Study Assessment

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Q1. What question(s) does the study address?
Which factors predict central lymph-node metastasis (CLNM) in patients with papillary thyroid carcinoma (PTC)?

Q2. Is this study an experiment or an observational study (who decides who gets the treatment)?
It's an observational, retrospective study: The researchers reviewed records of PTC patients, who were treated between 2014 and 2016.

Q3. What is the 'treatment'? (Is there a treatment?) How many treatments are there?
There is no treatment controlled by the researchers. The risk factors are naturally occurring patient or tumor features such as multifocality or lymphovascular invasion (LVI).

Q4. Is there a control group? Is a placebo used for the control group?
Yes, patients without CLNM can be seen as a control group when analysing risk factors. There is no treatment and therefore also no placebo.

Q5. (If controlled experiment) Is the experiment run blind? Double-blind?
Not applicable; this is not a controlled experiment.

Q6. (If controlled experiment) Is the experiment randomized? (Is the assignment to the treatment group or control group governed by a chance procedure, rather than by judgement or a haphazard procedure?)
Not applicable; this is not a controlled experiment.

Q7. What are the experimental units?
Each individual PTC patient represents one experimental unit.

Q8. What is the experimental design?
Clinical data were reviewed for all patients who underwent PTC surgery at Anhui Hospital (China) between 2014 and 2016. The patient group was restricted to individuals with a first PTC and no history of other head and neck malignancies. Electronic medical records and surgical pathology reports were investigated for the features tumour size, multifocality, Hashimoto thyroiditis (HT), lymphovascular invasion (LVI) and extrathyroidal extension (ETE).

Categorical variables were compared with the χ^2 test. Univariate logistic and binary logistic regression were performed to investigate the relationship between the clinicopathologic features and CLNM. A p-value less than 0.05 was considered statistically significant.

Q9. What confounding factors may be involved?
Several factors are plausibly linked both to the putative predictors and to the probability of detecting CLNM, yet were not included in the regression model:

- *Extent of surgery and surgeon preference*: completeness of the central-compartment dissection can influence the probability of finding metastases and may correlate with tumour size or multifocality.
- *Histological tumour variant (e.g. tall-cell, diffuse sclerosing)* that carries a higher metastatic propensity and may co-occur with multifocality.
- *Molecular alterations* (e.g. $\text{BRAF}^{\text{V600E}}$) associated with both HT and nodal spread.
- *Iodine status and other environmental/ethnic factors* that affect both auto-immune thyroiditis prevalence and tumour aggressiveness.
- *Quality of pre-operative imaging*: patients with better ultrasound work-up might have smaller occult nodes detected intra-operatively.

Q10. Are any confounding factors controlled for?
Partially. The multivariate logistic regression simultaneously adjusted for all *measured* variables (age, gender, tumour size, multifocality, HT, LVI, ETE), which helps control confounding from those covariates (see Table 3 in the article). However, unmeasured factors listed in Q9 were not captured, so residual confounding cannot be ruled out.

Q11. What type of data are collected?
Clinicopathological data, including: Age, gender, tumor size Presence/absence of multifocality, Hashimoto's thyroiditis (HT), lymphovascular invasion (LVI), extrathyroidal extension (ETE) CLNM status (positive/negative)

Q12. Are data values measured or self-reported?
Measured. Data were obtained from medical records, histopathology reports, and imaging studies, not self-reported by patients.

Q13. What potential sources of bias are there?
Selection bias: Only patients who underwent surgery at a single hospital were included. Detection bias: Limitations in ultrasound's sensitivity for detecting CLNM. Retrospective bias: Data quality relies on the accuracy and completeness of past records.

Q14. Is the study exploratory or confirmatory?
Exploratory. Although it uses statistical analysis to identify independent risk factors, the study is not testing pre-specified hypotheses and is looking for associations in existing data.

Q15. Are the statistical hypotheses articulated before the study is carried out, or are they suggested by the study?
They appear to be suggested by the study, not pre-specified. The research aim is broadly defined as identifying associated risk factors for CLNM.

Q16. How are the data analyzed? Is the analysis appropriate for the design?
Univariate and multivariate logistic regression were used to assess associations between risk factors and CLNM. This is an appropriate statistical method for binary outcomes (presence/absence of CLNM) in retrospective cohort studies.

Q17. Is there adequate power? Is the sample size appropriate for the stated aims?

Yes, reasonably adequate. Of 180 patients, 122 experienced the event (CLNM). With 7 candidate predictors in the final model, that yields ≈17 events per variable, comfortably above the usual 10-events-per-parameter rule of thumb. Small or modest effect sizes (e.g. OR ≤ 1.5) could still be missed, but the study was sufficiently powered to detect the large effects it reports (ORs 3–25).

Q18. Does the study adequately address the question(s) it attempts to answer? (Can the question(s) possibly be answered by this study?)
Largely, yes. A retrospective cohort cannot prove causation, but it can estimate associations between readily measured clinicopathological features and CLNM. All key variables were abstracted from surgical pathology, ensuring accurate outcome ascertainment. However, being single-centre and retrospective limits external validity and leaves room for residual confounding.

Q19. In light of your answers to the above, does the evidence support the conclusions?
Within those limitations, the evidence *does* support the authors' main conclusion that multifocality, Hashimoto's thyroiditis, and LVI are independent predictors of CLNM. Each predictor remained significant in multivariate analysis with large effect sizes and non-overlapping confidence intervals (e.g. LVI OR = 25.4, 95% CI 9.4–69.7). The authors appropriately caution that their findings need confirmation in larger, prospective, multi-centre cohorts before influencing guidelines.

General Questions (from moodle):

Q20. Biomedical Background, question, hypothesis The article discusses Papillary thyroid carcinoma (PTC), the most common form of thyroid cancer, which often has a favorable prognosis. A noticeable fact is that central lymph node metastasis (CLNM) is associated with increased risk of local recurrence and worse outcomes of PTC. The main treatment, Prophylactic central neck dissection (PCND) in clinically node-negative (cN0) PTC patients, has mixed effects on patients, due to its potential complications and unclear benefits. The hypothesis of the study is that certain clinicopathological features can independently predict CLNM in PTC, improving decision making regarding PCND adoption.

Q21. Data collected, individuals, variables inclusion/exclusion criteria

- **Initial number of patients:** 202 patients; 22 were excluded for non-primary PTC or other head/neck pathologies.
- **Final Population:** 180 patients with histologically confirmed PTC, treated between 2014 and 2016 at a single hospital in China.
- **Variables collected:**
  - Age, gender
  - Tumor size (with pre-op ultrasound)
  - Multifocality (≥ 2 tumor foci)
  - Hashimoto's thyroiditis (HT)
  - Lymphovascular invasion (LVI)
  - Extrathyroidal extension (ETE)
  - Central lymph node metastasis (CLNM) (outcome variable)
- **Inclusion criteria:** Histologically confirmed, untreated PTC undergoing surgery.
- **Exclusion criteria:** Non-primary PTC, cancers that are not papillary thyroid carcinoma (PTC).

Q22. Carried out analyses, appropriateness to the problem

- Descriptive statistics to summarize demographics and pathology.
- **Chi-squared tests** employed to compare categorical variables with respect to CLNM.
- **Univariate logistic regression** to assess odds ratios (OR) for CLNM.
- **Multivariate logistic regression** to identify independent predictors of CLNM, adjusting for covariates.

These analyses are appropriate given the binary outcome (presence or absence of CLNM). Also, logistic regression is the standard method to evaluate such associations and control for measured confounding variables.

Q23. Other possible analysis

- **Model validation/assessment:** e.g. bootstrapping or cross-validation to evaluate the stability of the multivariate model.
- **Interaction terms:** Testing whether the effect of HT depends on multifocality (or tumour size) by including interaction terms.
- **Stratified analysis:** By age groups or tumour size (e.g. micro-PTC vs. macro-PTC) to explore effect modification.

Q24. Power analysis The article does not report a formal power analysis. A post-hoc check suggests at least 10 events per predictor variable (EPV) were available (122 CLNM events / 7 predictors ≈17 EPV), indicating sufficient power for the main effects.

Q25. Author conclusions and validity Conclusion: According to authors, multifocality, Hashimoto's thyroiditis (HT), and lymphovascular invasion (LVI) are independent predictors of central lymph node metastasis (CLNM) in PTC patients.

- Statistically significant results: Multifocality (OR = 3.436), HT (OR = 10.096), LVI (OR = 25.430) with $p < 0.05$ for all.
- Limitations: small sample, retrospective single-centre design, possible residual confounding, no long-term recurrence or survival endpoints.
- Overall, conclusions are supported by the data but should be interpreted with caution and need external validation.