Clinical Study

Pattern and Risk Factors of Central Compartment Lymph Node Metastasis in Papillary Thyroid Cancer: A Prospective Study from an Endocrine Surgery Centre

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Lymphatic metastasis in papillary thyroid cancer (PTC) is eminent; however, the extent of central compartment lymph nodes dissection (CCD) is controversial and requires the knowledge of pattern and risk factors for central compartment lymph nodes metastasis (CCM). We did a prospective study of 47 cases with PTC who underwent total thyroidectomy (TT) with CCD with/without lateral lymph nodes dissection (LND). Clinicopathological profile including CCM as ipsilateral and contralateral was documented. On histopathology, the mean tumour size was 3.57 ± 2.42 cm 59.6% had CCM, which was bilateral in the majority (60.72%). The tumour-size was the most important predictor for lymph nodes metastasis-(P = 0.018) whereas multicentricity- (P = 0.002) and ipsilateral CCM-(P = 0.001) were the predictors for contralateral CCM. The long-term morbidity of CCD done in primary setting is comparable with TT-alone. Bilateral CCD should be done with thyroidectomy in PTC, otherwise the risk of residual diseases and subsequent recurrence is high. The long-term morbidity is comparable in experienced hands.

1. Introduction

Papillary thyroid cancer (PTC) is the most common thyroid malignancy with the predilection for lymphatic spread [1]. Like any other head and neck malignancy, the lymphatic spread of PTC is supposed to follow a sequential pattern with the central compartment or level VI lymph nodes being first to involve [2–4], which besides containing the pre- and paratracheal lymph nodes, also contains the parathyroid glands and recurrent laryngeal nerves on either side, which are prone to injury while dissecting the central compartment lymph nodes [4]. The central compartment lymph nodes dissection (CCD) in PTC has the advantages of complete clearance of the disease, thereby reducing the chances of recurrence and the subsequent morbidity of reoperation, also it provides the nodes for exact nodal staging to plan further adjuvant therapy and prognosticate the patient [5, 6]. The central compartment lymph nodes dissection (CCD) in PTC has the advantages of complete clearance of the disease, thereby reducing the chances of recurrence and the subsequent morbidity of reoperation, also it provides the nodes for exact nodal staging to plan further adjuvant therapy and prognosticate the patient [5, 6]. Therefore, it is associated with increased risk of hypoparathyroidism and recurrent laryngeal nerve palsy [7]. Therefore for high-risk with clinically involved nodes the routine CCD is acceptable; however, it is controversial for low-risk, clinically uninvolved nodes [8], with some advocating for [9, 10] and some against [11] routine bilateral clearance while a third group of surgeons adopted a midway, by dissecting the ipsilateral side only, thus sparing the contralateral parathyroid glands and recurrent laryngeal nerve [12–14]. The extent of lymphadenectomy in PTC is still controversial and requires the knowledge of pattern of central compartment lymph nodes metastasis. Therefore, we aim our study to find out the pattern and risk factors of central compartment lymph node metastasis (CCM), and the morbidity of CCD.

2. Material and Method

We did a prospective study of all patients with papillary thyroid cancer, who underwent total thyroidectomy (TT) with CCD as a primary surgery from September 2008 till November 2010 at Department of Endocrine Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India. The study was approved by department review board,
Clinical staging based on 6th AJCC [15] was done. Final and any suspicious cervical lymph nodes, and a preoperative and fine-needle aspiration cytology of the thyroid nodules detailed history and examination, we did the ultrasound neck as per the department protocol. Preoperatively, besides a written and informed consent was taken from the patients, patients who did not undergo CCD, reoperative surgeries (like com-

| Table 1: Demographic profile of the patients; n = 47 (% age). |
|---------------------------------------------------------------|
| Mean age ± SD (range) years | 35.79 ± 12.65 (9–69) |
| Age group | |
| (i) ≤45 years | 40 (85.1) |
| (ii) >45 years | 7 (14.9) |
| Sex (male : female) | 31 : 16 |
| Clinical presentation | |
| (i) Solitary thyroid nodule | 42 (89.4) |
| (ii) Multinodular goiter (MNG) | 2 (4.3) |
| (iii) MNG with dominant nodule | 3 (6.4) |
| Occult papillary thyroid cancer | 4 (8.5) |
| Functional status | |
| (i) Euthyroid | 41 (87.2) |
| (ii) Hypothyroid | 6 (12.8) |
| Clinical nodal staging (TNM-classification) | |
| (i) cN0 | 29 (61.7) |
| (ii) cN1b | 18 (38.3) |
| Surgical procedure | |
| (i) TT + B/L CCD | 28 (59.6) |
| (ii) TT + B/L CCD + U/L MRND | 13 (27.7) |
| (iii) TT + B/L CCD + B/L MRND | 4 (8.5) |
| (iv) TT + U/L CCD + U/L MRND | 2 (4.3) |

written and informed consent was taken from the patients, as per the department protocol. Preoperatively, besides a detailed history and examination, we did the ultrasound neck and fine-needle aspiration cytology of the thyroid nodules and any suspicious cervical lymph nodes, and a preoperative clinical staging based on 6th AJCC [15] was done. Final staging was done after the histopathology report (p-TNM). We excluded patients with missed initial diagnosis of PTC who did not undergo CCD, reoperative surgeries (like completion thyroidectomy and locoregional recurrence), and concomitant hyperparathyroidism. “Central compartment” is defined as an area that is bounded superiorly by the hyoid bone, inferiorly by the innominate vein, and on either side by the carotid sheaths [16]. We did the thyroidectomy with standard technique of capsular dissection. The thyroid along with the central compartment lymph nodes was removed en bloc in all the cases and the fibrofatty tissue was divided in midline and sampled as right and left paratracheal lymph nodes [9]. Formal lateral lymph nodes dissection involving the level II, III, and IV were done in patients with proven lateral lymph nodes metastasis. We routinely identified all the parathyroid glands, external branch of superior laryngeal nerves and recurrent laryngeal nerves and tried to save them in situ. Any at-risk gland was autotransplanted in sternocleidomastoid muscle. We grossed the specimen in operation theatre and in pathology department under supervision of a single pathologist (SI) involved in the study. Along with detailed grossing of thyroid, the individual lymph nodes from lymph nodes basins were also separated, counted, and embedded. Following processing 3 μm thick sections were examined under microscope. For the purpose of description, the term “ipsilateral” was designated to the side with largest tumor size [9]. The complications were assessed in immediate postoperative period and 6 months following surgery and compared with a group of benign thyroid disorders, who underwent total thyroidectomy alone in primary setting during the same period. “Hypocalcemia” was defined as corrected serum calcium ≤8 mg/dL with or without clinical features of hypocalcemia. Any patient with significant postoperative hoarseness underwent vocal cord examination by indirect laryngoscopy to document recurrent laryngeal nerve (RLN) palsy. Hypocalcemia and RLN palsy are termed as temporary when it is resolved within 6 months of surgery. Patients with hypocalcemia were managed with oral/parenteral calcium and vitamin D, as per department protocol [17–19]. Following 6 months after surgery we did the serum parathyroid hormone analysis in any patient with persistently low serum calcium and requiring calcium and vitamin D support, thereby documenting permanent hypoparathyroidism. Similarly in all the patients with RLN palsy, vocal cord assessment was done at 6 months following surgery to document permanent RLN paralysis.

2.1. Statistical Analysis. Analysis was done by the SPSS 17. We used frequency, percentages, mean ± standard deviation, range, Student’s t-test, chi-square test, and Fischer exact test, wherever applicable. Univariate and multivariate analysis is done using logistic regression.

3. Results

As shown in Table 1 at the end of study 47 cases were included. The mean age was 35.79 ± 12.65 years with female preponderance (31 : 16). Majority were presented with solitary thyroid nodule (42/47). 4/47 cases presented with lateral lymph node metastasis with occult PTC. Majority were node negative (29/47) on clinical examination and imaging. CCD was done in all cases. 19/47 patients underwent lateral lymph nodes dissection also Table 2. Histopathology of thyroid showed, mean tumor size 3.57 ± 1.265 years with female age.

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age group (±45 years), sex, tumor size, pathological tumor staging, tumor subtypes, multicentricity, bilaterality, and extrathyroidal extension (Table 3). We did find a significant association of tumor size with the CCM (4.2 ± 2.45 versus 2.58 ± 2.02; \( P = 0.018 \)). Similarly, ipsilateral CCM was significantly associated with primary tumor size (4.4 ± 2.4 versus 2.5 ± 2.0; \( P = 0.013 \)), and contralateral CCM was significantly associated with multicentricity (36.8% versus 18.5%; \( P = 0.003 \)) and ipsilateral CCM (89.5% versus 33.3%; \( P = 0.000 \)). Multivariate analysis showed ipsilateral CCM metastasis as a significant risk factor for contralateral CCM (\( P = 0.02 \)). In our series, 42 patients initially presented with solitary thyroid nodule confined to one lobe only, but on final histopathology, 8/42 were found to have tumor foci in both the lobes (bilateral tumors) and 16/42 was multicentric. Two patients in our series had skip metastasis to contralateral CCM, skipping the ipsilateral CCM, one of them was a 40-year-old male, who presented with right lateral lymph nodes metastasis with occult PTC, underwent TT with CCD with right MRND, and on final histopathology was detected to have 0.5 cm tumor in right lobe thyroid with multicentricity and bilaterality; second patient, was a 44-year-old male with clinically evident solitary thyroid nodule with absent nodes, underwent TT with CCD, and on histopathology was found to have 4 cm tumor with no evidence of multicentricity and normal opposite lobe. Similarly, for skip lateral metastasis that is skipping the CCM, out of two patients, one was a 33-year-old male with lateral lymph nodes metastasis with occult PTC, histopathology showed a 0.4 cm tumor, with multicentricity with normal opposite lobe; the second patient was a 62-year-old lady, who presented with solitary thyroid nodule with lateral lymph nodes metastasis, the histopathology again revealed a 0.3 cm tumor with no multicentricity and normal opposite lobe; however, the extrathyroidal extension was present. All the above-mentioned cases had classical variant of PTC. All 47 cases underwent whole-body radioactive iodine scan 4 to 6 weeks following thyroxin withdrawal, and radioactive remnant ablation was done in 41/47 patients. All patients received suppressive L-thyroxin therapy. The morbidity was compared with age- and sex-matched group of benign thyroid disorders operated during the same period that underwent total thyroidectomy alone (Table 4). In our series, though the rate of inadvertent parathyroidectomy, temporary hypocalcaemia, and temporary RLN palsy was significantly high in group with CCD (\( P < 0.05 \)), the long-term morbidity, that is, rate of permanent RLN palsy and hypoparathyroidism was comparable to those with total thyroidectomy alone.

### 4. Discussion

PTC has propensity for lymphatic spread [1]. The metastasis is found in 20–50% of lymph nodes examined by conventional pathologic examination whereas the rate of micrometastasis has been found to be much higher in clinically node negative-cases [21]. The lymph node metastasis in papillary thyroid cancer has been found to have significant impact on disease-free and overall survival of patients [22, 23]. Giles et al. [24] in their retrospective series of 343 patients with thyroidectomy but without CCD, found a locoregional recurrence rate of 6% with a median followup of 9 ± 4 years, where central compartment lymph nodes were involved in 6 recurrent cases. Similarly, Moo et al. [5], in their series, during a mean followup of 3.1 years, reported increased locoregional recurrences in the group undergoing total thyroidectomy alone (16.7%) compared to those with prophylactic central lymph nodes dissection (4.4%). Similarly, Ito et al. [25] reported 10-year

### Table 2: Histopathological features; \( n = 47 \) (% age).

| Lymph nodes                                      | Thyroid                                      |
|--------------------------------------------------|----------------------------------------------|
| Overall lymph nodes metastasis                   | Mean tumor size (cm) ± SD (range)            |
| Overall central compartment lymph nodes metastasis (CCM) | 3.57 ± 2.42 (0.3–12)                         |
| (i) Bilateral CCM                                | 4 (8.5)                                      |
| (ii) Isolated ipsilateral CCM                    | 19 (40.4)                                    |
| (iii) Isolated contralateral CCM                 | 11 (23.4)                                    |
| (iv) T4                                          | 13 (27.7)                                    |
| Papillary microcarcinoma                         | 8 (17)                                       |
| PTC subtypes                                     |                                              |
| (i) Classical variant (CV)                       | 35 (74.5)                                    |
| (ii) Follicular variant (FV)                     | 8 (17)                                       |
| (iii) Oncocytic variant (OV) [20]                 | 1 (2.1)                                      |
| (iv) Tall cell variant (TCV)                     | 3 (6.4)                                      |
| Laterality                                       |                                              |
| (i) Right side                                   | 29 (61.7)                                    |
| (ii) Left side                                   | 18 (38.3)                                    |
| Multicentricity                                  | 18 (38.3)                                    |
| Bilateralally                                    | 9 (19.1)                                     |
| Extrathyroidal extension                         | 13 (27.7)                                    |

| Overall lateral compartment lymph nodes metastasis (LLNM; \( n = 19 \)) | 30 (63.8) |
| (i) Ipsilateral LLNM                                           | 28 (59.6) |
| (ii) Bilateral LLNM                                            | 17 (60.72) |
| (iii) Contralateral LLNM                                        | 9 (32.14)  |
| Final pathological nodal staging (TNM-classification)           | 28 (59.6) |
| (i) pN0                                                        | 19 (100)   |
| (ii) pN1a                                                      | 15 (78.95) |
| (iii) pN1b                                                     | 3 (15.8)   |
| Skip lateral metastasis (\( n = 19 \))                         | 1 (5.3)    |
| Skip contralateral central lymph node metastasis (\( n = 47 \)) | 2 (10.5)   |

### Table 3: Multivariate analysis of clinicopathological features for contralateral CCM.

\( P \theta 0.02 \). In our series, 42 patients initially presented with solitary thyroid nodule confined to one lobe only, but on final histopathology, 8/42 were found to have tumor foci in both the lobes (bilateral tumors) and 16/42 was multicentric. Two patients in our series had skip metastasis to contralateral CCM, skipping the ipsilateral CCM, one of them was a 40-year-old male, who presented with right lateral lymph nodes metastasis with occult PTC, underwent TT with CCD with right MRND, and on final histopathology was detected to have 0.5 cm tumor in right lobe thyroid with multicentricity and bilaterality; second patient, was a 44-year-old male with clinically evident solitary thyroid nodule with absent nodes, underwent TT with CCD, and on histopathology was found to have 4 cm tumor with no evidence of multicentricity and normal opposite lobe. Similarly, for skip lateral metastasis that is skipping the CCM, out of two patients, one was a 33-year-old male with lateral lymph nodes metastasis with occult PTC, histopathology showed a 0.4 cm tumor, with multicentricity with normal opposite lobe; the second patient was a 62-year-old lady, who presented with solitary thyroid nodule with lateral lymph nodes metastasis, the histopathology again revealed a 0.3 cm tumor with no multicentricity and normal opposite lobe; however, the extrathyroidal extension was present. All the above-mentioned cases had classical variant of PTC. All 47 cases underwent whole-body radioactive iodine scan 4 to 6 weeks following thyroxin withdrawal, and radioactive remnant ablation was done in 41/47 patients. All patients received suppressive L-thyroxin therapy. The morbidity was compared with age- and sex-matched group of benign thyroid disorders operated during the same period that underwent total thyroidectomy alone (Table 4). In our series, though the rate of inadvertent parathyroidectomy, temporary hypocalcaemia, and temporary RLN palsy was significantly high in group with CCD (\( P < 0.05 \)), the long-term morbidity, that is, rate of permanent RLN palsy and hypoparathyroidism was comparable to those with total thyroidectomy alone.

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Table 3: Univariate analysis of central compartment lymph nodes metastasis (CCM), ipsilateral CCM and contralateral CCM with known risk factors.

|                     | Present  | Absent  | P value | Present  | Absent  | P value | Present  | Absent  | P value |
|---------------------|----------|---------|---------|----------|---------|---------|----------|---------|---------|
| Age (years)         | 34.96 ± 14.41 | 37 ± 9.74 | 0.594   | 34.42 ± 14.83 | 37.48 ± 9.38 | 0.410   | 34.68 ± 15.77 | 36.67 ± 11.03 | 0.602   |
| Age group ≤45 years | 24       | 16      | 1.000   | 22       | 18      | 1.000   | 16       | 23      | 0.928   |
| Age group >45 years | 4        | 3       | 4       | 3        | 3       | 4       |          |         |         |
| Sex Male            | 9        | 7       | 0.763   | 76       | 9       | 0.355   | 7        | 8       | 0.608   |
| Sex Female          | 19       | 12      |         | 19       | 12      |         | 12       | 19      |         |
| Tumor size (cm)     | 4.2 ± 2.45 | 2.58 ± 2.02 | 0.018*  | 4.4 ± 2.4 | 2.5 ± 2.0 | 0.013*  | 4.02 ± 2.23 | 3.38 ± 2.5 | 0.378   |
| Tumor staging       |          |         |         |          |         |         |          |         |         |
| T1                  | 2        | 2       | 1       | 3        |         |         | 2        | 1       |         |
| T2                  | 8        | 11      | 0.326   | 8        | 11      | 0.760   | 5        | 14      | 0.324   |
| T3                  | 8        | 3       | 8       | 3        | 5       | 6       |         |         |         |
| T4                  | 10       | 3       | 9       | 4        | 7       | 6       |         |         |         |
| Tumor subtype       |          |         |         |          |         |         |          |         |         |
| Classical variant   | 22       | 13      | 20      | 15       | 14      | 20      |         |         |         |
| Follicular variant  | 3        | 5       | 0.580   | 3        | 5       | 0.619   | 2        | 6       | 0.434   |
| Oncocytic variant   | 1        | 0       | 1       | 0        | 1       | 0       |         |         |         |
| Tall cell variant   | 2        | 1       | 2       | 1        | 2       | 1       |         |         |         |
| Multicentricity     | 13       | 5       | 0.169   | 12       | 6       | 0.245   | 12       | 5       | 0.002*  |
| Bilaterality        | 6        | 3       | 0.631   | 5        | 4       | 1.000   | 6        | 3       | 0.085   |
| Extrathyroidal       | 10       | 3       | 0.144   | 10       | 3       | 0.102   | 7        | 5       | 0.170   |
| Ipsilateral CCM     | —        | —       | —       | —        | —       | —       | 17       | 9       | 0.001*  |

Table 4: Comparison of morbidity following total thyroidectomy with CCD (n = 47); with total thyroidectomy alone (benign thyroid disorders; n = 130).

| Total thyroidectomy with CCD; n = 47 | Total thyroidectomy alone; n = 130 | P value |
|--------------------------------------|-----------------------------------|---------|
| Inadvertent parathyroidectomy        | 13 (27.7)                        | 0       |
| Temporary hypocalcemia               | 41 (87.2)                        | 67 (51.5) | 0.000*  |
| Temporary RLN palsy                  | 8 (17)                           | 9 (6.9)  | 0.044*  |
| Permanent hypoparathyroidism         | 1 (2.1)                          | 3 (2.3)  | 0.458   |
| Permanent RLN palsy                  | 1 (2.1)                          | 1 (0.8)  | 0.419   |

disease-free survival (DFS) of 97% with elective lymph nodes dissection in low-risk PTC even without radio-iodine treatment. On the other hand Rosenbaum and McHenry [7], reported, no significantly reduced recurrence rate with central neck dissection, but an increased risk of temporary hypocalcemia, compared with no central cervical lymph nodes dissection group. The rationale behind the routine dissection of central compartment lymph nodes in preoperatively diagnosed cases of PTC with clinically uninvolved lymph nodes is manifold; first, the PTC has the tendency for lymphatic spread, which tends to follow a sequential pattern with ipsilateral paratracheal followed by contralateral paratracheal and ipsilateral lateral cervical lymph nodes [3, 4]; secondly, it provides accurate tumor staging to facilitate accurate prognosis and adjuvant therapy [6]; lastly, the long-term morbidity of CCD in primary setting in experienced hands is comparable with total thyroidectomy alone [5, 9] and even though if it is higher [10, 26], it is still lower than the morbidity of central compartment lymph nodes dissection (CCD) done in reoperative setting [27]. Roh et al. [28], in their prospective series of 45 patients with recurrent PTC detected 86.7% recurrences in central compartment, with high rates of temporary and permanent complications with reoperation. There are few reports documenting no increased risk of complications following reoperative surgery
The rate of central compartment lymph node metastasis is high in PTC. Tumour size is an important risk factor for CCM. Multicentricity and ipsilateral lymph node metastasis
are risk factors for contralateral CCM. Bilateral CCM is most frequent rather than ipsilateral CCM. The long-term morbidity of bilateral CCD done in primary setting is comparable with total thyroidectomy alone, and is safe in the hands of experienced endocrine surgeons.

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