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## Original research

Autotransplantation of Inferior Parathyroid glands during central neck dissection for papillary thyroid carcinoma: A retrospective cohort study<sup>☆</sup>Tao Wei<sup>a</sup>, Zhihui Li<sup>a</sup>, Judy Jin<sup>b</sup>, Rui Chen<sup>a</sup>, Yanping Gong<sup>a</sup>, Zhenhong Du<sup>a</sup>, Rixiang Gong<sup>a</sup>, Jingqiang Zhu<sup>a,\*</sup><sup>a</sup> Department of Thyroid & Breast Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, PR. China<sup>b</sup> Department of Endocrine Surgery, Endocrine & Metabolism Institute, Cleveland Clinic, Cleveland, OH, USA

## HIGHLIGHTS

- Autotransplantation or preservation of inferior parathyroid can be performed.
- Autotransplantation reduced permanent hypoparathyroidism and lymph node recurrence.
- Routine autotransplantation of the inferior parathyroid might be considered.

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## ABSTRACT

**Introduction:** The management of inferior parathyroid glands during central neck dissection (CND) for papillary thyroid carcinoma (PTC) remains controversial. Most surgeons preserve inferior parathyroid glands in situ. Autotransplantation is not routinely performed unless devascularization or inadvertent parathyroidectomy occurs. This retrospective study aimed to compare the incidence of postoperative hypoparathyroidism and central neck lymph node (CNLN) recurrence in patients with PTC who underwent inferior parathyroid glands autotransplantation vs preservation in situ. **Methods:** This is a retrospective study which was conducted in a tertiary referral hospital. A total of 477 patients with PTC (pN1) who underwent total thyroidectomy (TT) and bilateral CND with/without lateral neck dissection were included. Patients' demographical characteristics, tumor stage, incidence of hypoparathyroidism, CNLN recurrence and the number of resected CNLN were analyzed. **Results:** Three hundred and twenty-one patients underwent inferior parathyroid glands autotransplantation (autotransplantation group). Inferior parathyroid glands were preserved in situ among 156 patients (preservation group). Permanent hypoparathyroidism rate was 0.9% (3/321) versus 3.8% (6/156) respectively ( $p = 0.028$ ). Mean numbers of resected CNLN were  $15 \pm 3$  (6–23) (autotransplantation group) versus  $11 \pm 3$  (7–21) (preservation group) ( $p < 0.001$ ). CNLN recurrence rate was 0.3% (1/321) versus 3.8% (6/156) respectively ( $p = 0.003$ ). **Conclusion:** Inferior parathyroid glands autotransplantation during CND of PTC (pN1) might reduce permanent hypoparathyroidism and CNLN recurrence. Further study enrolling more patients with long-term follow-up is needed to support this conclusion.

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## 1. Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy worldwide and its incidence has increased dramatically over the past decades [1–4]. Although the 10-year survival is over 90%, PTC frequently recurs and metastasizes to the regional lymph nodes [5–7]. A central neck dissection (CND) is strongly recommended for PTC patients who have positive central neck lymph nodes (CNLN) [8,9].

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The superior parathyroid glands can be routinely preserved in situ during CND unless devascularization occurred or there was tumor involvement. For the inferior parathyroid glands however, the management remains controversial. Most surgeons prefer to preserve the inferior parathyroid glands in situ. Elective excision with autotransplantation is not performed unless devascularization occurs [10,11]. While Kikumori et al. demonstrated in their study that autotransplanted parathyroid gland could survive and function [12,13], it is difficult to estimate the functional status of the parathyroid glands preserved in situ. Further more, it is unclear whether inferior parathyroid glands preservation could potentially jeopardize the extent of CND.

In this study, we sought to compare the incidence of postoperative hypoparathyroidism and CNLN recurrence in PTC patients who underwent inferior parathyroid glands autotransplantation vs preservation in situ.

## 2. Materials and methods

### 2.1. Study population

Seven hundred and thirteen patients with PTC (pN1) underwent total thyroidectomy (TT) and bilateral CND with/without lateral neck dissection by the same surgeon at West China Hospital of Sichuan University from February 2007 to February 2012. Patients were enrolled in the study if they (1) were evaluated by preoperative imaging studies including neck ultrasonography and computed tomography (CT); (2) had biopsy proven PTC; (3) underwent total thyroidectomy and bilateral CND as initial treatment; (4) staged as pathological N1.

From the initial cohort of 713 patients, 27 had no records of parathyroid glands, 49 had one or two superior parathyroid glands autotransplantation, 14 had no inferior parathyroid glands found intraoperatively (9 had parathyroid glands identified in the final pathology), 146 had one inferior parathyroid gland autotransplantation and the other one preservation in situ (63 had parathyroid glands at the thymus tongue which could be preserved in situ viably). These patients were excluded.

As a result, 477 patients with both their superior parathyroid glands preserved in situ were included in the final analysis, who had either both of their inferior parathyroid glands preserved in situ or they were both autotransplanted and both their superior parathyroid glands preserved in situ.

### 2.2. Preoperative imaging studies

All patients underwent ultrasonography and contrast-enhanced CT scan preoperatively. Ultrasound was performed by one of the 2 doctors who specialize in head and neck ultrasonography, which included both thyroid and neck lymph nodes (I–VI levels). CT scan was performed to identify suspected lateral neck lymph nodes involvements and lung metastasis.

### 2.3. Fine needle aspiration (FNA)

All patients underwent FNA of thyroid nodule and had cytological diagnosis of PTC or suspicious for PTC preoperatively. For suspicious cases, intraoperative frozen section was performed.

### 2.4. Surgical conduct for PTC at West China Hospital

Total thyroidectomy (TT) was performed for confirmed PTC larger than 1 cm, or bilateral foci, or extrathyroidal extension, or lymph node metastasis, or distant metastasis.

A complete CND was performed first on the side of PTC. If more than 1 lymph node (ipsilateral paratracheal, pretracheal and prelaryngeal nodes) were found to be positive in the central contents by frozen section, a contralateral CND would follow. We did bilateral CND for bilateral foci or isthmus foci. Based on preoperative imaging study, patients with suspected lateral neck lymph nodes metastases will undergo concurrent unilateral or bilateral modified lateral neck dissection.

All surgeries were performed by a single experienced surgeon with high-volume thyroid surgeries. TT and bilateral CND was performed for all patients in this study. Compartment of the central neck is bounded superiorly by the thyroid cartilage, inferiorly by the innominate artery, medially by the trachea, and laterally by the carotid artery (level VI–VII).

Harmonic Scalpels and bipolar coagulation forceps were used. A meticulous capsular dissection technique was applied for. An “en-bloc” resection was used for all cases. The recurrent laryngeal nerve was identified and preserved in the aid of the intraoperative nerve monitoring.

### 2.5. Parathyroid glands management

When TT and CND was performed, we routinely identified the superior parathyroid gland and preserved it in situ. For inferior parathyroid glands, they were preserved in situ (preservation group) if vascular pedicle was kept intact by the surgeon's verdict. Autotransplantation was performed when devascularization or inadvertent parathyroidectomies occurred (autotransplantation group). A small piece of the suspected inferior parathyroid gland was sent for frozen section, and the rest was placed in iced saline. After pathological confirmation, the parathyroid tissue would be minced into 1 mm pieces and transplanted into sternocleidomastoid. The same procedure is performed for the contralateral CND. We reestimated the viability of preserved parathyroid glands at the end of the surgery. Autotransplantation was then performed if the surgeon predicted a low probability of gland survival.

### 2.6. Postoperative complications

All patients underwent total serum calcium and intact parathyroid hormone (iPTH) level measurements the first postoperative day. Hypoparathyroidism was defined as a serum iPTH level (the first postoperative day) lower than 1.60 pmol/L (normal range 1.60–6.90 pmol/L). Transient hypoparathyroidism was defined as serum calcium and iPTH level normalization within 6 months after surgery. Permanent hypoparathyroidism was defined as a serum iPTH level lower than 1.60 pmol/L, associated with low serum calcium level and requiring oral calcium supplementation for more than 6 months after surgery. Oral calcium supplementation was administered for all patients with hypoparathyroidism.

If hoarseness occurred postoperatively, a laryngoscopy would be performed to confirm vocal cord palsy.

### 2.7. Radioiodine treatment and follow-up strategy

Patients were referred to endocrinologist for further treatment after surgery. Radioactive iodine remnant ablation was performed using 100–200 mCi <sup>131</sup>I for patients who indicated according to the American Thyroid Association guidelines. All patients received suppressive doses of levothyroxine immediately after surgery according to risk stratification.

Patients received regular follow-up every 3–6 months. For all patients, the first diagnostic whole body nuclear scan with <sup>131</sup>I (due to unavailability of <sup>123</sup>I) and measurement of thyroglobulin levels during thyroid hormone withdrawal were carried out at 6–8

months after remnant ablation. Diagnostic <sup>131</sup>I whole body scans, thyroglobulin, antithyroglobulin antibody and thyrotropin were obtained yearly thereafter. When the stimulated serum thyroglobulin level was >5 ug/L or in cases wherein recurrence was clinically suspicious, neck ultrasonography and/or positron emission tomography/computed tomography (PET/CT) was performed to diagnose and localize the recurrence. When suspicious lesion was identified, FNA biopsy was performed and if confirmed, excision of the recurrence would be undertaken.

### 2.8. Statistical analysis

SPSS 20.0 (SPSS Statistics 20.0) was used for data analysis. Continuous variables are represented as mean ± standard deviation. *T*-test was used to compare continuous variables, while Chi-square test or Fisher's exact test was used for categorical variables. Statistical significance was defined as a *p* value of <0.05.

## 3. Results

The demographic information is listed in Table 1. There were 321 patients in the autotransplantation group vs 156 patients in the preservation group. There was no significant difference between the two groups.

### 3.1. Histopathological examinations

All patients had CNLN metastases and 206 (206/477, 43.2%) patients had both CNLN and lateral neck lymph node (LNLN) metastases. There were 190 patients (190/321, 59.2%) with ipsilateral and 131 patients (131/321, 40.8%) with bilateral CNLN metastases in autotransplantation group vs 94 patients (94/156, 60.3%) with ipsilateral and 62 patients (62/156, 39.7%) with bilateral CNLN metastases in preservation group. Of these, 165 patients (165/321, 51.4%) were staged pT1–2N1 and 156 patients (156/321, 48.6%) were staged pT3–4N1 in autotransplantation group vs 80 patients (80/156, 51.3%) were staged pT1–2N1 and 76 patients (76/156, 48.7%) were staged pT3–4N1 in preservation group. There were 141 (141/321, 43.9%) patients with both CNLN and LNLN metastases (pN1b) in autotransplantation group vs 65 (65/156, 41.7%) patients in preservation group. There was no significant difference between the 2 groups with respect to the pathological stage (pT1–2, pT3–4, pN1a, pN1b), and CNLN metastases (ipsilateral, bilateral) (Table 2). Mean number of resected CNLN was 15 ± 3 in autotransplantation group vs 11 ± 3 in preservation group. Mean number of metastatic CNLN was 10 ± 3 in autotransplantation group vs 7 ± 3 in preservation group. Those were significantly greater in autotransplantation group than in preservation group (*p* < 0.001) (Table 2).

**Table 1**  
Patients' demographics.

	No. of patients (%)		<i>p</i> value
	Autotransplantation group	Preservation group	
Total patients	321	156	–
Age (yrs)			
Mean ± SD	46.41 ± 8.36	44.09 ± 8.34	0.173 <sup>a</sup>
Range	(14–72)	(15–69)	
Gender (female: male ratio)	5.29	5.00	0.828 <sup>b</sup>
Female	270 (84.8)	130 (83.5)	–
Male	51 (15.2)	26 (16.5)	–

<sup>a</sup> *t*-test.

<sup>b</sup> Chi-square test.

**Table 2**  
Pathologic stage and lymph node status.

	No. of patients (%)		<i>p</i> value
	Autotransplantation group	Preservation group	
Total patients	321	156	–
pTN status			
pT1–2	165 (51.4)	80 (51.3)	0.98 <sup>b</sup>
pT3–4	156 (48.6)	76 (48.7)	0.98 <sup>b</sup>
pN1a	180 (56.1)	91 (58.3)	91 (58.3)
pN1b	141 (43.9)	65 (41.7)	65 (41.7)
Resected CNLN <sup>a</sup>			
Mean ± SD	15 ± 3	11 ± 3	<0.001 <sup>c</sup>
Range	(6–23)	(7–21)	
Metastatic CNLN			
Mean ± SD	10 ± 3	7 ± 3	<0.001 <sup>c</sup>
Range	(1–20)	(1–19)	
CNLN Metastases			
Ipsilateral	190 (59.2)	94 (60.3)	0.824 <sup>b</sup>
Bilateral	131 (40.8)	62 (39.7)	0.824 <sup>b</sup>
Recurrence			
CNLN	1 (0.3)	6 (3.8)	0.003 <sup>b</sup>
LNLN <sup>d</sup>	12 (3.7)	7 (4.5)	0.695 <sup>b</sup>

<sup>a</sup> CNLN central neck lymph node.

<sup>b</sup> Chi-square test.

<sup>c</sup> *t*-test.

<sup>d</sup> LNLN lateral neck lymph node.

### 3.2. Surgical complications

Surgical complications of CND are listed in Table 3. The incidence of transient hypoparathyroidism was similar in 2 groups. With regard to permanent hypoparathyroidism, the incidence was significantly lower in the autotransplantation group than in the preservation group. There was no unintentional recurrent laryngeal nerve injury in either group. In this study, 4 and 8 patients had voice change post surgery in preservation and autotransplantation group respectively. They all had an ipsilateral recurrent laryngeal nerve of tumor invasion, so a nerve segment resection with/without reconstruction was performed for these patients. For them, a laryngoscopy would not be performed even though they had voice change.

### 3.3. Follow-up time, CNLN recurrence and radioiodine treatment

The mean follow-up time was similar in 2 groups (52 ± 11 months in autotransplantation group and 51 ± 9 months in preservation group) (Table 3). During the follow-up period, 1 in 321 patients experienced CNLN recurrence in the autotransplantation group, representing a recurrence rate of 0.3%. By contrast, CNLN recurrence rate was 3.8% (6/156) in the preservation group (*p* = 0.003). In the autotransplantation group, the only recurrence

**Table 3**  
Follow-up time, postoperative complications and radioiodine treatment.

	No. of patients (%)		<i>p</i> value
	Autotransplantation group	Preservation group	
Total patients	321	156	–
Radioiodine treatment	315 (98.1)	151 (96.8)	0.362 <sup>b</sup>
Transient hypoparathyroidism	85 (26.5)	39 (25.0)	0.73 <sup>b</sup>
Permanent hypoparathyroidism	3 (0.9)	6 (3.8)	0.028 <sup>b</sup>
Follow-up time (months)			
Mean ± SD	52 ± 11	51 ± 9	0.225 <sup>a</sup>
Range	(23–80)	(24–81)	

<sup>a</sup> *t*-test.

<sup>b</sup> Chi-square test.

was in level VII. In the preservation group, level VII lymph nodes recurred in 1 case and level VI (in the vicinity of preserved inferior parathyroid) lymph nodes recurred in 5 cases. There was no recurrence in the thyroid bed in either group. LNLN recurrence was similar in the 2 groups, 3.7% (12/321) versus 4.5% (7/156). Among the 6 patients with CNLN recurrence in preservation group, 3 were staged pT3N1a, 2 were pT2N1b, 1 was pT4N1a. The time interval post surgery when recurrence occurred ranged from 18 to 34 months. The only patients with CNLN recurrence in autotransplantation group, which was found in 24 months post surgery, was staged pT2N1a. All of the patients with CNLN recurrence underwent radioiodine therapy.

A similar proportion of patients received radioiodine treatment in 2 groups, 315/321 (98.1%) versus 151/156 (96.8%) ( $p = 0.362$ ).

#### 4. Discussion

Regional lymph node metastases develop in 20–90% of patients with PTC [14–17]. There is a consensus on performing CND for patients with CNLN metastases [8,18]. CND may convert some patients from clinical N0 to pathologic N1a, upstaging patients over age 45 from American Joint Committee on Cancer (AJCC) stage I to III [19]. The most common adverse event associated with CND is hypoparathyroidism. Studies have showed that the incidence of transient hypoparathyroidism and permanent hypoparathyroidism were up to 20–25% and 5–7%, respectively, when total thyroidectomy with or without CND was performed [20–24].

Most surgeons manage parathyroid glands based on their intraoperative assessment during CND, by either preservation in situ or autotransplantation. In our experience, the superior parathyroid glands are easier to be identified and preserved in situ during CND because the anatomic location and the vessels of superior parathyroid glands are relatively constant compared with inferior parathyroid glands. For the inferior parathyroid glands however, the management remains controversial. Most surgeons prefer to preserve the inferior parathyroid glands in situ. Elective excision with autotransplantation is not performed unless devascularization occurs [10,11]. Further more, it is unclear whether inferior parathyroid glands preservation could potentially jeopardize the extent of CND because the inferior parathyroid glands and enlarged lymph nodes usually mixed together. So we sought to compare the incidence of postoperative hypoparathyroidism and CNLN recurrence in PTC patients who underwent inferior parathyroid glands autotransplantation versus preservation in situ. To obtain the aim of the study, the typical patients who had either both of their inferior parathyroid glands preserved in situ or they were both autotransplanted and both their superior parathyroid glands preserved in situ were included.

In the results, the patients' demographic, pathologic stage and postoperative radioiodine were similar in 2 groups (Table 1, Table 2). Mean number of resected CNLN and positive CNLN was greater in autotransplantation group than in preservation group statistically (Table 2). Increased yield of CNLN might mean better dissection of CNLN for PTC with similar primary tumor and lymph node status. LNLN recurrence rate was similar in 2 groups while CNLN recurrence rate significantly reduced in autotransplantation group within a similar follow-up period. And among the 6 recurrence cases in the preservation group, 5 were in level VI (in the vicinity of preserved inferior parathyroid). The lower CNLN recurrence rate in the autotransplantation group might be due to a better CND without the interference of inferior parathyroid glands. Radioiodine treatment might contribute to reduce local lymph nodes recurrence [25,26]. The proportion of radioiodine treatment was similar in the 2 groups. The period of follow up is not long

enough for PTC, which is a slowly progressive cancer, may be it is the reason that the incidence of recurrence in this study was low.

The incidence of transient hypoparathyroidism was similar in 2 groups. With regard to permanent hypoparathyroidism, the incidence was significantly lower in the autotransplantation group than in the preservation group. It is well-known that autotransplants may take several weeks to several months to function. If one group is having their parathyroid glands removed and reimplanted, one would have to anticipate a higher rate of transient hypoparathyroidism. The fact is that the autotransplantation patients actually did the same when considering transient hypoparathyroidism and better when considering permanent hypoparathyroidism, which means that is unreliable to judge the function of preserved parathyroid glands by gross eye. Even if the surgeons are confident that the vascular supply of parathyroid glands are preserved, there is no effective way of estimation the function of preserved parathyroid glands. Intraoperative PTH assay may be predictive of postoperative hypoparathyroidism however, normal PTH levels do not exclude permanent hypoparathyroidism after thyroidectomy [27,28]. A study by Kikumori et al. demonstrated that the parathyroid gland could be grafted successfully and function [12]. These findings have been confirmed by other study [13]. Based on our study, even this highly experienced surgeon does not seem reliable at determining which parathyroid gland are functioning, hence the better results in the autotransplantation group.

A benefit from inferior parathyroid glands autotransplantation is that it might achieve comprehensive central neck compartment dissection. Theoretically and technically, it is hard to find a balance between a complete CND and protection of parathyroid glands, especially when inferior parathyroid and enlarged lymph nodes mixed together. In order to avoid hypoparathyroidism, lymph node “berry picking” were performed in practice, and this might have been the most important causation of CNLN recurrence. It is considered inappropriate and not recommended [16]. Based on our study results, an interesting conception is if we can preserve superior parathyroid glands in situ and routinely autotransplant inferior parathyroid glands during CND. Some other studies reported that parathyroid autotransplantation could reduce the risk of permanent hypoparathyroidism [29–31]. The difference with these previous studies is that the autotransplantation of inferior parathyroid gland during CND would lead to a better CND and reduce permanent hypoparathyroidism.

As a retrospective study, the bias of selectivity is unavoidable. The results should be interpreted in the context of a major tertiary referral center. Most of the patients referred to the hospital were relatively late-staged. Previous studies reported that unilateral PTC with a maximal diameter of >1 cm is associated with a high rate of ipsilateral CNLN metastasis, and ipsilateral CNLN metastasis was a potential independent predictor of concomitant contralateral paratracheal metastasis [32–34]. In order to obtain a better initial treatment result, a bilateral CND should be considered. This would not be common practice in western countries but common in China. So our experience is helpful for developing countries with much more advanced thyroid cancers.

In summary, we found that autotransplantation of inferior parathyroid glands during CND for PTC provided lower incidence of permanent hypoparathyroidism and CNLN recurrence for patients. Among experienced surgeons, this surgery can be safely and effectively performed. Obviously, it is much easier for surgeons to perform parathyroid gland autotransplantation than to perform parathyroid gland preservation in situ. Although further prospective study enrolling more patients with long-term follow-up is needed, routine autotransplantation of inferior parathyroid glands during CND might be considered based on this study.

## Ethical Approval

This is a retrospective study with just data collection and analysis. Ethical Approval was not necessary for this type of study in our institution.

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## Conflict of interest

There is no any personal conflicts of interest of any of the authors.

## Author contribution

Tao Wei<sup>1</sup> M.D data analysis and writing.  
 Zhihui Li<sup>1</sup> M.D, PhD data collections and analysis.  
 Judy Jin<sup>2</sup> M.D read paper and correct English grammar.  
 Rui Chen<sup>1</sup> M.D data collections.  
 Yanping Gong<sup>1</sup> M.D data collections.  
 Zhenhong Du<sup>1</sup> M.D data collections.  
 Rixiang Gong<sup>1</sup> M.D data collections.  
 Jingqiang Zhu<sup>1</sup> M.D study design.

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