Optimizing treatment for children and adolescents with papillary thyroid carcinoma in post-Chernobyl exposed region: the roles of lymph node dissections in the central and lateral neck compartments

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23 **Running Head:** Lymph node dissection in young patients with papillary thyroid carcinoma

ABSTRACT

There is lack of data to predict lymph node metastases in pediatric thyroid cancer. The aims are to study (1) the factors affecting the lymph node metastases in children and adolescence with papillary thyroid carcinoma in region exposed to radiation and (2) to evaluate the predictive significance of these factors for lateral compartment lymphadenectomy. Five hundred and nine patients with papillary thyroid carcinoma underwent total thyroidectomy and lymph nodes resection (central and lateral compartments of the neck) surgery during the period of 1991 to 2010 in Belarus were recruited. The factors related to lymph node metastases were studied in these patients. In the patients with papillary thyroid carcinoma, increase number of cancer-positive lymph nodes in the central neck compartment were associated with a risk to develop lateral nodal disease as well as bilateral nodal disease. Furthermore, positive lateral compartment nodal metastases are associated with age and gender of the patients, tumour size, minimal extra-thyroidal extension, solid architectonic, extensive desmoplasia in carcinoma, presence of psammoma bodies, extensive involvement of the thyroid and metastatic ratio index revealed after examination of the central cervical chain lymph nodes. The presence of nodal disease, degree of lymph node involvement and the distribution of lymph node metastases significantly increase the recurrence rates of patients with papillary thyroid carcinoma. To conclude, the lymph nodes metastases in young patients with papillary thyroid carcinoma in post-Chernobyl exposed region are common and the pattern could be predicted by many clinical and pathological factors.

Keywords: papillary carcinoma; thyroid; lymph node dissection; pediatric; radiation

1. Introduction

The aetiology, clinical and morphological characteristics, as well as the clinical outcome of papillary thyroid carcinoma in children and adolescents are unique [1]. However, many findings in this group of patients were based on the personal experiences of researchers biased by the regional population characteristics and there is absence of randomised studies [2, 3].

We have addressed the characteristics of paediatric patients with thyroid cancer (observed since 1990) in Belarus related to the consequences of the Chernobyl accident [4, 5]. Our first report studied children with papillary thyroid carcinoma in the region. Young age at diagnosis, multiple foci of the disease, presence of nodal disease at presentation and the lack of initial neck lymph node dissection were associated with lymph node recurrence [4]. In the subsequent study, children and adolescents in the region were included in the study [5]. The outcome of this group of patients with papillary thyroid carcinoma was favourable. Total thyroidectomy with radioactive iodine therapy was recommended for minimizing loco-regional or distant relapses [5].

In Belarus, the approaches to management of papillary thyroid carcinoma in children and adolescents are as follows [6]: (1) Total thyroidectomy is the initial surgical approach. (2) If a compartment-oriented central and ipsilateral lymph node dissection was not performed during the initial surgery, the decision of repeated surgery is based on the risk of nodal disease. For instance, metastases to central and bilateral cervical lymph nodes are frequently present in cases of diffuse sclerosing variant of papillary thyroid carcinoma or in carcinoma in close proximity to the isthmus. (3) Treatment of papillary thyroid carcinoma in childhood needs special expertise including dedicated surgeons and pathologists. (4) Presence of vascular invasion, young age at diagnosis, and radioactive iodine therapy not performed during the initial management increase the risk of distant recurrence in children after total thyroidectomy. Therefore, children and adolescents with papillary thyroid carcinoma could be assigned to two risk groups: those in

whom all three risk factors are absent (low risk) and those in whom at least one factor presents (high risk).

The predictive value of lymph node metastases is the most controversial topic and the calculation of the lymph node metastatic index as risk factor for recurrence in adults with papillary thyroid carcinoma was introduced recently [7-10]. The total number of lymph nodes dissected (nodal yield) and metastatic index (MI: number of positive lymph nodes divided by the total amount of lymph nodes) are independent predictive factors in patients with papillary thyroid carcinoma. The metastatic index is recommended for use in conjunction with existing cancer staging systems. However, the disease burden, the extent of the neck dissection and factors in pathological examination influence the metastatic index. The factors related to the pathological examination may include the experience of the pathologists as well as diligence and quality of pathological reporting. In addition, there is no optimal number of central lymph node recommended to be collected in patients with papillary thyroid carcinoma [11, 12].

There is a need to predict probability of lymph node metastases in lateral compartment accompanying central nodal disease in papillary thyroid carcinoma in adults as well as in children/adolescents [12, 13]. As a rule, the spread of papillary thyroid carcinoma to regional lymph nodes appears to occur in a sequential pattern from the thyroid to the central compartment (Levels VI and VII: the lymph nodes of the central neck compartment include the pre-tracheal, pre-laryngeal, and bilateral para-tracheal lymph nodes) and then to the ipsilateral compartment – Levels II, III, IV). Generally, both chains of lymph nodes are involved in children and adolescents with papillary thyroid carcinoma.

In patients having papillary thyroid carcinoma with clinical evidence of lymph node metastases, the surgeons would do lymph node dissection. However, in situation when lymph node metastases discovered only at pathological examination, the subsequent treatment and the outcome are still uncertain. Therefore, indications and rationale for lymph node dissections in patients with papillary thyroid carcinoma need clarification. In this study, we investigated the

importance of the number of positive central lymph nodes in predicting lateral nodal disease in patients with papillary thyroid carcinoma aged ≤ 18 years old at surgery in the region affected by Chernobyl accident. Besides, we studied the extent of metastases in the lymph nodes in risk stratification for cancer recurrence and follow-up recommendations in children and adolescents with papillary thyroid carcinoma.

2. Material and methods

2.1 Study cohort

The Review Board of the Minsk Municipal Clinical hospital for Oncology in Minsk of Belarus approved the study. The patients with thyroid cancer gave the consents at the time of surgery to share epidemiological, clinical, and morphological individual data for further investigations. The details of the patients' presentations, family history of cancer, history of radiation exposure, surgical and pathological findings, use of adjunctive therapy and clinical outcomes were acquired from hospital charts and electronic medical records (in computerized database). Patients grouped in the "post-Chernobyl group" (n=373) were children (≤ 14 years old) by April 26, 1986 (the date of Chernobyl accident). They were exposed to radiation at several occasions after the accident, under various circumstances and to various amounts of I^{131} . Furthermore, the area-specific degree of radioactive I^{131} contamination exceeding 185 kBq/m^2 was taken into account. On the other hand, the "sporadic" group (n=136) comprised juveniles who were born during the years 1987–2002 (from April 1, 1987 to December 31, 2002) and were operated for papillary thyroid carcinoma during the period of 1991–2010 was taken as controls. These children and adolescents were born long after the full decomposition of the effect of I^{131} (April 26, 1986–July 28, 1986). They were not exposed to the internal irradiation with I^{131} and had no history of external therapeutic irradiation.

2.2 Initial treatment

The patients with papillary thyroid carcinoma underwent resection of the thyroid (total thyroidectomy) and lymph nodes (in the central and lateral compartments of the neck) according to the extent of disease at the time of diagnosis (Figure 1). Patients with multiple foci of cancers, diffuse sclerosing variant of papillary thyroid carcinoma, isthmus-localized carcinomas as well as having only central (Level VI) or only with ipsilateral (Levels II, III, IV) lymph node dissections were excluded from this study (Figure 1). In addition, patients with residual thyroid

carcinoma or distant metastases were treated with post-operative I^{131} ablation (radioactive iodine therapy given 4–6 weeks after surgery). This was followed by thyroid stimulating hormone-suppressive doses of levothyroxine with a mean dose of 2.0 to 2.5 g/kg body weight.

2. 3 Follow-up

All the patients were screened for 6-26 years (median 16 years) through local and regional address bureaus, departments of public health and forensic medical establishments (for patients that have suicided). Follow-up information consisted of clinical examination, thyroid function tests, serum thyroglobulin and anti-thyroglobulin antibodies. Neck ultrasound scan, chest radiograph, diagnostic whole-body scans (WBSs) with I^{131} (2–5 mCi) and serum thyroglobulin assay (off thyroid hormone therapy) were performed every 6 to 12 months during the first 2 years after surgery and every 12 months after the first 2 years of observation.

Complete disease remission is defined as negative diagnostic results on whole-body scans and undetectable or low serum thyroglobulin levels [<2 ng/mL] tested with thyroid stimulating hormone stimulation as well as the absence of anatomically definable disease on neck ultrasound scanning or chest computerized tomography. In these patients with complete remission, repeated evaluation was performed every 2 years for 4 years and every 5 years thereafter. On the other hand, repeated I^{131} courses were given to patients with evident local recurrence or distant metastases.

2.4. Pathological diagnosis

We used the eight edition of TNM classification for pathological staging of the papillary thyroid carcinoma [14]. The dimension of the thyroid gland and the cancer it contained were based on direct measurements of the surgical thyroid specimens during macroscopic examination. Histological features examined included: histological pattern, extra-thyroidal extension in perithyroid adipose tissue, skeletal muscle, sizable vascular structures & nerves,

growth pattern (as well circumscribed or infiltrative tumour growth), lymphovascular invasion, intratumoral fibrosis (desmoplastic stromal reaction), and extranodal extension (Figures 2 and 3). Micrometastases in neck lymph node were defined as the presence of metastatic deposits ≤ 2 mm in diameter, and macrometastases were defined as deposits > 2 mm in maximal diameter.

2.5. Statistical analysis

Classical metastatic index (MI) was calculated as the number of positive lymph nodes divided by the total amount of lymph nodes. Metastatic ratio index (MRI) was calculated as the number of positive lymph nodes divided by the difference between the total amount of lymph nodes minus the number of positive lymph nodes +1.

Receiver operating characteristic (ROC) curve analysis was performed to estimate ability of metastatic index and metastatic ratio index to differentiate between patients with papillary thyroid carcinoma having disease in the central neck compartment lymph node(s) (N1a), in ipsilateral neck lymph node(s) (N1b) and bilateral neck lymph nodes.

We used multifactor ordinal (proportional odds) logistic regression to establish factors associated with the risk of lymph nodal metastatic spread. At first, we included variables with significant values in univariate analysis. Then backward elimination was applied to the preliminary model to remove nonsignificant variables based on Bayesian information criterion (BIC). Once the most appropriate model was determined, the estimates of the respective parameters and their 95% confidence intervals (CIs) were calculated. Odds ratios (ORs) for variables (and their 95% CIs) were calculated as the exponential transformation of the respective parameters. The final model was validated using cross validation method (5-folds).

The survival rates of the patients with thyroid cancer were calculated from the date of initial surgery until the event of interest or loss of contact. Kaplan-Meier estimator was used to analysis the survival of the patients with papillary thyroid carcinoma. A Mantel-Haenszel log-

rank test was used to establish significant risk factors in univariate analysis for relapse-free survival of the patients. Hazard ratio was calculated from Cox proportional hazard regression.

Baseline characteristics between groups were compared using Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. All statistical analyses were performed using R (version 3.3.2) [R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>] with packages *rms* [Frank E Harrell Jr (2017). *rms*: Regression Modeling Strategies. R package version 5.1-1. <https://CRAN.R-project.org/package=rms>] , *survival* [Terry M. Therneau and Patricia M. Grambsch (2000). *Modeling Survival Data: Extending the Cox Model*. Springer, New York. ISBN 0-387-98784-3.]

A p value < 0.05 was considered statistically significant for final inferences.

3. Results

Clinical and morphological differences between patients with papillary thyroid carcinoma having pN1a (metastasis to Level VI neck lymph nodes: pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes or upper/superior mediastinum) (n = 79) versus patients having pN1b (metastasis to unilateral, bilateral, or contralateral cervical or retropharyngeal lymph nodes) (n = 231) were presented in Table 1. Overall, patients having papillary thyroid carcinoma with pN1b were characterized by younger age at operation ($p < 0.001$), less pronounced gender ratio ($p = 0.001$) and larger tumour size ($p < 0.001$). Besides, the presence of minimal extrathyroid extension, solid component in tumour, extensive intratumoral fibrosis, vascular invasion, and peritumoral/intra-thyroid psammoma bodies dissemination significantly varied between the two groups. Moreover, the number of positive central lymph nodes in both groups showed significantly difference ($p < 0.001$) albeit central compartment nodal yield was similar for patient with ipsilateral and bilateral lymph node metastases (N1b). In addition, in patients with lateral nodal disease, the predominance of micrometastases in the lymph nodes of the Level VI (N1a) was characteristic (58.2%). On the other hand, Level VI nodal disease with extranodal extension (81.5%) was common in children and adolescents treated for papillary thyroid carcinoma with N1b status ($p < 0.001$).

The present study aims to introduce the metastatic ratio index (MRI) as an independent variable that influence the decision to carry out lateral lymph nodes compartment surgery in addition to routinely performed central lymph nodes dissection. Classical MI scatterplot (Figure 4a) illustrates that the increase in the total amount of lymph nodes that was removed from central neck compartment significantly correlated with gradual diminishing of diagnostic value of lymph node ratio ($\rho = -0.16$, $p < 0.001$). MI-variable heavily relied on the surgeon's experience and anatomical variety, inquisitiveness and patience of the individual pathologist as well. On the contrary, MRI (Figure 4b) lacks aforementioned biases (does not depend on the human factor

and/or anatomical peculiarities). Therefore, MRI is much stable ($\phi = -0.05$, $p = 0.309$) to reflects the fraction of positive lymph nodes in total lymph nodes yield.

ROC curves were used to examine predictive efficacy of both indexes to expect N1b using the total amount of lymph nodes and the number of positive lymph nodes in central compartment. DeLong test was used to analyze the significance of the difference between these two correlated areas under the curve. The prognostic accuracy of the MRI was greater than that for classical MI, and the difference was statistically significant ($p = 0.005$). The ROC curves are represented in Figure 5.

Factors associated with the degree of lymph node involvement in central nodal disease are shown in Table 2. Female patients with papillary thyroid carcinoma were characterized by less pronounced involvement of the lymph nodes in the central compartment ($p < 0.001$). Besides, mononuclear peritumoral infiltration or extensive lymphocytic thyroiditis were typical in children and adolescents with the absence of nodal disease or with micrometastases only. On the other hand, cases with macroscopic metastases and metastases with extra-nodal extension were accompanied by the very low frequency of inflammatory reaction in peritumoral areas or elsewhere in the thyroid gland. Furthermore, extensive intratumoral fibrosis was regularly observed in patients with more advanced central nodal disease ($p < 0.001$).

Widespread pN1a was predictably associated with larger tumour size ($p < 0.001$), minimal extrathyroid extension ($p < 0.001$), the presence of solid component ($p < 0.001$), blood vessel invasion ($p < 0.001$) and peritumoral/intraglandular psammoma bodies dissemination ($p < 0.001$). Also, there are associations between cancer architecture and lymph nodal status in patients with papillary thyroid carcinoma. Papillary thyroid carcinomas with predominately follicular pattern are usually with no lymph node metastasis (pN0) whereas those with predominantly papillary architecture are often with minimal central nodal disease (micrometastases; pN1a). In patients with papillary thyroid carcinoma having solid architecture, extranodal extension of cancer is common. In accordance with the aforementioned results, macroscopic metastases and

metastases with extra-nodal extension predominated in children and adolescents with post-Chernobyl papillary thyroid carcinoma ($p < 0.001$).

Using the statistical methods as described above, four or five metastatic central lymph nodes were associated with a risk to develop lateral nodal disease (table 1). Moreover, six or more lymph node metastases in central compartment were linked with a risk to develop bilateral lymph node metastases (table 1). Alternatively, central compartment MI = 0.5 (from 0.07 to 1) or MRI = 0.75 (from 0.07- to 11) were associated with lymph node metastases in lateral neck compartment (Levels II, III, IV). In addition, MI = 1 (from 0.14 to 1) or MRI = 4 (from 0.15 to 12) were associated with bilateral lymph node metastases. Furthermore, macrometastases (one or more) in central lymph nodes per se were associated with a risk to develop lateral nodal disease. Furthermore, macrometastases in one or more central lymph nodes accompanied by extranodal extension were connected to the spreading of papillary thyroid carcinoma to bilateral lymph nodes (table 1).

To predict either ipsilateral or bilateral lymph nodes metastases in according with clinical and post-surgical histological data, we counted the number and the extensiveness of central lymph nodes involved in metastatic process. In this study, we used multifactor ordinal (proportional odds) logistic regression to establish factors linked to the risk of metastatic spread (table 3). The risk to develop lateral lymph node metastases was higher in younger children with papillary thyroid carcinoma that is disseminated in the thyroid and metastasized to the central compartment lymph nodes with macrometastases and metastases with extranodal extension. The probability of metastases to lymph nodes of the lateral neck compartment (s) decrease with increasing age of the patients. Thus, the probability of pN1b has been decreasing on 14% (5-22 %) per every year of patients age at presentation.

Both MI and MRI can be used for predicting lymph node metastases (N1b) in patients with papillary thyroid carcinoma. However, the likelihood ratio tests of ordinal regression models showed that the model with MRI is much better ($p < 0.001$) in predication of lymph node

metastases when compared with the model using classical MI. Figure 6 shows our nomogram for predicting ipsilateral or bilateral lymph nodes metastases in patients with papillary thyroid carcinoma by utilizing variables from table 3.

As shown in table 4, cancer relapses were registered only in 14 of 509 (2.75%) patients with papillary thyroid carcinoma. Of these 14 patients, 10 had distant metastases that were diagnosed according to the results of whole-body scans and 4 had regional recurrences that were confirmed by pathology. All these children and adolescents with relapses of papillary thyroid carcinoma presented with pN1b nodal disease. Pre-pubertal children aged 4-10 years old at surgery had a 9-fold increased risk of recurrence. Besides, extensive intratumoral fibrosis, extrathyroid extension, vascular invasion and macroscopic metastases and/or metastases with extra-nodal extension in central compartment lymph nodes significantly influenced relapse-free survival. In addition to the aforementioned variables, the number of metastatic lymph nodes (≥ 6 of 9 in classical MI or ≥ 4 of 9 in MRI) appeared as a strong prognostic factor for disease recurrence.

Figure 7 shows the relapse-free survival (RFS) rate. The 10-years RFS in this research is 97.2% (95% CI, 95.8 - 98.7). Besides, according to the AJCC/ TNM system, the 10-years RFS in patients with N1b is 96.1% (95% CI, 94.1 - 98.1). Patients with pN0-N1a had no recurrence during follow-up. On the other hand, according to the American Thyroid Association (ATA) risk stratification system, patients with lymph nodes macro-metastases and/or metastases with extra-nodal growth had 95.% (CI, 93.7- 98.1) 10-years RFS.

4. Discussion

In this study, we noted that clinical and morphological factors could aid in risk stratification for clinical care of children and adolescents with papillary thyroid carcinoma. Postoperative risk-stratification systems such as American Thyroid Association risk categories or any “scores” of local significance could base on the assesment of relatively small cohorts and relatively short median follow-up period [15,16]. In Belarus and Ukraine (where children were exposed to post-Chernobyl irradiation), huge cohorts of young patients with papillary thyroid carcinoma have been follow-up at special centres with the rigorous surveillance protocol. This could allow detail investigation of the predicative factors that affect the management of patients with thyroid cancer.

The strength of the current study stems from: (a) the large number of children and adolescents with papillary thyroid carcinoma; (b) their long-term follow-up and detailed clinical annotation; (c) the unique, and, to the best of our knowledge, largest papillary thyroid carcinoma clinical and morphological data set available for this cohort & (d) the comprehensive analytical approaches.

In our previous publications, we have presented the clinical and morphological factors associated with regional metastases of papillary thyroid cancer in children and adolescents. However, we have not investigated the characteristics associated with the lateral neck (Levels II-IV) lymph nodes metastases. In the current study, we showed for the first time the differences between the ipsilateral and bilateral lymph node extension of papillary thyroid carcinoma (Table 1) in this cohort of patients. In addition, the aetiological, morphological and clinical features of papillary thyroid cancer that predisposed to the regional distribution of lymph node metastases (N1a, N1b ipsilateral and N1b bilateral) in Belarusian children and adolescents were analysed (Tables 1 and 2).

In our previous study for thyroid cancer in Belarus, we noted that the aetiology of cancer significantly influences the course of disease at presentation [17]. Multivariate analysis showed

that lymphatic invasion was the strongest independent factor associated with both extrathyroid extension and lymph node metastases in patients with sporadic papillary thyroid carcinoma. Also, nodal disease in patient with post-Chernobyl papillary thyroid carcinoma was linked to cancer size, invasive or diffuse growth, extrathyroid extension, papillary growth pattern, lymphatic invasion and peritumoral/intraglandular psammoma bodies dissemination of the tumour [5, 18]. In the present study, we noted that aetiological differences are losing their significance when factors, associated with nodal disease have been investigated. In addition, we noted no difference in characteristics in the “sporadic” and “post-Chernobyl” groups in terms of lymph node metastases (Table 1).

It should be stressed that the post-Chernobyl exposed cohort of patient and the so-called sporadic group could be discussed from two different points of view: to predict disease recurrence and to predict survival in patients with cancer. Therefore, using the AJCC/ TNM system, we did not reveal significant differences between patients with pN1a, pN1b or pN1b bilateral (table 1). On the other hand, to apply the American Thyroid Association (ATA) risk stratification system, we showed that the nodal burden in the post-Chernobyl exposed cohort of patient group are substantially higher (table 2).

Total thyroidectomy and neck lymph node dissections have been the routine practice for patients with papillary thyroid carcinoma in Belarus since 1998. The lymph node dissection includes central (Level VI) and bilateral (Levels II-IV or II-IV and V which are largely prophylactic rather than therapeutic) neck regional lymph nodes. Conservative surgery is done only in cases of very small solitary intrathyroidal nodule with no clinical evidence of metastases. This surgical approach makes possible to describe the true prevalence of lateral nodal disease at presentation. Therefore, we had invaluable data to stratify patients according to the completeness of thyroidectomy and lymph node surgery. Consequently, we used a large cohort of cases to study thoroughly the features of papillary thyroid carcinoma associated with regional spreading and the degree of lymph node involvement.

In our previous investigations, we studied the morphological characteristics and effect of age of exposure to radiation in children and adolescents with papillary thyroid carcinoma in Belarus [15, 16]. In the current study, we hypothesized that the results of post-surgical evaluation of central lymph nodes could be useful for considering next steps in the management of papillary thyroid carcinoma in children and adolescents. Therefore, the aims of this study was (1) to determine probability of the lateral neck compartment nodal disease using clinical and morphological characteristics of primary thyroid carcinoma and its central lymph node(s) metastasis and (2) to clarify the question if these characteristics have impacted relapse-free survival. Similar studies were conducted in adult patients with papillary thyroid carcinoma. However, no study has been performed in children and adolescents with papillary thyroid carcinoma, especially in cases that associated with post-Chernobyl irradiation.

First, we analysed factors related to nodal disease in children and adolescents with papillary thyroid carcinoma (table 1). The completion of this stage was necessary in order to check whether the dependencies established by the results of previously published studies have changed after careful selection of patients, as it was described in “materials and methods”. Thus, we have proved that the continuity in the material of the study was preserved: key characteristics of the patients such as age, sex ratio, tumour size, and a number of morphological features have not lost relevance. In addition, we presented an improved approach to assess the metastatic index and proved that this new indicator (MRI) predicts the development of ipsilateral and bilateral metastases in the lymph nodes of the neck in papillary thyroid carcinoma in children and adolescents much more effectively.

In Belarusian patients, the number of removed lymph nodes in the central and lateral compartment of the neck differs from the numbers given by other researchers. In particular, Vas Nunes and colleagues in 2013 reported that the total amount of lymph node noted in patients with papillary thyroid carcinoma was different in different types of lymph node resection. The median number of lymph nodes obtained in central, ipsilateral lateral and bilateral lateral neck

lymph node dissection was 6, 36 and 64 respectively [8]. In addition, Zeng and colleagues in 2013 counted 16.8, 14.8 and 13.7 mean numbers of lateral lymph nodes removed in their groups of patients [11]. On the other hand, Schneider and colleagues in 2013 revealed that the median number of lymph nodes dissected in the patients for papillary thyroid carcinoma was only 3 [7]. Thus, the exclusion of subjective influences on the final indicator (MRI), which is provided in the formula, serves as another indicator of the superiority of the proposed approach before that used by other researchers.

The next step of our study was to analyse factors associated not only with the presence of metastases in the central lymph nodes of the neck, but also with their qualitative characteristics such as micro-metastases, macroscopic metastases (clinically apparent), and metastasis in lymph node(s) fixed to one another (matted) or to other structures (with extranodal extension). There was an opportunity, using the obtained results, to predict the presence of micro-metastases in the lymph nodes. This is important for clinical practice in those centres where central lymphadenectomy is not routinely performed. In addition, the results of the study make it possible to calculate the odd ratio to detect metastases in the ipsilateral or bilateral lymph nodes based on changes in the central lymph nodes of the neck.

We propose an improved tool (MRI) that is superior in sensitivity and specificity to the currently used (MI) approach (Figures 4, 5) in determining the probability of metastatic disease in the ipsilateral lymph nodes of the neck in patients with papillary thyroid carcinoma. If patients develop bilateral lymph node metastases, the sensitivity and specificity of MRI is not inferior to MI. The use of MRI can provide valuable information in the clinical situation when the involvement of lymph nodes in solitary papillary carcinoma with localization in the thyroid lobe failed to be proven before surgery and the patient underwent thyroidectomy with removal of only the central lymph nodes of the neck (level VI). A combined assessment of the risk of metastases in this group of lymph nodes of the neck (Tables 1, 2, 3 and Figure 6) will help determine the need for one- or two-sided lateral compartment lymph node dissections.

At the final step, we showed what the risk of cancer recurrence in patients with papillary thyroid carcinoma in children and adolescents depended on the presence of certain clinical and morphological characteristics of the primary cancer and its metastases in the central lymph nodes of the neck. Our data (Table 4) could predict cancer relapses precisely and determine the necessary "aggressiveness" of primary surgical treatment.

In adult patients with node-positive papillary thyroid carcinomas, the primary carcinoma and all involved loco-regional nodes have to be removed during the same session whereas prophylactic dissections of the central and lateral lymph node compartments are generally unwarranted in clinically no metastatic tumours [19, 20]. Demidchik et al. have presented the arguments in favour of routine prophylactic cervical lymph node dissections in children with clinically node-negative papillary thyroid carcinoma [4]. In the study, we added new arguments in support of such decision.

The surgical complications of the neck dissection include recurrent laryngeal nerve palsy and hypoparathyroidism. The frequency of adverse effects depends on the tumour extension and the degree of extent of the surgery [4]. In this study, we do not recommend radical surgery in a whole group of patients who have no fatal outcomes with significant follow-up. However, surgical decisions need to be personalized according to patient/tumour-related factors. Also, there is no substantial association between bilateral neck lymph node dissection and the risk of recurrent nerves palsy and hypoparathyroidism in high-volume centers where surgical experience and general improvement of the treatment strategy making surgical options switch to more extensive interventions [4].

The results of our study allowed us to supplement and refine the algorithms proposed by specialists of the American Thyroid Association [15]. In Belarus, where the incidence of childhood papillary thyroid carcinoma is high, surgical treatment of patients with this disease is much more radical than in other centres. Our experience could be of value for other medical institutions as we have comprehensive morphological information of the primary thyroid cancer.

421 The results of the examination of the central lymph nodes of the neck will make it possible to
422 determine the necessity of carrying out a preventive ipsilateral or bilateral dissection.
423 Nevertheless, it remains to determine whether the central and lateral lymph node dissection
424 should be performed at the time of total thyroidectomy or as multi-staged treatment.

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5. Conclusion

In the current report, we showed that both central and lateral neck dissections yielded very important information for tailoring individual treatment strategy for children and adolescents with papillary thyroid carcinoma. For example, our MRI combined with the data of the degree of lymph node involvement could be used to consider lateral lymph nodes dissections and radioactive iodine therapy for prevention of cancer relapse.

We created a nomogram with excellent discriminatory ability and accuracy in predicting probability of ipsi or bi-lateral nodal disease. Using the nomogram, post-surgical factors should be considered to aid in risk stratification for routine clinical care of children and adolescents with papillary thyroid carcinoma. These include many clinical and morphological features associated with nodal disease (age and gender of the patients, tumour size, minimal extra-thyroidal extension, solid architectonic, extensive intratumoral fibrosis, psammoma bodies peritumoral and/or intraglandular dissemination). Besides, the location of the involved lymph nodes (N1a vs N1b), the number of lymph nodes sampled, the number of involved lymph nodes, the size of the largest metastatic focus within a lymph node, the presence/absence of extranodal extension should be taken into the account. It is likely that some of these additional issues may be incorporated in assessing the risk of recurrence and early response to therapy to refine and optimize initial risk stratification further.

Nodal metastases in the lateral compartment of patients with papillary thyroid carcinoma are correlated with age of the patients, pathological features and status of lymph nodes in the central compartment. The presence of nodal disease, degree of lymph node involvement and the distribution of lymph node metastases significantly increase recurrence rates of the thyroid cancer in children and adolescent. As we revealed no significant difference in the lymph nodes metastases rate between sporadic and post-Chernobyl cases of papillary thyroid carcinoma in children and adolescents, the results of our study could be considered in the management of papillary thyroid carcinoma in this age-group in other countries too.

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Figure Legends

Figure 1. Schematic representation of the initial surgical approach in patients included into the study.

Figure 2. Childhood papillary thyroid carcinoma, two most typical gross appearances are showed: top – small papillary thyroid carcinoma as sub-capsular yellowish nodule of the right thyroid lobe which is bulging in the close proximity to the isthmus (arrow), cystic nodal disease is apparent; bottom – solid tumour tissue is nearly totally replacing the right thyroid lobe. Metastatic lymph nodes fixed to one another (with extranodal extension).

Figure 3. Childhood papillary thyroid carcinoma microscopic characteristics: a (x40) – numerous intra-thyroidal psammoma bodies (peritumoral/intraglandular psammoma bodies dissemination), heavy mononuclear infiltration with germinal centers, dense fibrosis; b (x100) – marked fibro-sclerotic changes in papillary thyroid carcinoma; c (x200) – extra-thyroidal papillary thyroid carcinoma extension in muscle tissue. All slides were stained with hematoxylin and eosin.

Figure 4. Scatterplots illustrating the differences between classical metastatic index (MI) and metastatic ratio index (MRI).

Figure 5. Receiver operating characteristic (ROC) curves for classical MI and MRI to examine prognostic efficacy of both indexes to predict N1a vs N1b (a) and N1b-bilateral versus N1a & N1b- ipsilateral (b).

Figure 6. Postoperative nomogram for predicting N1b and/or N1b bilateral regional papillary thyroid carcinoma spreading in accordance with the extension of metastatic disease in the lymph nodes in the central neck compartment. Psam – Peritumoral/intraglandular psammoma bodies dissemination; central MTS – positive lymph nodes in the central neck compartment (Level VI); MiMet – Micrometastases (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm); MaMet – Macroscopic metastases (clinically apparent), micrometastases combined with macroscopic metastases; ExNoEx – Metastasis in lymph node(s) fixed to one another (matted) or to other structures (with extranodal extension); Probs ipsilat MTS – probability of

565 ipsi-lateral nodal disease in patients with papillary thyroid carcinoma based on post-surgical
566 evaluation of the central neck compartment; Probs contralat MTS – probability of contra-lateral
567 nodal disease in patients with papillary thyroid carcinoma based on post-surgical evaluation of
568 the central neck compartment.

569 Figure 7. The relapse free survival (RFS) of the patients with thyroid carcinoma of different
570 clinical groups. The 10-years RFS in this research is 97.2% (95% CI, 95.8 - 98.7).

Table 1. Factors associated with nodal disease in children and adolescents with papillary thyroid carcinoma

Clinical and morphological characteristics	N1a n = 79	N1b n = 231		p-value N1a Vs N1b ipsilateral	p-value N1a Vs N1b bilateral
		Ipsilateral (level II, III, IV) n=177	Bilateral (level II, III, IV) n= 54		
Age at operation				0.646	<0.001
4-10	2 (2.5)	9 (5.1)	9 (16.7)		
11-14	22 (27.8)	53 (29.9)	26 (48.1)		
15-18	55 (69.6)	115 (65)	19 (35.2)		
Aetiology				0.311	0.088
Sporadic	29 (36.7)	53 (29.9)	12 (22.2)		
Post-Chernobyl	50 (63.3)	124 (70.1)	42 (77.8)		
Sex				0.190	<0.001
male	20 (25.3)	61 (34.5)	30 (55.6)		
female	59 (74.7)	116 (65.5)	24 (44.4)		
Ratio male/female	1:3	1:1.9	1:0.8		
Tumour size, mm					
Median (range)	10 (3...31)	12.5 (4...35)	15.5 (8...37)	<0.001	<0.001
1-10	43 (54.4)	60 (33.9)	10 (18.5)	0.007	<0.001
11-20	31 (39.2)	93 (52.5)	34 (63)		
≥21 mm	5 (6.3)	24 (13.6)	10 (18.5)		
Minimal extra-thyroidal extension	30 (38)	115 (65)	52 (96.3)	<0.001	<0.001
<i>In tumours sized 1-10 mm</i>	<i>13 (16.5)</i>	<i>31 (17.5)</i>	<i>9 (16.7)</i>		
<i>In tumours sized ≥11 mm</i>	<i>17 (21.5)</i>	<i>84 (47.5)</i>	<i>43 (79.6)</i>		
Patterns				0.018	<0.001
Predominantly papillary	27 (34.2)	33 (18.6)	3 (5.6)		
Predominately follicular	12 (15.2)	22 (12.4)	4 (7.4)		
Papillary and follicular	25 (31.6)	63 (35.6)	20 (37)		
Solid present	15 (19)	59 (33.3)	27 (50)		
<i>Pure solid</i>	<i>0</i>	<i>8 (4.5)</i>	<i>5 (9.3)</i>		
<i>Papillary and solid</i>	<i>5 (6.3)</i>	<i>16 (9)</i>	<i>5 (9.3)</i>		
<i>Follicular and solid</i>	<i>6 (7.6)</i>	<i>15 (8.5)</i>	<i>6 (11.1)</i>		
<i>Papillary-follicular-solid</i>	<i>4 (5.1)</i>	<i>20 (11.3)</i>	<i>11 (20.4)</i>		
Extensive fibrosis in carcinoma	16 (20.3)	72 (40.7)	29 (53.7)	<0.001	<0.001
Vascular invasion	5 (6.3)	35 (19.8)	14 (25.9)	0.005	0.002
Lymphatic invasion	77 (97.5)	177 (100)	54 (100)	0.094	0.514
Extensive psammoma bodies in thyroid and the carcinoma	42 (53.2)	139 (78.5)	41 (75.9)	<0.001	0.021
Mononuclear infiltration	10 (12.7)	37 (20.9)	8 (14.8)	0.161	0.799

Comorbidity				0.189	0.085
no	59 (74.7)	148 (83.6)	46 (85.2)		
autoimmune thyroiditis	18 (22.8)	26 (14.7)	5 (9.3)		
benign hyperplasia/ follicular adenoma	2 (2.5)	3 (1.7)	3 (5.6)		
Surgery for lymph nodes					
Central compartment lymph node dissections					
Number of lymph nodules removed (median)	9 (2...27)	9 (1...28)	8.5 (1...29)	0.644	0.763
Of these with lymph node metastases (median)	2 (1...10)	4 (1...14)	6 (1...14)	<0.001	<0.001
Central compartment lymph nodes metastases (N1a)				<0.001	<0.001
Micrometastases only	46 (58.2)	49 (27.7)	2 (3.7)		
Macroscopic metastases (clinically apparent), micrometastases combined with macroscopic metastases	21 (26.6)	80 (45.2)	8 (14.8)		
Metastasis in lymph node(s) fixed to one another (matted) or to other structures (with extranodal extension)	12 (15)	48 (27.3)	44 (81.5)		
MI ,Median (range)	0.29 (0.04-1)	0.5(0.07-1)	1 (0.14-1)	<0.001	<0.001
MRI, Median (range)	0.33 (0.04-7)	0.75 (0.07-11)	4 (0.15-12)	<0.001	<0.001

Table 2. Clinical and pathologic characteristics of 390 patients with papillary thyroid carcinoma by the degree of central compartment lymph node involvement

Clinical and morphological characteristics	The degree of central lymph node involvement				Total, n=390 100%	p-value
	No central nodal disease (of these pN0 n = 52 pN1b* n = 28) n=80 (20.5%)	Micro-metastases only, n=97 (24.9%)	Macroscopic metastases (clinically apparent), micro-metastases and macroscopic metastases n=109 (27.9%)	Metastasis in lymph node(s) fixed to one another (matted) or to other structures (with extranodal extension) n= 104 (26.7%)		
Aetiology of papillary thyroid carcinoma						<0.001
Sporadic	39 (48.8)	41 (42.3)	27 (24.8)	26 (25)	133 (34.1)	
Post-Chernobyl	41 (51.2)	56 (57.7)	82 (75.2)	78 (75)	257 (65.9)	
Sex						<0.001
male	17 (21.2)	22 (22.7)	39 (35.8)	50 (48.1)	128 (32.8)	
female	63 (78.8)	75 (77.3)	70 (64.2)	54 (51.9)	262 (67.2)	
<i>Ratio male/female</i>	<i>1:3.7</i>	<i>1:3.4</i>	<i>1:1.8</i>	<i>1:1</i>	<i>1:2</i>	
Tumour size						<0.001
Median (range) 1-10 mm	46 (57.5)	50 (51.5)	45 (41.3)	18 (17.3)	159 (40.8)	
≥11 mm	34 (42.5)	47 (48.5)	64 (58.7)	86 (82.7)	231 (59.2)	
Minimal extra-thyroidal extension	25 (31.2)	39 (40.2)	67 (61.5)	91 (87.5)	222 (56.9)	<0.001
<i>In tumours sized 1-10 mm</i>	13 (16.2)	18 (18.6)	21 (19.3)	14 (13.5)	66 (16.9)	
<i>In tumours sized ≥11 mm</i>	12 (15)	21 (21.6)	46 (42.2)	77 (74)	156 (40)	
M1	1 (1.2)	4 (4.1)	5 (4.6)	27 (26)	37 (9.5)	<0.001

Patterns						<0.001
Predominately papillary	19 (23.8)	37 (38.1)	18 (16.5)	8 (7.7)	82 (21)	
Predominately follicular	18 (22.5)	10 (10.3)	12 (11)	16 (15.4)	56 (14.4)	
Papillary and follicular	24 (30)	30 (30.9)	43 (39.4)	35 (33.7)	132 (33.8)	
Solid component is present	19 (23.8)	20 (20.6)	36 (33)	45 (43.3)	120 (30.8)	
Extensive fibrosis in carcinoma	25 (31.2)	39 (40.2)	67 (61.5)	91 (87.5)	222 (56.9)	<0.001
Vascular invasion	12 (15)	6 (6.2)	18 (16.5)	30 (28.8)	66 (16.9)	<0.001
Lymphatic invasion	48 (60)	95 (97.9)	109 (100)	104 (100)	356 (91.3)	<0.001
Extensive psammoma bodies noted in tumour or thyroid	27 (33.8)	68 (70.1)	75 (68.8)	79 (76)	249 (63.8)	<0.001
Mononuclear cells infiltration	9 (11.2)	27 (27.8)	13 (11.9)	15 (14.4)	64 (16.4)	0.005
Comorbidity						0.002
no	57 (71.2)	73 (75.3)	85 (78)	95 (91.3)	310 (79.5)	
autoimmune thyroiditis	16 (20)	23 (23.7)	20 (18.3)	6 (5.8)	65 (16.7)	
Nodular hyperplasia/ follicular adenoma	7 (8.8)	1 (1)	4 (3.7)	3 (2.9)	15 (3.8)	

*cases of skip metastases to the lateral compartment (with the central neck being negative)

Table 3. Risk Factors for Nodal Disease Extension in Pediatric papillary thyroid carcinoma (multivariate ordinal logistic regressions)

variable	p-value	OR	95% CI
Age (year).	0.002	0.86	0.78- 0.95
Psammona	0.002	2.16	1.28-3.68
MRI	<0.001	1.34	1.18-1.54
MaMet	<0.001	2.73	1.53-4.93
ExNoEx	<0.001	6.91	3.33-14.7

Psammoma - psammoma bodies dissemination in the tumour and thyroid gland

MaMet -Macroscopic metastases (clinically apparent), micrometastases combined with macroscopic metastases

ExNoEx - Metastasis in lymph node(s) fixed to one another (matted) or to other structures (with extranodal extension)

Table 4. Clinical & pathologic characteristics of all 509 patients with papillary thyroid carcinoma by relapses

Clinical & pathologic characteristics	RELAPSE	HR (95% CI HR)	p-value
Age at operation (year)			
4-10	5/54	9 (2.1-38)	0.003
11-14	6/175	3.3 (0.8-13)	0.096
15-18	3/280	ref	
Etiology			
Sporadic	2/136	ref	
Post-Chernobyl	12/373	2.2 (0.5-9.8)	0.306
Gender			
female	8/341	ref	
male	6/168	1.5 (0.5-4.5)	0.419
Tumour size (mm)			
1-10	4/186	ref	
11+	10/323	1.4 (0.5-4.6)	0.532
Minimal extra-thyroidal extension			
no	1/188	ref	
yes	13/321	7.8 (1.02- 60)	0.048
N			
N0	0/58	ref	
N1a	0/91	ref	
N1b	14/360	Inf	0.015*
Patterns			
Predominately papillary	1/94	ref	
Predominately follicular	1/70	1.3(0.08-21.6)	0.832
Papillary and follicular	7/165	4.1 (0.5-33.2)	0.188
Solid present	5/180	2.7 (0.3-23.2)	0.366
Extensive fibrosis in tumour			
no	4/315	ref	
yes	10/194	4.1 (1.3- 13.1)	0.016
Vascular invasion			
no	7/399	ref	
yes	7/110	3.7 (1.3- 10.6)	0.014
Lymphatic invasion			
no	0/38	ref	
yes	14/471	Inf	0.283*
extensive psammoma bodies in the tumour and thyroid			
no	4/182	ref	
yes	10 /327	1.4 (0.4 -4.5)	0.557
Mononuclear cell infiltration			
no	9/246	ref	
yes	5 /83	3 (1 -8.8)	0.052
Comorbidity			
no	14/418	ref	
yes	0 /91	Inf	0.077*
Central compartment lymph nodes			

metastases N0 + micro metastases only	1/195	ref	0.044
Macroscopic metastases (clinically apparent), micro metastases combined with macroscopic metastases+Metastasis in lymph node(s) fixed to one another (matted) or to other structures (with extranodal extension)	13 /314	8.1 (1.1 -62)	
Classical MI (0-0.64) (0.65-1)	5/329 9/180	ref 3.3 (1.1 -10)	0.026
MRI (0-0.44) (0.45-12)	2/224 12/285	ref 4.8 (1.1 -21)	0.016

* significant on log-rank test; Inf - infinitum

Accepted Manuscript

Optimizing treatment for children and adolescents with papillary thyroid carcinoma in post-Chernobyl exposed region: the roles of lymph node dissections in the central and lateral neck compartments

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