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Clinicopathological Predictors of Central Compartment Lymph Node Metastases in cN0 Papillary Thyroid Carcinoma

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Introduction
Papillary thyroid carcinoma (PTC) is the most found thyroid carcinoma. The prevalence is up to 75% of all thyroid malignancies and more than 90% of all well differentiated thyroid carcinoma.1 PTC mostly give the feature of slow–growing tumors with a good prognosis. The average of 10-year survival rate was 90%. Unfortunately the regional metastasis to the lymph nodes (LN) in neck area is quite common (90%); while as distant metastases is quite rare found (4%).2 In the central compartment, which is the first location of the metastatic pathway of PTC to the regional LN, metastasis is found as much as 80%.3 As the regional LN metastasis prevalence is of a great possibility, high regional recurrance is then quite high (30%).2 This high rate of regional recurrence becomes an important issue in terms of increasing the morbidity and mortality of PTC.4,5 i.e. 30% and 1.6%, respectively.3 The involvement of regional LN increases the risk of death by 46%.6 Therefore, to improve overall survival a good management of PTC is required to control the regional metastasis adequately.

Following the respect of the American Thyroid Association, British Thyroid Association and the European Thyroid Association, Medical centers in the United States and Europe argued that the management of PTC that addressed to control regional metastasis could be achieved by a combination of total thyroidectomy and the administration of ablative radioiodine and suppression of thyroid stimulating hormone (TSH) postoperatively. Meanwhile, centers in Japan implements the recommendations of the Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons 2011, where they were routinely performed the central prophylactic compartment dissection (CPCD) in patients with thyroid carcinoma, as the strategy to control the regional metastasis; and followed by the increased of recurrence–free survival as well as overall survival rate. Total thyroidectomy and CPCD is carried out in one step, to achieve the goal which is a better loco regional control.6,7 Somehow, the procedure shows both of advantages and disadvantages. The selection of appropriate and adequate treatment resulted in more than 90% average of survival rate.1 CPCD showed the advantage in achieving a greater control of regional metastasis.1 Such a procedure can be implemented in a rural hospital in Indonesia where the radio-ablative facility was unavaialable. On the other side, the procedure is followed by risks. Hypoparathyroidism and laryngeal nerve injury (7% and 5.5%, respectively) were the risks followed by increased of morbidity.8,9 By this mean, CPCD is then indicated selectively to those who were predicted where metastasis in the LN of central compartment is to be found.

Studies in Korea, China, and Japan that run out identifying these predicting factors of metastatic regional lymph nodes showed a
plenty number of factors, namely age, gender, tumor size, extra
extensive thyroid, the presence of distant metastases, and
completeness of the resection, and variants of histopathology
and invasion of vascular–lymph.\textsuperscript{23,79}

Unfortunately, studies addressed to these predicting factors in patients
– with our characteristics – managed in Cipto Mangunkusumo
General Hospital were never been run yet. We do believe that such a
study is required to find out the clinical predicting factors. Should
these factors be identified, then it will be useful in patient selection
where CPCD is indicated.

Method

A retrospective study conducted with consecutive sampling enrolling
those with PTCs cN0 who underwent CPCD during period of
January 2014 to July 2015. Those with previous thyroid surgery and
those with insufficient data in the medical record were excluded. The
correlation between above mentioned variables were statistically
analyzed. Chi square or Fisher, t-test and stratification test were
conducted. Significance met when p value is <0.05 with 95% confidence
intervals. Ethical committee of FMUI and approved the
study (718/UN2.F1/EITIK/2015) and research bureau of dr. Cipto
Mangunkusumo General Hospital (LB.02.01/X.2/648/2015).

Results

There were 62 subjects enrolled in the study. Mostly (33 subjects, 53.3%)
they were under 45 years old, and 53 (85.5%) were females. We
found 42 subjects (67.7%) with tumor sized larger than 4 cm. The
extension of extra thyroid found in six (6.7%) subjects. Distant
metastases was found in four (6.5%) subjects. There were 57 (91.9%)
underwent incomplete resection (completeness of negative
resection, and variants of histopathology and
invasion of vascular–lymph.\textsuperscript{23,79}

In addition, tumor size which is analyzed categorically, was also
analyzed numerically. Correlation between tumor sizes with the
incidence of central compartment metastasis showed p 0.52 (table 3).
To determine the independent association between the age and other
variables, we run stratified analyzes based on other factors in the
bivariate analysis. This was found showing a significant correlation
with metastasis. On the stratification of vascular–lymph invasion and
its variants, OR value of age was found consistent (table 4 and 5).

### Table 2. Variables of predicting factors

| Variables                      | N  | %   | Variables                      | N  | %   |
|--------------------------------|----|-----|--------------------------------|----|-----|
| Age (years)                    |    |     | Completeness of resection       |    |     |
| <45                            | 33 | 53.3| Incomplete                     | 5  | 8.1 |
| ≥45                            | 29 | 46.7| Complete                       | 57 | 91.9|
| Gender                         |    |     | Histopathological variants     |    |     |
| Male                           | 9  | 14.5| Classic                        | 8  | 12.9|
| Female                         | 53 | 85.5| Follicular                     | 34 | 54.8|
| Tumor size                     |    |     | Micro–carcinoma                |    |     |
| <4 cm                          | 20 | 32.3| Tall cell                      | 15 | 24.0|
| ≥4 cm                          | 42 | 67.7| Vascular–lymph invasion        |    |     |
| Extra thyroid extension        |    |     | Positive                       |    |     |
| Positive                       | 6  | 9.7 | Negative                       | 4  | 6.5 |
| Negative                       | 56 | 90.3|                               | 58 | 93.5|
| Distant metastasis             |    |     | Central lymph nodes metastasis |    |     |
| Positive                       | 4  | 6.5 | Positive                       | 13 | 20.9|
| Negative                       | 58 | 93.5| Negative                       | 49 | 79.1|

### Table 3. Correlation of variables with the central compartment metastasis

| Variables                      | LN meta (+) | LN meta (−) | OR (CI 95%) | p    |
|--------------------------------|-------------|-------------|-------------|------|
| Age (years)                    |             |             |             |      |
| <45                            | 11 (37.9%)  | 18 (62.1%)  | 0.47 (1.28) | 0.68 |
| ≥45                            | 2 (6.1%)    | 31 (93.9%)  | 0.08 (0.08) | 0.93 |
| Gender                         |             |             |             |      |
| Female                         | 11 (20.8%)  | 42 (79.2%)  | 3.37 (0.48) | 0.28 |
| Male                           | 2 (22.2%)   | 7 (77.8%)   | 0.06 (0.06) | 0.91 |
| Tumor size                     |             |             |             |      |
| <4 cm                          | 10 (23.8%)  | 32 (76.2%)  | 0.78 (0.5)  | 0.09 |
| ≥4 cm                          | 3 (15.0%)   | 17 (85.0%)  | 0.29 (0.29) | 0.19 |
| Extrathyroid extension         |             |             |             |      |
| Positive                       | 4 (66.7%)   | 2 (33.3%)   | 0.04 (0.04) | 0.19 |
| Negative                       | 9 (16.1%)   | 47 (83.9%)  | 0.1 (0.1)   | 0.06 |
| Distant metastasis             |             |             |             |      |
| Positive                       | 2 (50.0%)   | 2 (50.0%)   | 1 (1)       | 0.37 |
| Negative                       | 11 (19.0%)  | 47 (81.0%)  | 0.54 (0.54) | 0.09 |
| Completeness of Resection      |             |             |             |      |
| Complete                      | 10 (17.0%)  | 47 (82.5%)  | 0.14 (0.14) |      |
| Incomplete                     | 3 (60.0%)   | 2 (40.0%)   | 0.21 (0.21) |      |
| Histopathological variants     |             |             |             |      |
| Follicular                     | 1 (2.9%)    | 33 (97.1%)  | 0.01 (0.01) | 0.52 |
| Tall cell                      | 10 (66.7%)  | 5 (33.3%)   | 0.06 (0.06) | 0.19 |
| Micro-ca                       | 1 (20.0%)   | 4 (80.0%)   | 0.12 (0.12) | 0.39 |
| Classic                        | 1 (21.2%)   | 7 (78.8%)   | 0.13 (0.13) |      |
| Vascular–lymph invasion        |             |             |             |      |
| Positive                       | 3 (75.0%)   | 1 (25.0%)   | 0.41 (0.41) |      |
| Negative                       | 10 (17.2%)  | 46 (82.8%)  | 0.04 (0.04) |      |

### Table 4. Tumor size correlation with lymph nodes central compartment metastasis

| Variables                      | n | Mean | SD | p    |
|--------------------------------|---|------|----|------|
| Tumor size                     |   |      |    |      |
| Positive lymph nodes           | 13| 3.91 | 3.57| 0.77 |
| Negative lymph nodes           | 49| 3.57 | 3.41|      |

Factors that showed correlation with LN metastasis were positive
vascular–lymph invasion (OR 14.40), tall cell variant (OR 14.00),
positive extra thyroid extensions (OR 10.44) and age more than 45
years old (OR 9.47), respectively (table 2). We found there were four variables indicated statistically significant
correlation with metastasis that unable to be analyzed using
multivariate analysis, due to the number of central compartment
metastasis output in the study consists only 13 subjects. Thus, only
a variable allowed to be included into the multivariate model.

Table 1. Subjects’ characteristic on the study

| Variable                | Mean (±SD) | Median | Min–Max |
|-------------------------|------------|--------|---------|
| Age (years)             | 48.5 (±8.5)| 49     | 33–69   |
| Body weight (kg)        | 61.5 (±10.5)| 60   | 40–90   |
| Height (m)              | 1.55 (±0.06)| 1.55 | 1.43–1.77 |
| BMI (kg/m\textsuperscript{2}) | 25.43 (±4.08)| 25.39 | 16.65–35.59 |
| Length of stay (days)   | 4.6 (±1.5) | 4 | 5–8    |
| Total seroma (mL)       | 502.3 (±207.8)| 504 | 134–990 |
| Daily seroma (mL)       | 109.6 (±32.1)| 106.7 | 44.7–170.8 |
| BMI body mass index.    |           |       |         |
Table 5. Correlation between age factor with vascular-lymph invasion and metastasis of central lymph nodes

| ILV       | Age | LN meta (%) | LN meta (%) | Total | OR(CI95%) | p    |
|-----------|-----|-------------|-------------|-------|-----------|------|
| ILV negative | <45 | 30          | 0           | 30    |            |      |
|           | ≥45 | 62.5%       | 0%          | 51.7% |            |      |
| Total     |     | 48          | 10          | 58    | 17.95      | 0.001|

Table 6. Correlation between age with variants and metastasis of central lymph nodes

| Variants  | Age | LN meta (%) | LN meta (%) | Total | OR(CI95%) | p    |
|-----------|-----|-------------|-------------|-------|-----------|------|
| Follicular | <45 | 21          | 0           | 21    |            |      |
|           | ≥45 | 63.60%      | 0%          | 61.80%|            |      |
| Total     |     | 33          | 1           | 34    | 3.39       | 0.55 |

Discussion

In our study, the age and gender of enrolled subjects were found consistent to the findings of studies in Asia (China and South Korea). The prevalence of LN metastasis of the central compartment in the study was of 20.9%, which is found lower than those reported by Chen (84.3% and 54.1%), and Koo. However, it showed no difference to study of Anand in Canada (20%). Subjects’ characteristics were also like those reported by Chen, Koo and Anand: most subjects’ age were over 45 years old, predominated by female, and tumor size were mostly larger than 1 cm. The difference in the prevalence of output found in the study was due to the difference in the number of samples enrolled. Study of Chen enrolled of 153 subjects with a study span for three years. Likewise, formerly Koo enrolled of 111 subjects in a three years’ study period (2005–2007), while as Anand enrolled a smaller number of samples (70 subjects).

The aggressiveness type of variant, particularly tall cells, might be rolled out in the prevalence. However, the variants were unable to be analyzed in the study, as this variable wasn’t enclosed in the former study of Chen, Koo and Anand. Subjects’ age was a variable strongly associated with the incidence of metastases in the LN central compartment (p<0.05). This is consistent to related literatures that stated that the age factor is an independent one for the occurrence of lymph nodes metastasis. This is also found consistent with the published reports that the prognosis is worsening in those over 45 year’s old. The prognosis scoring system of Memorial Sloan Kettering (grade, age, metastases, extent, size abbreviated with mnemonic of GAMES) and American Joint Committee on Cancer Tumor Nodal Metastasis (AJCC TNM) categories patients over 45 years old into the high risk group for the recurrence and low survival rate category. In accordance to the AJCC TNM system, patients under 45 years old were categorized into stage one or two, while as subjects of 45 years old and above were categorized into stage three or four. Consequently, these subjects were categorized of high risk group with low survival rate. Estrogen exposure and the mutation of thyroid's beta receptor (TRβ) were responsible factors for the aggressiveness, in which it depends on age. Based on the stratification, our study showed that age indicates the tendency of independent association with the incidence of metastasis; when it is linked to tall cell variant.

Tumor size seems to be a factor tends to be correlated with the incidence of metastasis. Tumor size of >4 cm was found in 23.8% subjects and metastasized to the central lymph nodes, compared to 15% tumor size of <4 cm. Still, this correlation showed no statistical significance in our study (p 0.52). The total low output and uneven distribution were assumed to be responsible to insignificant correlation with metastatic LN in the central compartment. Tumor size was numerically analyzed as well and showed no significance correlation (p 0.77). In published reports, tumor size referred to variable correlated with the outcomes in papillary thyroid carcinoma. In accordance to AJCC TNM, tumor size >4 cm is followed by increased of mortality. Larger tumor size often accompanies both of regional and distant metastases. A published study reported that tumor size of <1 cm is seldomly correlated with mortality.

The mortality rate in the study ranged of 0 to 2.2% and the risk of recurrence and cancer-specific mortality rate increases with increase of tumor size. Tumor size of <1.5 cm showed average of cancer-specific mortality of 30 years (0.4%) compared to 22% in tumor sized of >4.5 cm. However, a study reported that tumor size may not associated independently with the recurrence rates.

Aggressive variants such as tall cell and their extensions is likely affects the extra thyroid recurrence. In our population, mostly subjects of papillary thyroid carcinoma presented with tumor sized of >2 cm. In the study there were just two subjects with tumor sized of <2 cm (3.2%), the tumor sized of >2 cm found in 67.7%. With these small number of subjects with <2 cm tumor, it was necessarily an obstacle to conduct statistical analysis. Future study is required to find out the correlation between tumor size and the incidence of central compartment LN metastasis. Including the subjects with tumor sized of <2 cm and considering the variants as well as extensions of extra thyroid, it is expected that tumor size affects the metastasis in the
central compartment LN and the independence of the extra thyroid variants and extensions to be able to be identified.

Extra thyroid extensions in this study showed a statistically significance correlation with the occurrence of metastasis in the central compartment (p < 0.05). It is in accordance to the published reports in which the thyroid extra extensions had been identified to increase the risk of local recurrence.22,23 Extra thyroid extensions is an important prognostic factor in papillary thyroid carcinoma and correlated to the recurrence rates with high mortality. The extra thyroid extensions indicated tumor aggressiveness and significantly improved the mean mortality by 6–71% with the mean recurrence by 37–64%.24

Distant metastases are a component established in the assessment of prognosis of MACIS score. According to Koo, it showed correlation with metastasis in the central compartment LN.5 However, we found it showed no correlation with central compartment LN metastasis (p 0.19). This just showing that the distant metastases in the study is more likely to occur due to hematogenic propagation.

Completeness of resection is also a component in MACIS score, which is in the study found to have correlation with metastasis of central compartment LN. Out of 60% subjects with incomplete resection showed metastatic central compartment. While as out of the subjects experiencing complete resection, there is only 17.5% found. This suggested that incomplete resection may be correlated with metastases in central compartment. However, no statistically significant correlation found (p 0.06), although data indicating that a complete resection might results in protective effect against metastasis in the central compartment LN (OR 0.14). Completeness of resection is influenced by the presence of tumor attachment to the surrounding tissue of an important structures. Presence of adhesions indicated tumor infiltrated across the thyroid capsule. In our study, the extra thyroid extensions were significantly correlated with metastatic central thyroid compartment LN. Insignificant correlation between completeness of resection with metastasis in the central compartment was allegedly due of the small number of samples of subjects who received incomplete resection (n = 5; 8.1%).

The tall cell variant showed statistically significance correlation with the central compartment metastasis (p < 0.05). This is found consistent to the published reports, showed that rather than other variants the tall cell variant found to have higher central compartment metastasis. This variant generally accepted as a more aggressive variant of PTC and possesses a high risk of recurrence. Kazaure reported such a variant is associated with reducing of five–year survival rate (80.6% compared 93.5% of classic PTCs).17 Aggressive biological character in the form of higher, more invasive, easily move and turn to poorly differentiated or anaplastic miotic count.5 The overexpression of genetic components such as MUC1, MMP2, Braf V600E and cMET is thought to be responsible for this specialized character.20,26,27 Tall cell variant which is first described by Hawk and Hazard in 1976, defined as a tumor composed by cells with a height of two to three times its width, with eosinophilic cytoplasm, basilecular–oriented nucleus and core surface as found in the classic PTCs. Benninato reported that the variant may covers up 1.3–12% PTC area. Kazaure found in their study it covered up 3.2–19% PTC area. Other studies found that such a variant often turned out to be underdiagnosed. In cases where the tumor was first diagnosed as a classical variant of PTC, 1–13% evidently referred to tall cell variant following a reviewed by endocrine pathologist. Another study reported that 90% tall cell variants have been erroneously classified or underreported. A potential obstacle in instituting the diagnosis exactly is the absence of international consensus on the number criterion of tall cell should be found. A recommendation proposed 30–70% as the cutoff point and the selection is up to the local institutions. In our Department of Anatomical Pathology, the cutoff point applied is 50%. In addition, a tumor with tall cells than the cutoff point consequently defined as PTC with a chance of tall cells. Some centers recommended that should the tumor contains less than 30% of tall cell then it should be categorized as classic PTC. Given these differences, coupled with the lack of data regarding the differences between clinical features of tumors contained a small number of tall cells with that of those containing a great number of tall cells, the diagnostic criteria is considered not universally established yet. Although some study as Benninato did showed that of 10% tall cell alone can resulted in aggressive output.13,14

Vascular–lymph invasion showed a statistically significance correlation with the central compartment LN metastasis (p <0.05). This is in accordance to the study of Koo et al., reporting that the invasion of vascular–lymph showed a substantial correlation with metastasis of PTC's central compartment.8,15 However, in our study vascular–lymph invasion referred not to an independent factor. The study found vascular–lymph invasion Odds ratio of 14.40, higher than the former four factors showed statistically significant correlation with metastatic central compartment LN. Thus, the invasion of vascular–lymph in this study referred to the strongest predicting factor showed from the perspective of the risk it might have on the central compartment metastasis. The discovery of vascular–lymph invasion in our study provide the evidence that the process of metastasis in PTC is in accordance to the theory of metastasis, in which the tumor cells invade in advance into the lymph vessels and subsequently invasion to the LN.10,27

Out of the eight factors we studied, there were four factors statistically showed significant correlation with the occurrence of central compartment LN metastasis, and thus referred to be a predicting factor of metastatic LN central compartment. These factors were positive vascular–lymph invasion, tall cell variant, positive extra thyroid extensions, and age >45 years old, respectively.

Factor of age can simply be noted prior to the first surgical intervention. Through macroscopic assessment, extra thyroid extension can be identified intra operatively in the first surgical intervention. Microscopic extra thyroid extensions, tall cells variant, and invasion of vascular–lymph was identified following the first surgical intervention, which is following the definitive pathological assessment. Therefore, should the first surgical intervention in a 45 years old papillary thyroid carcinoma subjects macroscopically found an extra extension of thyroid, then prophylactic central compartment dissection might be considered. Otherwise, should one microscopically found extra thyroid extension, tall cell variant, vascular–lymph invasion following the first surgery, then the patient can be treated as high–risk subject.

The fundamental thinking is, we should find at least two of the four factors of prognosis scoring system. Age of 45 is a component that determines high risk category in the assessment of prognosis per AJCC TNM and extra thyroid extension on the AMES and MACIS. The fundamental thinking is, we should find at least two of the four factors of prognosis scoring system. Age of 45 is a component that determines high risk category in the assessment of prognosis per AJCC TNM and extra thyroid extension on the AMES and MACIS. Therefore, in patients with identified these four factors, which is high risk ones, ablative radioiodine therapy with 100–300 mCi (doses for high risk subjects) that suppress L–tyrosine with a TSH target being less than 0.1 U/mL and more rigorous postoperative observation.
focusing on regional recurrence (recurrence in the central compartment of LN) can be carried out.

In PTC patients of whom a completion will undergo, should the four factors have found, then a prophylactic central compartment dissection is advisable. However, technical difficulty of central compartment dissection in cases of completion is considerably higher with the possibility of adhesions and fibrotic tissue following the former surgical intervention. This is somehow leading to increase the risk of complications particularly hypoparathyroidism is greater in folds as parathyroid glands hard to be identified. The surgeon’s experience in this specialized field should be of ones’ consideration. Central compartment dissection aimed to achieve a better regional control remain controversies. The risk and benefit showed in varies. Therefore, central compartment dissection remains an interesting topic to be investigated. The predicting factors found in this study can be applied in selection of patients to precede the prophylactic central compartment dissection. However, since there’s limited to just two factors that could be identified in the first surgery (namely, age and macroscopic extra thyroid extension), expertise is further required to come up with essential ways to have the better assessment of a central compartment of LN during the first surgery. LN sentinel biopsy may be considered in the first surgery. Somehow, a further investigation is needed to find out the accuracy of sentinel LN biopsy. The limitation of this study referred to the number of subjects enrolled as well as output. Therefore, further study is required. Despite the shortcomings, this study provides the prevalence of metastasis in lymph nodes central compartment in this PTC patient managed in Cipto Mangunkusumo hospital, which might be valuable for further investigation. Furthermore, the clinically pathological predicting factors found in this study can be applied in clinical daily practice, as the consideration in the management of the PTC cN0 patients.

Conclusion
We found vascular–lymph invasion, tall cell variant, extra thyroid extensions, and age >45 years old were predictor factors showed significant correlation with metastasis of LN. Prevalence of LN metastasis in the central compartment on the subjects with PTC cN0 in RSCM was 20.9%.

Conflict of interest
Author disclose no conflict of interest.

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