literature revealed only 12 cases of thyroid carcinoma metastasizing to the parotid

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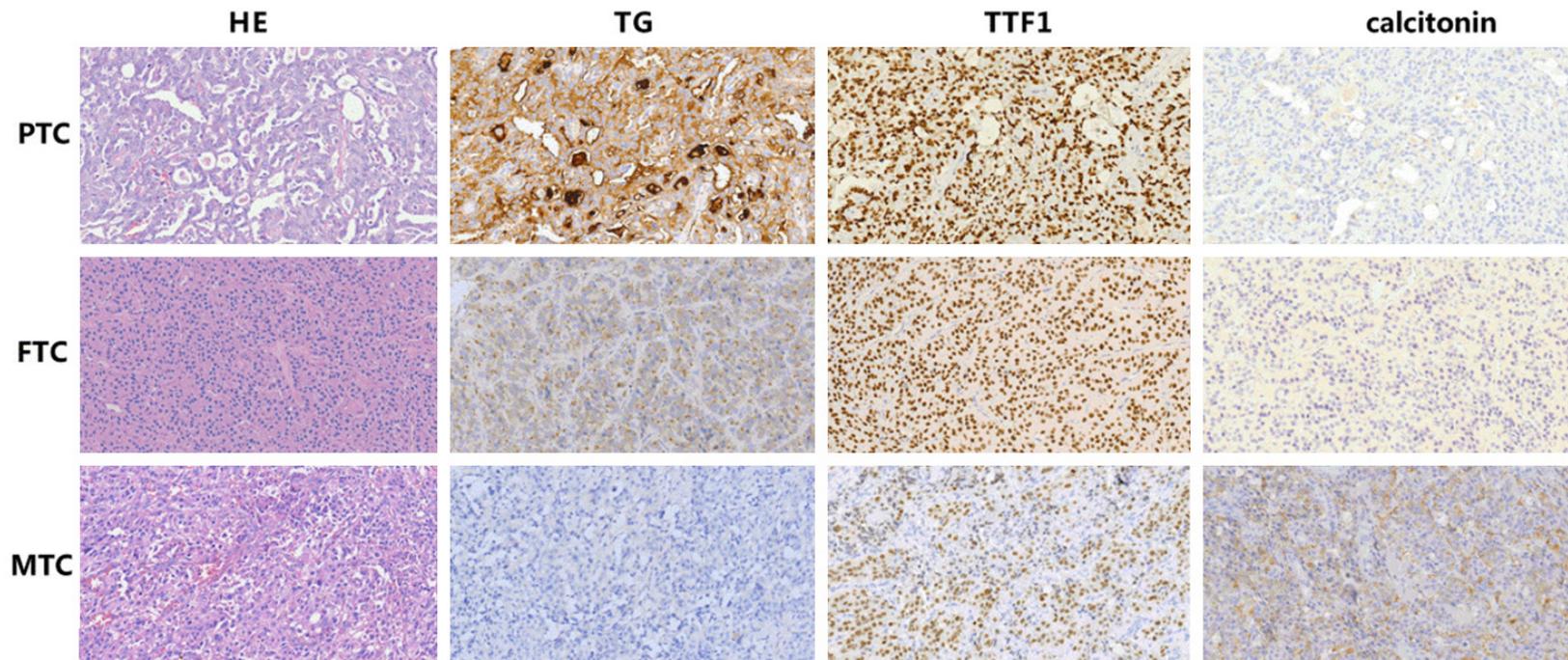


Figure 1. Hematoxylin and eosin (HE) staining and immunohistochemistry (IHC) of parotid metastases (PM) originating from thyroid carcinoma (TC). PTC (Patient 1): Higher magnification of papillary carcinoma nuclei showing nuclear clearing, enlargement and occasional grooves, and the cells were strongly positive for thyroglobulin (TG) and thyroid transcription factor-1 (TTF-1) and negative for calcitonin on IHC. FTC (Patient 2): Cells arranged in a follicular structure, and the nucleus size was consistent, and the cells were positive for TG and TTF-1 and negative for calcitonin on IHC. MTC (Patient 3): Cells arranged in solid and/or follicular structure, and the cytoplasm was amphophilic, and the cells were positive for calcitonin and TTF-1 and negative for TG on IHC.

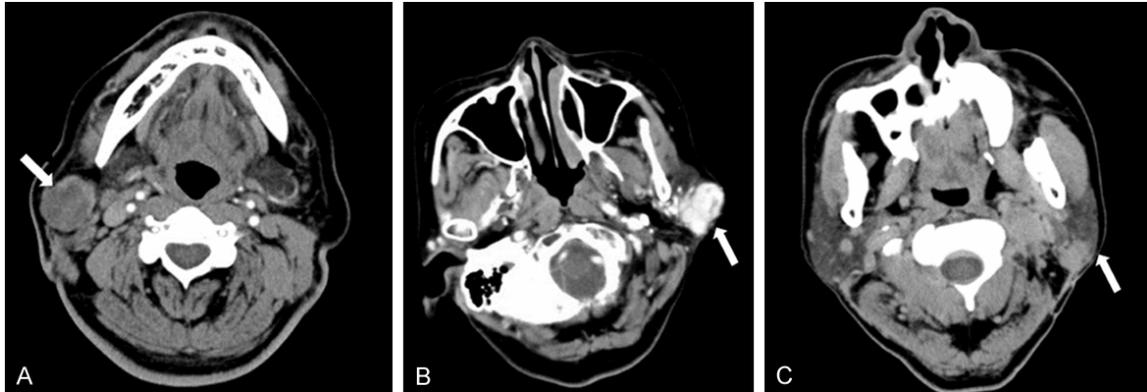


Figure 2. Computed tomography (CT) of parotid metastatic thyroid carcinoma. A: Contrast enhanced CT scans of parotid metastatic PTC (Patient 1); B: Contrast enhanced CT scans of parotid metastatic FTC (Patient 2); C: Non-contrast enhanced CT of parotid metastatic MTC (Patient 3).

gland (**Table 1**). However, all these are retrospective studies with an inherent bias.

The diagnosis of PM from TC is very difficult. The radiological (**Figure 2**) and cytological recognition of thyroid metastasis to parotid gland may be difficult to diagnose, especially when the parotid gland metastases of TC occurred 20 or more years after the initial diagnosis of TC [6, **Table 1**], and/or the TC presents initially at the metastatic site [7, 8, 13]. At this time, it may raise clinical doubts concerning the accuracy of the diagnosis. Therefore, a careful history, radiological evaluation, and physical examination are vital in eliminating potential pitfalls. In addition, a coarse needle biopsic histopathology is recommended in diagnosing the parotid gland mass when possible. PM originating from PTC showed cell nuclear clearing, enlargement and occasional grooves; PM originating from FTC showed cells arranged in a follicular structure, with a consistent nuclear size and; PM originating from MTC showed cells arranged in a solid and/or follicular structure, with an amphophilic cytoplasm. Furthermore, immunohistochemical markers of thyroid tumors like TG, TTF-1, and calcitonin are useful diagnostic tools in distinguishing a thyroid primary from other metastatic lesions.

The treatment of TC with parotid gland metastasis currently depends on tumor extension. Thus, patients with greater extension and/or at a higher risk of recurrence are treated more aggressively and monitored more closely. Nevertheless, in localized low-risk tumors, a more conservative treatment is equally effective. In

addition, the different histologic subtypes of TC have to be taken into account, as they directly influence the prognosis of the patients. Once parotid gland metastasis of differentiated thyroid carcinoma (DTC) is diagnosed, a total thyroidectomy with central and/or bilateral lymph node dissection and parotid tumor resection is recommend, whenever possible [20-22]. Radioactive iodine remnant ablation may be useful in DTC, but its effect on parotid gland metastases is ambiguous. In cases that are refractory to radioiodine ablation therapy or in other cases, the best therapeutic method is local radiotherapy [21, 22]. Although the prognosis of PTC is good, even in metastatic sites, the columnar cell carcinoma and diffuse follicular variant of papillary carcinoma of the thyroid appears to have a more aggressive clinical course, as seen in the reported cases [5, 6, 8]. Sometimes, PTC with indolent behavior has a potential to transform into a poorly differentiated pattern, and the occurrence of parotid gland metastasis, in spite of its relative low occurrence, indicates that less differentiated tumors may spread to unusual regions [6]. MTC is the most aggressive of the well-differentiated malignancy of the thyroid gland, with a propensity for widespread metastasis both at the time of diagnosis and following treatment. Treatment of PM from MTC relies primarily upon surgical treatment. Tumors do not concentrate radioactive iodine, and responsiveness to external beam radiation is variable. Serum calcitonin and carcino embryonic antigen (CEA) are valuable markers for assessing the disease burden, at presentation and tumor progression after therapy [23, 24]. Thus, normalizing the

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levels of calcitonin and CEA may have an overall impact on long-term prognosis. Clinicians should be aware of unusual presentations of this malignancy to ensure early identification of recurrent disease.

Conclusions

The parotid gland is a very rare site of metastasis from carcinoma of the thyroid gland, and the cytological diagnosis of thyroid metastasis to parotid gland may be difficult, especially when the primary has been removed many years before and/or the TC presents initially at the metastatic site. Thus, coarse needle bioptic histopathology is recommended when possible. Immunohistochemically, TG, TTF-1, and calcitonin are important markers for thyroid tumors. Thus, whenever a neoplasm is assessed in the parotid region, and/or the patient has a history of previously diagnosed TC, careful clinical, ultrasound, and radiological evaluation is required to rule out the possibility of thyroid metastasis in spite of its relative low occurrence. The treatment of TC with parotid gland metastasis currently depends on tumor extension and the different histologic subtypes of TC.

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All the patients, or their respective family members or legal guardian signed informed consents.

Disclosure of conflict of interest

None.

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