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Experience of prophylactic lymphodissections for papillary thyroid carcinoma according to hospital registry data

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Abstract. Prophylactic central lymph node dissection (PCLND) of the neck for papillary thyroid carcinomas (PTC) is one of the widely discussed issues, on which there is still no consensus. Most researchers discuss the range of indications for PCLND, recognizing that along with increased oncologic radicality, it increases the risk of postoperative hypoparathyroidism and phonation disorders. **The aim.** To evaluate the outcomes of PCLND performance in PTC according to hospital registry data. **Material and methods.** To assess the effectiveness of PCLND, all surgeries performed between 2015 and 2023 in patients with PTC were analyzed. All cases of cN0 and thyroidectomy (TE) only and TE+PCLND (1781 and 801 cases, respectively) were selected. Reoperations for disease progression were analyzed by comparing groups using Pearson's χ^2 (mean follow-up 1.9 years). To analyze postoperative changes in phonation, a patient questionnaire was used. All cases of TE and TE+PCLND (1785 questions) were analyzed, and the comparison was also performed using Pearson's χ^2 method. To assess the level of ionized calcium the day after surgery, the means were compared by t-test method and Fisher's F-test (550 patients in total). **Results.** When analyzing reoperations in the entire group with a mean follow-up period of 1.9 years, no statistically significant difference was found between TE and TE+PCLND ($p>0.05$). Limiting the group to a follow-up period from 1 to 5 years (mean follow-up period 2.6 years) does not change the situation: 2.1% of reoperations for TE and 3% for TE+PCLND ($p>0.05$). According to the questionnaire data on phonation changes (total 1785 questions), it was revealed that after only TE, 55.2% of patients had complaints, whereas after TE+PCLND they were 60.2% ($p<0.05$). If we do not take into account the minimal complaint of minor voice hoarseness, the statistical significance of the differences becomes even more confident: $p<0.001$ (13.7% vs. 20.4%). Postoperative ionized calcium levels also had statistically significant differences between groups (for TE mean 1.15; for TE+PCLND mean 1.13). Comparison of means by the t-test method yielded $p<0.001$, and by Fisher's test $p<0.05$. **Conclusions:** according to our hospital registry, performing PCLND for PTC does not result in a reduction in the percentage of reoperation, but is associated with a higher percentage of phonation complaints and statistically significantly lower ionized calcium levels in the first day after surgery.

Keywords: thyroid, papillary carcinoma, thyroidectomy, central neck dissection, loco-regional recurrences, phonation abnormalities, ionized calcium levels.

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Indications for PCLND of the neck in PTC are one of the widely discussed issues, on which there is still no consensus. Most researchers discuss the range of indications for PCLND, recognizing that along with increased oncologic radicality, it increases the risk of postoperative hypoparathyroidism and functional voice disorders. Thus, the American Association of Endocrine Surgeons 2020 guidelines note that young patients, males, and large tumor size are more likely to have metastases, so PCLND is more likely to be justified [1]. American Thyroid Association guidelines and European experts tend to define indications for PCLND in patients with T3 and T4 categories, while T1 and T2 categories are suggested to be considered as not requiring it in case of cN0 [2, 3]. This view has been founded (and supported) by quite a wide range of authors [4-7]. According to H.N. Xuan et al., the incidence of hidden metastases in the central compartment of the neck in cN0 was 39.9%. The authors consider, that tumor size by ultrasound, young age (<29 years) and tumor stage increased the likelihood of central lymph node metastasis (CLNM). Hence, the authors conclude that PCLND should be considered in patients with risk factors such as young age or large tumor [8]. Some authors do not list young age as factors but add extrathyroid spread [4]. In a similar vein, it is concluded that performing PCLND for PTC cN0 is justified only in high-risk patients [9, 10]. A study with a mean follow-up duration of 107 months concluded that PCLND does not lead to a statistically significant reduction in lymph node recurrence among patients with non-invasive cN0 PTC [11].

A large meta-analysis conducted in the USA and published in 2023 noted that the latent metastasis rate in the central compartment of the neck ranges from 30.3% to 61.2% depending on the size of the primary focus. This allowed the authors to conclude that at least ipsilateral PCLND may be warranted in all patients with PTC, including for accurate differentiation of process staging. The article also suggested considering PCLND for patients with high-risk genetic mutations, such as BRAF V600E [12].

Researchers from Vietnam noted that PCLND increases the relapse-free period for children. However, as the authors note, there was no statistically significant difference in complications such as transient hypocalcemia and transient laryngeal nerve injury [13]. Similar conclusions in adult patients are reached by Y. Wang et al. from China, noting that TE+PCLND (compared to only TE), was more effective in reducing local recurrence without increasing the risk of complications, except for transient hypocalcemia and transient hypoparathyroidism. Nevertheless, the authors believe that PCLND should be recommended for patients with cN0 PTC [14]. Chinese scientists based on their research concluded that although PCLND reduces LRR in patients with PTC, but it is accompanied by an increased incidence of postoperative hypocalcemia [15].

But the literature also presents different views on this problem. According to K.M. Alsubaie et al. no significant difference was found between TE plus PCLND and only TE in terms of both the incidence of LRR and the incidence of postoperative complications [16]. As justification for this, we can cite a study by Korean authors who claim that according to their data occult CLNM rarely occur in patients with PTC, why their prophylactic excision is not necessary [17].

A very categorical point of view was expressed by American scientists who concluded on the basis of their data that PCLND was not associated with improved oncologic outcomes during the short-term follow-up period (38±3 months), but led to an increase in postoperative complications. The authors conclude that PCLND should not be routinely performed for cN0 patients with PTC [18]. Similar conclusions were reached by N. Chereau et al. (France) who noted that PCLND in PTC does not reduce LRR and is associated with a twofold increase in the incidence of transient hypoparathyroidism [19]. According to C. Dobrinja et al., the overall complication rate was significantly higher in the group of patients who underwent PCLND (39.2% vs. 17.8%, p = 0.0006). The results of this study do not support the feasibility of routine use of PCLND in the treatment of patients with cN0 PTC [20]. Similarly, PCLND is associated with higher rates of postoperative complications such as laryngeal nerve injury and hypoparathyroidism, with unclear oncologic benefits [5].

J. Yang et al. came to interesting conclusions in a meta-analysis of eighteen studies involving 5346 patients. They noted that for patients with PTC, performing TE with PCLND showed a significantly lower incidence of LRR with a higher incidence of temporary hypoparathyroidism (HPT) in Europe, America, and Australia; however, it showed no significant difference in reducing the incidence

of LRR with a significant increase in the incidence of temporary and permanent HPT in China [21].

Some authors advocate for the wider use of ipsilateral central dissection compared to bilateral dissection, noting that it has the advantage (over bilateral dissection) not only in reducing the incidence of some complications, but also in having a similar recurrence rate compared to bilateral PCLND [22, 23].

There is another question regarding the rationale for performing PCLND, namely in the presence of a metastatic lesion in the subgular lymphatic collector. To answer this question, V. Harries et al. from the USA conducted a focused study and concluded that some patients with cN1b PTC may not require or benefit from PCLND [24]. A similar conclusion is contained in the article of Israeli scientists [25].

While reviewing the literature on different views on PCLND performance, we also came across the work of researchers from Colombia who decided to assess the methodological quality of systematic reviews evaluating the efficacy of PCLND in combination with TE to reduce LRR in patients with PTC [26]. The authors noted that the published reviews were of critically low methodological quality and concluded that the results and recommendations based on these studies should be used with caution.

One of the modern trends in addressing the issue of indications for PCLND is the development of algorithms based on multifactorial analysis, but so far such developments have not been widely used in clinics and mainly remain the subject of scientific research [27, 28]. It should be noted that they are also based primarily on risk factors, i.e. they actually reflect the same factors (age, invasiveness, size, and other tumor characteristics), only presenting a more convenient and flexible mechanism for their simultaneous consideration. Nevertheless, even in the presence of very effective mathematical models of prognosis, practice remains the main criterion. At the same time, our Ukrainian region represents a very unique cohort due to the fact that it experienced the consequences of the Chornobyl disaster of 1986, the consequences of which continue to be studied. All these prerequisites justified the need for the present study.

The aim – to evaluate the outcomes of PCLND performance in PTC according to hospital registry data.

Material and methods

The data of the hospital registry served as the material of the present retrospective study. First, all surgeries from 2015-2023 in patients with a pathohistologic diagnosis of PTC, TE and TE+PCLND surgery types, and cN0 were selected. Of the 2582 selected patients, there were 1781 cases of only TE and 801 cases of TE+PCLND. The mean age for the entire group was 47.9 (TE, 49.0; TE+PCLND, 45.7). Females were 82.8% of the group, reflecting the well-known sex ratio in thyroid disease. We analyzed reoperations (38 in total) for disease sequelae by comparing groups using the Pearson's χ^2 method.

To analyze postoperative changes in vocal function, a patient questionnaire was used, which was implemented from the end of 2022. The questionnaire we developed included questions about postoperative complaints and was filled out by the patients themselves. To facilitate both filling out and analyzing the data, items were provided in which the patient only needed to mark the items corresponding to their condition. In particular, the following ones concerning changes in vocal function were taken into account in this study:

- minor hoarseness of voice,
- significant voice hoarseness,
- cannot pronounce the letter «I» audibly,
- cannot cough effectively,
- choking when drinking.

All cases of TE and TE+PCLND were analyzed, a total of 1785 questionnaires. It should be noted that the questionnaires were used in full, since we were talking about the first days after surgery and this analysis was not tied to the fact of recurrence in the future. Thus, the questionnaires included patients operated on in 2024. The comparison was performed using the Pearson's χ^2 method.

To assess ionized calcium levels the day after surgery, the means by t-test method and using Fisher's F-test were compared (550 patients were analyzed). All cases with hospital registry data on ionized calcium levels after TE and TE+PCLND were included in the study. Randomization was not performed because all cases identified in the hospital registry during the specified period were included in the groups (group 1), all questionnaires were included in group 2, and all cases with postoperative ionized calcium in group 3.

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The study was conducted in accordance with the basic principles of bioethics of the Council of Europe Convention on Human Rights and Biomedicine (April 4, 1997), the World Health Association Declaration of Helsinki for the Ethical Principles of Medical Research Involving Human Subjects (1964-2013). The study protocol was approved by the Local Ethics Committee for all participants. The Commission on Biomedical Ethics of the State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine» did not find any violations of moral and legal standards during the study.

Results

To evaluate the efficacy of PCLND, we compared the reoperation rate for LRR in the TE and TE+PCLND groups, which is presented in **Table 1**.

Table 1. Comparison of reoperations for LRR in TE and TE+PCLND groups, n (%)

Type of surgery	No recurrence	Surgery for LRR	Total
TE	1757 (98.7)	24 (1.3)	1781 (100.0)
TE+PCLND	787 (98.3)	14 (1.7)	801 (100.0)
Total	2544 (98.5)	38 (1.5)	2582 (100.0)

In the comparison, the value of χ^2 was 0.6, which corresponds to $p<0.9$. A similar result was obtained when calculated with Yate's correction for continuity (Yate's correction: $\chi^2=0.4$ and $p<0.9$), and Likelihood correction ($\chi^2=0.6$ ta $p<0.9$). The mean follow-up period in this group was 1.9 years.

Taking into account that some of the reoperations in the group were performed in the first year, and therefore could be the result of insufficient preoperative identification, we performed a similar comparison for all surgeries with a reoperation time of more than a year from the primary operation (**Table 2**). The mean follow-up time in this group was 2.6 years.

Table 2. Comparison of reoperations at more than one year for LRR in TE and TE+PCLND groups, n (%)

Type of surgery	No recurrence	Surgery for LRR	Total
TE	936 (97.9)	20 (2.1)	956 (100.0)
TE+PCLND	384 (97.0)	12 (3.0)	396 (100.0)
Total	1320(97.6)	32(2.4)	1352(100.0)

The results obtained were similar and showed no statistically significant difference between the groups. Thus, the value of χ^2 was 1.0, which corresponds to $p<0.9$. When calculated with Yates's correction for continuity (Yate's correction: $\chi^2=0.7$ and $p<0.9$), and Likelihood correction ($\chi^2=1.0$ ta $p<0.9$), no statistically significant difference was also found.

To assess changes in phonation after TE and TE+PCLND, a questionnaire was used, which has been implemented since the end of 2022 and is administered the day after surgery. There were 1785 questionnaires corresponding to the types of surgery. Comparisons were made between the groups without any complaints of phonation changes and those with at least one complaint (**Table 3**).

Table 3. Comparison of TE and TE+PCLND groups if there is any complaints of phonation change, n (%)

Type of surgery	No complaints	At least one complaint	Total
TE	551 (44.8)	679 (55.2)	1230 (100.0)
TE+PCLND	221 (39.8)	334 (60.2)	555 (100.0)
Total	772(43.2)	1013(56.8)	1785(100.0)

The differences between the groups were found to be statistically significant, $\chi^2=3.8$ ($p<0.05$) and remained the same when calculated with Likelihood correction ($\chi^2=3.9$ and $p<0.05$). However, no statistically significant difference was obtained when calculated with Yate's correction ($\chi^2=3.6$ and $p<0.1$).

Given that the most common complaint is minor voice hoarseness, we further compared the combined group with no complaints and only minor voice hoarseness with the group with at least one of the other complaints (**Table 4**).

Table 4. Comparison of TE and TE+PCLND groups for absence of complaints and minimal with presence of all other phonation change complaints, n (%)

Type of surgery	No complaints + slight hoarseness	At least one other complaint	Total
TE	1062 (86.3)	168 (13.7)	1230 (100.0)
TE+PCLND	442 (79.6)	113 (20.4)	555 (100.0)
Total	1504(84.3)	281(15.7)	1785(100.0)

A significant statistical significance of the differences was found when comparing such groups:

χ^2=12.9 and p<0.001, which is maintained when calculated with Yate's correction (χ^2=12.4 and p<0.001), and Likelihood correction (χ^2=12.5 and p<0.001).

Measurement of ionized calcium levels the day after surgery was performed in 550 patients. Q-test comparisons revealed one outlier: a value of 0.77 in the TE+PCLND group. This value was removed, which did not affect the statistical significance of the differences between the groups **(Table 5)**.

Table 5. Comparison of ionized calcium levels after TE and TE+PCLND

Indicator	TE	TE+PCLND
N	338	211
Minimum	0.89	0.86
Maximum	1.35	1.35
Arithmetic mean	1.151	1.129
The median	1.16	1.14
Dispersion	0.007	0.008
Standard deviation	0.082	0.092
Standard error	0.004	0.006
The coefficient of variation	7.1%	8.1%
Asymmetry	0.416	0.495
Excess	0.394	0.188

When assessing the significance of differences by t-test method, the coefficient was 3.98 and p<0.001. Calculation by Fisher's F-test gave a result of 1.255 and p<0.05. These results indicate that when TE+PCLND are performed, the level of ionized calcium the day after surgery is statistically significantly lower than when TE alone is performed, although in absolute numbers the mean values differ only by 0.032.

Discussion

In the introduction, we reviewed the available publications, which reveal the breadth of available opinions from categorical denial of the efficacy of PCLND to its active proponents. Our comparison of TE and TE+PCLND showed no statistically significant differences in the number of LRR, which coincides with the opinion of several authors [18, 19].

Although the postoperative follow-up period in our study is not long (the mean was 2.6 years, if we exclude recurrences in the first year of follow-up), similar results were also obtained for longer periods [11]. At the same time, it is impossible to ignore the reports about the high frequency of detection of hidden metastases when performing PCLND [12, 29], which form the basis of recommendations for their wide implementation.

The question arises: where is the source of such opposing opinions? All these different approaches are based on real data, often numerous and even extensive meta-analyses. Of course, there may be some discrepancies due to the specifics of the studies, from the thoroughness of the histologic examination to the specifics of group selection, since clinical groups can never be completely identical for comparison. However, the differences in opinions are so cardinal and numerous that they cannot be attributed only to differences in the peculiarities of research. In our opinion, there are several reasons for this. First of all, let's pay attention to the fact that despite the differences in estimates and statistical significance of the results, among both supporters and opponents of PCLND, there is still a gap between the frequency of detection of hidden metastases in the central compartment in PCLND and the number of recorded recurrences.

Whereas the rate of detection of hidden metastases is in the tens of percent reaching up to 60% according to some data [12], the rate of recurrence detection in the condition of not performing PCLND varies in clearly smaller ranges, not always reaching even 10%. If we take as a basis that any latent metastasis must necessarily appear as a significant focus, then sooner or later it will be detected and recorded as a LRR. However, even the longest observation periods do not give comparable values. At the same time, it has long been known that, for example, the detection of occult carcinomas in autopsies of those who died from other causes is quite high and amounts to about 10% and even more percent according to different data. One study, for example, indicated 35.6% [30]. On the other hand, reports on the results of clinical follow-up without surgery for small PTC are increasingly common. In this case, the authors claim that observation provides a safe alternative in properly selected patients with low-risk PTC [31].

Putting these data into a single logical chain, we can conclude that a part of the detected latent metastases in PCLND apparently has no development, which may explain the discrepancy in the percentage of detection and cases of clinically sig-

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nificant LRR. Another explanation, in our opinion, may be the fact that some patients undergo radioiodotherapy, which can affect such microscopic foci and successfully destroy them.

In addition, we would like to point out that in our study the percentage of reoperations in only TE was even lower (2.1%) than in PCLND (3.0%), although not statistically significant. It would seem that this is a paradoxical result, because according to the logic of our impact, performing PCLND should lead only to a decrease in the number of recurrences, and therefore in reoperations. This can be partially explained by the fact that our study did not have a very long follow-up period, but we allow for another factor. The fact is that in this study, surgery with any volume of lymphodissection was considered as PCLND, and even 1-2 lymph nodes detected by histologic examination allowed to classify the case into the PCLND group.

At the same time, PCLND is not mandatory in our clinic and its performance depends on the surgeon's assessment of each specific situation. It follows that the higher percentage of recurrences in TE+PCLND may be due to the fact that this volume was more often chosen by surgeons for more significant lesions, which, of course, is also reflected in the frequency of LRR. It should also be noted that in some cases the LRR concerned not the central group of lymph nodes of the neck, but the southeastern lymph nodes. This, in our opinion, is another confirmation of the fact that not always PCLND is justified, as there were cases when the continuation of the disease occurred after TE without PCLND. Other researchers also pay attention to the fact of the possibility of N1b metastases in the absence of them in the central compartment [24].

But the main caveat to recommending widespread implementation of PCLND is, of course, the risk of complications such as vocal dysfunction and hypoparathyroidism. This is mentioned by all authors when addressing the topic of PCLND. Our data confirm the fact that PCLND contributes to the increase of negative consequences of the operation (Tables 3-5). A few words should be said about our questionnaire, which is our original design. We tried to gradiate possible functional voice disorders as completely as possible, giving the patient the opportunity to evaluate his/her complaints most adequately. This allows us to subsequently conduct a rather fine and complete analysis. It should also be noted that the minimal complaint of slight voice hoarseness is the most common. In addition, when analyzing complaints by questionnaires after non surgical neck, we obtained 8% of such minimal complaints, which, in our opinion, is eloquent evidence of a significant part of nonsurgical causes of such disorders (most likely, it is a consequence of intubation). This justifies an additional comparison to the division into the groups of no complaints and complaints of minimal voice hoarseness on the one hand, and all other complaints on the other (Table 4). In our opinion, this division more adequately reflects the consequences of surgical influences, in particular, the performance of PCLND. With this distribution of the comparison groups, the statistical significance of the differences was even higher ($p<0.001$).

Assessment of ionized calcium level on the next day after surgery (Table 5) certainly does not reflect the presence of even the fact of temporary hypoparathyroidism, much less can not serve as a reliable predictor of permanent hypoparathyroidism. Nevertheless, hypocalcemia is the first and most significant manifestation of all forms of hypoparathyroidism and certainly correlates with them. It is these considerations that allowed us to make this comparison, on the assumption that the most likely factor affecting the level of ionized calcium is precisely thyroid intervention. The fact of an additional effect of PCLND on hypocalcemia is also not disputed by anyone, only the presence or absence of statistical significance of differences in the groups with and without PCLND is discussed. According to our data, there are differences in these groups and they indicate a statistically significant effect of PCLND on the level of ionized calcium on the day after surgery. It is also worth noting that all cases of primary hyperapathyroidism were excluded from the compared groups.

Conclusions

1. PCLND according to our hospital registry does not result in a statistically significant reduction in reoperation for recurrence for PTC.
2. Decreased ionized calcium levels day after surgery and patient complaints of phonation disturbance are statistically significantly more common when PCLND is performed.
3. The decision to perform PCLND should be an informed decision by the surgeon based on the pre- and intraoperative pictures (images). Routine performance of PCLND in a number

of situations may not be more beneficial for the patient.

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Abbreviations

PTC – papillary thyroid carcinoma
TE – thyroidectomy
PCLND – prophylactic central lymph node dissection
TE+PCLND – thyroidectomy with prophylactic central lymph node dissection
LRR – loco-regional recurrences

Досвід проведення профілактичних лімфодисекцій при папілярній карциномі щитоподібної залози за даними госпітального реєстру

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Резюме. Виконання профілактичної центральної лімфодисекції (PCLND) шиї за папілярних карцином щитоподібної залози (PTC) є одним із широко обговорюваних питань, щодо якого досі не вироблено єдиної думки. Більшість дослідників обговорюють коло показань до виконання PCLND, визнаючи, що поряд із підвищенням онкологічної радикальності, вона збільшує ризик післяопераційного гіпопаратиреозу і порушень фонації. **Мета.** Оцінити результати виконання PCLND при PTC за даними госпітального реєстру. **Матеріал і методи.** Для оцінки ефективності виконання PCLND було проаналізовано всі операції за 2015-2023 рр. у пацієнтів із PTC. Були відібрані всі випадки cN0 і виконання тільки тиреоїдектомій (TE) і TE+PCLND (1781 і 801 випадок відповідно). Аналізувалися повторні операції з приводу продовження захворювання шляхом порівняння груп за χ^2 Пірсона (середній термін спостереження 1,9 року). Для аналізу післяопераційних змін фонації використовували анкетування пацієнтів. Проаналізовано всі випадки виконання TE і TE+PCLND (1785 анкет), порівняння виконували також за методикою χ^2 Пірсона. Для оцінки рівня іонізованого кальцію на наступний день після операції порівнювали середні за методикою t-test і за допомогою F-тесту Фішера (всього 550 пацієнтів). **Результати.** Під час аналізу повторних операцій за всією групою із середнім терміном спостереження 1,9 року не виявлено статистично значущої різниці між виконанням TE і TE+PCLND ($p>0,05$). Обмеження групи терміном спостереження від 1 року до 5 років (середній термін спостереження 2,6 року) не змінює ситуації: 2,1% повторних операцій за TE і 3% за TE+PCLND ($p>0,05$). За даними анкетування на зміну фонації (загалом 1785 анкет) виявлено, що після виконання тільки TE наявність скарг фіксували 55,2%, тоді як після виконання TE+PCLND їх було 60,2% ($p<0,05$). Якщо не враховувати мінімальну скаргу на незначну осиплість голосу, то статистична значущість відмінностей стає ще більш впевненою: $p<0,001$ (13,7% проти 20,4%). Післяопераційний рівень іонізованого кальцію також мав статистично значущі відмінності в групах (за TE середнє 1,15; за TE+PCLND середнє 1,13). Порівняння середніх за методикою t-test дало $p<0,001$, а за допомогою тесту Фішера $p<0,05$. **Висновки.** За даними нашого госпітального реєстру, виконання PCLND за PTC не призводить до зменшення відсотка повторних операцій, проте пов'язане з більшим відсотком скарг на зміну фонації та статистично значуще меншим рівнем іонізованого кальцію в першу добу після операції.

Ключові слова: щитоподібна залоза, папілярна карцинома, тиреоїдектомія, центральна дисекція шиї, локо-регіональний рецидив, порушення фонації, рівень іонізованого кальцію.

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