AZIENDA OSPEDALIERA UNIVERSITARIA PISANA
Università degli Studi di Pisa
"Ospedali Riuniti di Santa Chiara"
Ospedale di rilievo nazionale e di alta specializzazione
Dipartimento di Chirurgia e Medicina Endocrino Metabolica e dei Trapianti
U.O. ENDOCRINOCHIRURGIA Universitaria (cdc **9020**)
Direttore Prof. G. Materazzi
Via Paradisa, 2 – 56124 Cisanello Pisa

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PROTOCOLLO

Titolo dello Studio:	*Impact of **PRO**phylactic **C**entral c**OM**p**A**rtment **N**eck **D**issection for 2-4 cm Papillary Thyroid Carcinoma*
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Promotore	*Azienda Ospedaliero-Universitaria Pisana (AOUP) Via Paradisa 2, Pisa*
Responsabile scientifico	*Materazzi Gabriele, Via Paradisa 2, Pisa, Professore Ordinario*
Sperimentatori coinvolti	*Rossi Leonardo, Via Paradisa 2, Pisa, Assegnista di Ricerca* *Piermarco Papini, Via Paradisa 2, Pisa, Dirigente Medico* *De Palma Andrea, Via Paradisa 2, Pisa, Assegnista di Ricerca* *Ambrosini Carlo Enrico, Via Paradisa 2, Pisa, Dirigente Medico* *Rossella Elisei, Via Paradisa 2, Pisa, Professore Associato* *Antonio Matrone, Via Paradisa 2, Pisa, Ricercatore*
Centri coinvolti:	*U.O. Endocrinochirurgia Universitaria*

Informazioni di Contatto

Nome Contatto Promotore	*Prof. Gabriele Materazzi* *U.O. Endocrinochirurgia Universitaria* *Azienda Ospedaliero-Universitaria Pisana* *gabriele.materazzi@unipi.it*
Nome Contatto per la Dispositivovigilanza	*N.A.*

APPROVAZIONE DEL PROTOCOLLO

Gli Sperimentatori:

- approvano il presente Protocollo;
- dichiarano che lo studio verrà condotto in conformità alle Good Clinical Practice, alla Norma UNI EN ISO 14155:2012 e secondo quanto riportato nel presente protocollo.

_____	_____
Prof. Gabriele Materazzi	Data
_____	_____
Dott. Leonardo Rossi	Data
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Dott. Piermarco Papini	Data
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Dott. Andrea De Palma	Data
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Dott. Carlo Enrico Ambrosini	Data
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Prof. Rossella Elisei	Data
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Dott. Antonio Matrone	Data

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Background

Papillary thyroid carcinoma (PTC) represents the most common thyroid malignancy, accounting for approximately 80% of all thyroid cancer [1, 2]. Surgical intervention remains the gold standard treatment modality for PTC, aimed to achieving complete resection of the tumor while minimizing the risk of recurrence and preserving vital anatomical structures [3]. The prognosis following surgical therapy is favorable, with the 10-year survival rate having exceeded 90% in recent decades [4, 5].

Although central compartment lymph node dissection (CCND) is mandatory in case of clinical central compartment lymph node involvement (cN1), prophylactic CCND (pCCND) (CCND in patients without preoperative clinical evidence of lymph node involvement) is matter of debate [6]. Currently, up to 80% of cases present involvement of regional lymph node micrometastases [7, 8], which poses a significant challenge for the treatment of cN0 patients due to the uncertain clinical impact [9, 10]. Supporters of pCCND claimed that it has potential benefits that can improve the accuracy of staging, decrease postoperative serum thyroglobulin levels, enable better selection of patients for radioiodine treatment, and decrease the recurrence rate [11]. Nonetheless, the utility of pCCND in cN0 PTC remains a contentious issue, with opponents citing concerns over increased surgical morbidity and the lack of definitive evidence demonstrating significant oncological benefits [3, 12].

The 2015 ATA guidelines reported that the value of routine pCCND for cN0 disease remains unclear, leaving the debate open [3]. The guidelines recommend taking risk stratification into account to determine the most appropriate treatment; nonetheless, several prognostic factors are often not available pre-operatively (e.g. microscopic multifocality or extrathyroidal extension, central neck nodal status, aggressive histologic variant). Moreover, the recently published 2025 ATA guidelines still consider pCCND appropriate in selected cases, although it is not recommended for small, non-invasive papillary thyroid carcinomas (PTCs). In addition, the updated guidelines further strengthen the role of thyroid lobectomy (TL) in the management of cN0 PTCs up to 4 cm in size; however, the role of pCCND in this clinical setting remains debated [13].

Currently, both TT ±pCCND and TL ± pCCND are accepted by the scientific community for the management of cN0 PTC, in properly selected cases.

In the absence of consensus, rigorous scientific inquiry through prospective researches becomes imperative to elucidate the long-term implications of pCCND in cN0 PTC. We previously published a study which documented no oncologic advantages of pCCND over TT alone [13]. Nonetheless, the mean tumor size of enrolled PTC patients was very small (< 2 cm); besides, international guidelines published after that paper publication changed the treatment strategy for PTC [3], recommending more conservative treatments in selected cases.

We aim to evaluate the advantages and disadvantages of pCCND and the outcomes of cN0 PTC patients treated with TT alone or in combination with pCCND (TT + pCCND), as well as those treated with TL with or without ipsilateral pCCND, focusing on tumors measuring between 2 and 4 cm.**Objectives**

This study aims to evaluate the advantages and disadvantages of pCCND and the outcomes (either oncologic and surgical) of cN0 PTC patients who have been treated either with TT or TL alone or with in association to pCCND.

Ethical Considerations

All procedures performed in this study are in accordance with the ethical standards of the 1964 Helsinki Declaration and its subsequent amendments.

Informed consent

Patients will be thoroughly informed regarding the study during the surgical visit, and the informed consent will be signed concurrently or at the time of admission. Pediatric patients will not be enrolled. In the case of patients unable to express informed consent, such consent will be obtained from legal guardians. Emergency patients will not be enrolled.

Study population and emergency treatment

The study population will include patients affected by PTC sized between 2 and 4 cm and without clinical suspicious lymph node metastasis (cN0) with an indication to surgery of TT or TL. The surgical operations which will be compared adhere to the standard clinical practice and are highly standardized. No emergency circumstances are expected with the exception of those conventionally associated to thyroidectomy.

Previous Experience

A similar study was already conducted at our Institution between 2008 and 2010 [14]. Nonetheless, the Authors mainly enrolled small-sized PTCs which are well-known to harbor an excellent prognosis. We aim to assess the impact of pCCND (bilateral/ipsilateral) on patients with 2-4 cm PTC cN0.

Clinical Research Setting

Study Design

This is a national randomized prospective study. Enrolled patients will be dived in two groups on the basis of surgical indication: TT group or TL group. Moreover, they will be allocated to two different subgroups on the basis of randomization: control group (Group A-TT or Group A-TL; TT/TL) and intervention group (Group B-TT or Group B-TL; TT/TL + pCCND [bilateral or ipsilateral, respectively]). All

procedures are standardized and used for the treatment of PCT and are accepted by the latest international ATA guidelines [13]. The study has no financial purpose.

PHASE 1	PHASE 2	PHASE 3	PHASE 4
Patient selection and randomization	Informed consent acquisition and enrollment	Data collection from medical records and eventual tests or imaging (according to clinical practice for PTC management)	Data analysis and eventual publication on indexed journals

DATA FLOW – Impact of PROphylactic Central cOMpArtment Neck Dissection for 2-4 cm Papillary Thyroid Carcinoma

Enrollment	Data Collection	Data Processing	Data Analysis	Data Storage
Endocrine Surgery Unit - patient selection according to inclusion / exclusion criteria - randomization - informed consent acquisition - enrollment	**Endocrine Surgery Unit / Endocrinology Unit** Data collection and CRF data entry	**Endocrine Surgery Unit / Endocrinology Unit** All data will be pseudonymized by assigning an alphanumeric code	**Endocrine Surgery Unit / Endocrinology Unit** The data collected in the CRF will be jointly analyzed by the two Units that manage the patients for the disease under study as part of clinical practice	**Endocrine Surgery Unit / Endocrinology Unit** Storage of the informed consent forms, data collection forms, and all study documents in paper format at the Endocrine Surgery Unit (AOUP) for at least 7 years after the study's conclusion The paper documents will be kept in a locked cabinet at the Endocrine Surgery Unit, while the electronic format of the documents will be stored on a password-protected PC with access restricted to the PI's collaborators for the study. The PC does not have internet access

Primary and Secondary Objectives

The primary objective is to assess the impact of pCCND (bilateral for TT or only ipsilateral for TL) in cN0 PTC patients in terms of oncological outcomes. Secondary objective is to assess the impact of pCCND in cN0 PTC patients in terms of surgical complications and disease staging.

Endpoints

The primary endpoints of the study are the persistent / recurrent disease after 1, 3, 5 and 10 years of follow-up and the overall survival. The secondary endpoints are the rate of surgical complications and the impact of pCCND in the staging of the disease.

Measured Variables

Data collection will be carried out using the database. The workbook includes the following data:

- Patient ID
- Date of Birth
- Gender (M, F)
- Date of Surgical Operation
- US-estimated thyroid volume (in ml)
- Type of surgical Operation (TT/TL ± pCCND [bilateral or ipsilateral, respectively])
- Duration of Surgical Operation (in minutes)
- Serum albumin-corrected calcium on the first day post-operation: CA-DAY 1 (mg/dl)
- Serum PTH on the first day post-operation: PTH-DAY 1 (ng/L)
- Number of autotransplanted parathyroids (0, 1, 2, 3, 4)
- Post-operative hospital stay (days)
- Calcium supplementation post-operation (indicate grams per day)
- Duration of post-operative calcium therapy (days)
- Calcitriol supplementation post-operation (indicate mcg per day)
- Duration of post-operative calcitriol therapy (days)
- Transient hypoparathyroidism (YES, NO)
- Permanent hypoparathyroidism (YES, NO)
- Number of parathyroids on the surgical specimen
- Transient RLN palsy (YES, NO)
- Permanent RLN palsy (YES, NO)
- Bleeding (YES, NO, HEMATOMA)
- Wound infection (YES, NO)

- Perioperative mortality (YES, NO)
- PTC histologic variant
- Presence of extrathyroidal extension (YES, NO)
- Type of extrathyroidal extension (MINIMAL, GROSS)
- Multifocality (YES, NO)
- Bilaterality (YES, NO)
- Tumor Size (in mm)
- Presence of thyroiditis (YES, NO)
- Number of lymph nodes resected
- Number of metastatic lymph nodes
- Number of micrometastasis
- Number of macrometastasis
- Maximum metastatic lymph node size (in mm)
- TNM stage [15]
- Response to therapy (Excellent; biochemical incomplete response; structural incomplete response; indeterminate response)
- Recurrence (YES, NO)
- Further surgery required (YES, NO)
- Serum albumin-corrected calcium on the last follow-up: LASTFU-CA (mg/dl)
- Serum PTH at last follow-up: LASTFU-PTH (ng/L)
- Serum T.S.H. value at 1-year (in μU/mL)
- Serum Thyroglobulin (Tg) level at 1-year (in ng/mL)
- Presence of serum Ab-Tg at 1-year (YES, NO)
- Serum Ab-Tg at 1-year (in UI/mL)
- Serum T.S.H. value at 3-year (in μU/mL)
- Serum Thyroglobulin (Tg) level at 3-year (in ng/mL)
- Presence of serum Ab-Tg at 3-year (YES, NO)
- Serum Ab-Tg at 3-year (in UI/mL)
- Serum T.S.H. value at 5-year (in μU/mL)
- Serum Thyroglobulin (Tg) level at 5-year (in ng/mL)
- Presence of serum Ab-Tg at 5-year (YES, NO)
- Serum Ab-Tg at 5-year (in UI/mL)
- Serum T.S.H. value at 10-year (in μU/mL)
- Serum Thyroglobulin (Tg) level at 10-year (in ng/mL)
- Presence of serum Ab-Tg at 10-year (YES, NO)
- Serum Ab-Tg at 10-year (in UI/mL)
- Duration of follow-up (in months)

- Death (YES, NO)
- Date of death
- Cause of death
- Any additional notes

Systematic errors - bias

All procedures will be performed on patients with similar characteristics based on inclusion criteria. Randomization will mitigate selection bias. The surgical technique are thoroughly standardized. All procedures will be carried out by experienced surgeons (number of thyroidectomies performed per year > 100). Documentation related to the study and databases will be checked and preserved by the involved investigators and the scientific supervisor. In order to ensure an accurate assessment of the impact of pCCND, patients undergoing postoperative radioactive iodine therapy will be excluded.

Patients Selection

Inclusion criteria:

1. PTC documented by fine needle aspiration cytology (FNAC) (TIR 4 or TIR 5 according to the Italian consensus for the classification and reporting of thyroid cytology [16]);
2. no pre-operative evidence of lymph node metastases (cN0) at palpation and neck ultrasound (US);
3. no clinical evidence of distant metastasis at diagnosis;
4. age ≥ 18 years;
5. signing informed consent.

Exclusion criteria:

1. histotypes other than PTC;
2. evidence of lymph node metastases during surgery even if not previously diagnosed;
3. presence of distant metastasis;
4. refusal to sign informed consent.

Exit criteria:

1. withdrawal of informed consent;
2. post-operative radioactive iodine therapy.

Sample Size

A sample size calculation has been performed to provide the number of patients necessary to evaluate the difference in terms of persistence rate between the two Groups. Using an alpha of 0.05, a noninferiority margin of 15%, an expected clinical remission rate of 85% and a power of 90%, it was

determined that a sample size of 98 patients per treatment arm would be sufficient to evaluate a possible difference between the two surgical operations (TT/TL ± pCCND [bilateral or ipsilateral, respectively]). A simple randomization method will be used for patients allocation. It has been estimated an enrollment time of two years which may be amended on the basis of the acceptance to participate rate.

Enrollment

The patient will be considered enrolled after the informed consent has been signed (after evaluation of inclusion and exclusion criteria) and the histological examination has confirmed PTC.

Study Duration

The enrollment will last about 2 years. Patients will be followed for 10 years. The total duration of the study is 12 years

Surgical Procedure and Follow-up

Thyroidectomy will be performed with the patient in the supine position with the neck hyperextended. A 3 to 6 cm transverse cervicotomy, two fingers above the sternal notch, will be performed, and the midline will be opened. After the inferior laryngeal nerve and parathyroids are visualized, the TL will be achieved. In case of TT, the same surgical steps will be performed on the contralateral side.

When performed, pCCND will aim at removing the nodes of Level VI, which will be reported to contain the thyroid gland and the adjacent nodes bordered superiorly by the hyoid bone, inferiorly by the brachiocephalic artery, and laterally by the carotid sheaths [3]. In case of TL, only ipsilateral CC lymph nodes will be harvested; in case of TT, either ipsilateral and contralateral lymph nodes will be harvested.

The surgical treatment will be performed by experienced surgeons who will belong to the Endocrine Surgery Unit of the University Hospital of Pisa. They will also be in charge of randomizing the patients into the two groups. The study follow-up will adhere to the standard follow-up program of our Institution. Every 12 months, patients will undergo physical examination, neck ultrasound (US), blood tests (serum TSH, serum Tg, serum anti-Tg antibodies), diagnostic whole-body scan (WBS). Eventual further diagnostic examinations (e.g. CT-scan) will be performed according to the clinical findings

Known or predictable factors that may compromise outcomes and interpretation of results

None

Withdrawal of subjects and modifications to the intervention

Subjects who require discontinuation of the clinical investigation will be excluded. These patients will adhere standard follow-up according to the indications of their referring endocrinologist (which doesn't differ from that of the present study).

Early conclusion or suspension of the study

In case of early suspension, patients will adhere standard follow-up according to the indications of their referring endocrinologist (which doesn't differ from that of the present study).

Quality assurance, control procedures, data management, and documentation preservation

The documentation related to the study and the databases will be checked and preserved by the Principal investigators and by the investigators participating in the study team.

Deviation From the Present Clinical Assessment

The Ethical Committee will be promptly informed regarding any deviation from the present protocol.

Adverse Events

There are no expected adverse events. Potential surgical complications include those conventionally associated to standard thyroidectomy: transient / permanent recurrent laryngeal nerve injury; transient / permanent hypoparathyroidism; bleeding which requires reoperation; cervical hematoma; wound infection. There are no unconventional complications potentially associated to the present study. Both the surgery and the post-operative management do not differ from clinical practice.

Amendments to the clinical evaluation plan

In case of changes to the clinical evaluation plan, these will be promptly communicated to the relevant ethics committee for approval.

Early termination and suspension of the clinical evaluation

There is no planned interruption or early termination of the study.

Study Design

Study Timeline

- Screening and Case Evaluation: examination of the patient and thyroid disease.
- Assessment of adherence to inclusion criteria.
- Explanation of study details to the patient
- Signing of the informed consent
- Randomization and Assignment: assignment to experimental or control group.
    - Randomization through opening a sealed envelope with "pCCND YES" or "pCCND NO" (1:1 ratio).
-
- Objective and Endpoint Evaluation:
    - Data collection (pre-operative; intra-operative; post-operative)
    - Follow-up: data collection according to the scheduled follow-up (visits or phone contacts).

Sample Size

A sample size calculation has been performed to provide the number of patients necessary to evaluate the difference in terms of persistence rate between the two Groups in which patients will be stratified (TT/TL vs. TT/TL + pCCND [bilateral or ipsilateral, respectively]). Using an alpha of 0.05, a noninferiority margin of 15%, an expected clinical remission rate of 85% and a power of 90%, it has been determined that a sample size of 98 patients per treatment arm would be sufficient to evaluate a possible difference between the two Groups in which patients will be stratified. A simple randomization method will be used for patients allocation. It has been estimated an enrollment time of two years which may be amended on the basis of the acceptance to participate rate.

Screening Phase

- Examination of the patient and evaluation of adherence to inclusion criteria
- Enrollment Procedure
- Explanation of the study and informed consent
- Signing of the informed consent
- Randomization

Intervention Assignment

Randomization will performed by opening a sealed envelope with "pCCND YES" or "pCCND NO" (1:1 ratio).

Masking (Blinding)

The study does not involve blinding.

Other Study Procedures

Procedures (either considering surgical operation and follow-up) will follow conventional clinical practice. Researchers involved will manage data collection and annotation.

Data Management

Data collection in a database pseudonymized with ad ID. Data manager: Principal Investigator and researches involved.

Upon enrollment, each patient will be assigned a unique identification code/number. Data management will take place by completing the appropriate form (see CRF). The data collected will be strictly anonymous and the participant will only be identified with the pseudonymized code.

Storage of the informed consents, data collection forms and all study documents in paper format at the Endocrine Surgery Unit (AOUP) for at least 7 years from the conclusion of the study.

Paper documents will be kept in a locked cabinet at the Endocrine Surgery Unit while the electronic format of the documents will be maintained on a PC whose entry is protected by PW and whose access is limited to the collaborators of the PI for the study.

Protocol Deviations

No deviations are planned. In case of changes to the clinical evaluation plan, these will be promptly communicated to the relevant ethics committee for approval.

Statistical Analysis

The target sample size is 196 patients for each type of surgery (TT or TL ± pCCND [bilateral or ipsilateral, respectively]) with a power of 90% as reported above. Continuous quantitative data will be expressed as mean ± standard deviation and compared using Student's t test or Mann Whitney test when appropriate. Categorical qualitative data will be expressed as frequencies and percentages and compared using χ^2 test (or Fisher's exact test). Logistic regression analysis will be used to identify factors negatively associate to the "free of disease" outcome.

Overall Survival (OS) will be calculated as the difference between the date of diagnosis and the date of death. Survival curves will be estimated by the Kaplan-Meier method. Survival curves will be compared with the log-rank test.

Differences between groups will be considered significant when $p < 0.05$. All analyzes will be carried out with SPSS v.28 technology (IBM Corp., Armonk, NY, USA). Further statistical analysis will be

conducted on the basis of the results.

Additional Analyses

Further statistical analysis will be conducted on the basis of the results. Moreover, identification of possible subgroups will be performed. Comparison will follow the same statistical principles.

Administrative aspects

Study Funding

This study does not involve funding.

Insurance Coverage

Given the extremely low risk of this interventional study, which compares two standardized surgeries which adhere to the clinical practice and recommended by latest ATA guidelines [13], there is no need for insurance coverage to conduct the study.

Revision

All the researchers involved in the study, under the responsibility of the principal investigator, will perform a monthly check of the entered data and documents.

Protocol Amendments

Substantial protocol changes (e.g., changes to eligibility criteria, analysis, outcomes..) will be communicated to the involved parties (trial participants, ethics committee, etc.).

Ethics

All procedures performed in this study will be in accordance with the ethical standards of the 1964 Helsinki Declaration and its subsequent amendments.

Informed Consent

Patients will be informed about the study during the surgical visit, and the informed consent will be signed concurrently or at the time of admission. Pediatric patients will not be enrolled. In the case of patients unable to provide informed consent, consent will be obtained from legal guardians. Patients in emergency situations will not be enrolled.

Confidentiality

The personnel involved in the study commit to treating with absolute confidentiality the information regarding the personal data of eligible subjects, both before, during, and after the trial. All

information collected will be handled with utmost care and will only be accessible to authorized personnel involved in the study. This information will be used exclusively for the purposes of the study and will not be disclosed to third parties without the explicit consent of the participating subjects. Every member of the study personnel is required to strictly adhere to privacy regulations and personal data security measures to ensure maximum confidentiality and protection of participant data.

Conflict of interest

The involved researchers declare no conflict of interests.

Responsibilities and publication policies

The role of the sponsor and investigators

All involved researchers will contribute to the study design, data collection, management and interpretation, and manuscript writing. Authorship will be acknowledge to all the involved researchers. The principal Investigator will supervise all the study conduction. No sponsor will be involved.

Data Ownership

The data ownership belongs to the study promoter. The study personnel will have access to the final data.

Publication policies

The study will provide one or more scientific articles. Given the significant debate around the issue, the above-mentioned study will be of considerable interest to the literature and have high publishability. The articles will be submitted to journals with impact factors, indexed on PubMed, and subject to peer review.

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