

Ph.D. THESIS

DIFFERENTIATED THYROID CANCER: PROGNOSTIC FACTORS

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1. Introduction and aims

Malignant tumors of the thyroid count for approximately 1% of all diagnosed cancer cases each year. Prognostically, thyroid malignancies range from the most frequently seen differentiated carcinoma (papillary thyroid carcinoma – PTC, and follicular thyroid carcinoma – FTC), to the less common, but most aggressively growing anaplastic tumors. Differentiated thyroid carcinoma has a relatively favourable course. The tumor-specific mortality is low, and life expectancy has been continuously improving during the recent 10-15 years, due to the advanced diagnostic and therapeutic protocols. However, some cases have an extremely poor prognosis in this group. Due to its relative rarity and usually benign clinical course, opinions differ about the appropriate and optimal primary care, and follow-up strategy. The major differences in the treatment of thyroid carcinoma are about the extent of the surgical procedure (the primary and the completing operation, and metastatic lymph nodes operation), and about the need for ^{131}I -treatment. Surgery is the first step in the treatment of thyroid carcinoma which has the possibility of complications influencing the patient's quality of life significantly. Among these complications, paresis of the recurrent laryngeal nerve and postoperative hypoparathyreosis are the most important ones. The incidence of these complications is the lowest during the first operation. This is why it would be most beneficial to determine the extent of the surgical intervention before or during operation. Completing operations can not be avoided even if we opt for the most radical procedure, total thyroidectomy for all patients, as pre- and intraoperative diagnostic methods are not a hundred percent reliable, either separately, or in combination. Moreover in cases where the final histology reveals thyroid carcinoma without clinical symptoms, we face again the question of performing a completion operation.

The post-operative treatment, follow-up care, and changes in the quality of life of patients who underwent surgery for differentiated thyroid carcinoma is an important public health issue. These patients will require lifelong follow-up care. It is both possible and necessary to adhere to an individualized long-term follow-up plan in our age of cost-oriented health care system, as

- 1/ the number of lost workdays is significant
- 2/ certain diagnostic procedures are unpractical to use routinely due to either their high cost (such as CT, MRI, PET), or because they can also affect the patients adversely
- 3/ performing whole body ^{131}I scan, or ^{131}I therapy, the one-month suspension of thyroid substitution can adversely affect the patients' quality of life due to the hypothyreosis.

Sorting patients into groups based on the available data, and prognostic factors before the operation can be helpful to identify those cases that require more detailed preoperative investigation and therapy.

Due to the long survival period, the examination of factors present at the time of surgery requires long-term follow-up. These were therefore investigated by retrospective studies; data from prospective studies have yet to be published. Survival depends not only on tumor size, lymph node and distant metastases, determined by the commonly used TNM classification, but also on several other factors. Research groups in America and in Europe examined the effects of different factors. There is a difference in the number of cases examined, in the frequency of differentiated and undifferentiated tumors, and whether the study included papillary, follicular, or both carcinoma types.

The reason for the long-term good prognosis of differentiated thyroid carcinomas is still unknown. One possible explanation is the response of the immune system. Differentiated thyroid cancer is often accompanied by lymphocytic infiltration of the tumor. The possible connection between thyroid carcinoma and lymphocytic infiltration is not completely understood. Most

authors found the coexisting chronic thyroiditis to be a favourable prognostic factor.

The effects of moderate iodine deficiency on the above mentioned factors have not been investigated.

The effects of ionizing radiation on the pathogenesis of thyroid carcinoma, as an etiological factor, were examined by many investigators. Such studies were initiated by the angst the Chernobyl accident caused in 1986.

My goal was to find the answers to the following questions:

1/ What prognostic factors influence the long-term survival in patients with differentiated thyroid carcinoma?

1. gender
2. age
3. tumor size
4. distant metastasis
5. lymph node metastasis
6. lymphocytic infiltration
7. operation
8. histological characteristics
9. iodine supply

2/ How is prognosis influenced by the simultaneous presence of the tumor and lymphocytic thyroiditis?

3/ Does iodine deficiency significantly influence the clinical and morphological characteristics of thyroid tumors?

4/ What changes can be observed in the patients' TNM classification and in their surgical treatment during the study period?

5/ What clinical and morphological changes can be described in thyroid tumors following the Chernobyl accident?

6/ During operation, how can we utilize the results we gained by examining the prognostic factors?

7/ Which are the most important surgical techniques to follow during primary and completing operations?

2. Patients and methods

At the 1st Department of Surgery Medical and Health Science Center, University of Debrecen, 492 patients were operated on for differentiated thyroid carcinoma between 1971 and 1998 (386 for papillary carcinoma and 106 for follicular carcinoma). Data of 423 patients have been analyzed during our retrospective study. Survival data have been gained from operating and post-operative follow-up documents, and from questionnaires mailed to the patients. Histology specimens were re-evaluated and the diagnosis was revised based on the most up-to-date classification guidelines.

Tumor size, lymph node and distant metastases, age over 40, gender, the extent of the operation, multifocality, lymphocytic infiltration, and iodine supply as independent variables have been examined in our retrospective study both in the papillary and follicular groups.

Total thyroidectomy (the complete removal of the thyroid gland) and near-total thyroidectomy (when only a 0.5-1 cm³ portion of either thyroid lobe is spared, close to the rear capsule in order to make sure that the recurrent laryngeal nerve running behind it is spared) were considered “radical operations.” The thyroid tissue that is spared during near-total thyroidectomy can be ablated by ¹³¹I, thus practically achieving the condition after total thyroidectomy. Thus cases of total and near-total thyroidectomy were evaluated as one group. Cases where a larger amount of thyroid tissue was left during the operation (lobectomy, uni- or bilateral subtotal resection) were analyzed as a distinct group. The extent of lymphocytic infiltration in the tumor was also evaluated. Previous studies found that iodine intake in Hungary correlate well

with the iodine level in drinking water, therefore we calculated iodine intake levels from the iodine levels of the drinking water near the patients' residence. Survival curves were made by the Kaplan-Meier method, considering only tumor specific mortality. Data were then analyzed by by Cox regression. Statistical analysis and survival curve calculations were done by using the SPSS for Windows program.

We analyzed changes in TNM staging and operation types in two separate time periods, one between 1971 and 1984, the other between 1985 and 1998.

To evaluate epidemiologic and pathomorphologic changes resulted from the Chernobyl disaster, we analyzed all surgical cases in two years prior (1981 and 1985) and two years after (1989 and 1995) the accident in the nuclear reactor, a total of 1226 cases. We compared the incidence and the age distribution of the histologically different carcinomas. Among the pathologically benign abnormalities, we examined the frequency of degenerated goiter, Graves' disease, chronic lymphocytic thyroiditis, and adenomas, and were looking for pathological abnormalities such as atypical adenoma, Hurtle cell adenoma, cystadenoma, papilla formation, and oncocytic transformation.

3. Results

Follow-up and survival data

386 patients underwent surgery for papillary carcinoma (average age: 42.7 +/- 16.0 ys, male: 68, female: 318, male:female ratio 1:4.7) at the 1st Department of Surgery, University of Debrecen, Medical and Health Science Center. The 10- and 20-year survival was 87.9% and 84.0%, respectively. The average follow-up period was 9.6 +/- 6.9 ys. 106 patients were operated on for follicular carcinoma (average age: 48.5 +/- 14.9 ys, male: 20, female: 86, male:female

ratio 1:4.3). In this group both the 10- and the 20-year survival was 78.2%. The average follow-up period was 9.6 +/- 7.0 ys.

We found the usual TNM stage distribution among our patients. Most patients were in stage T₂ (PTC: 32.9%, FTC: 49.1%). Papillary carcinomas metastasized primarily to the regional lymph nodes of the neck. At the time of surgery, 134 (34.7%) of the 386 patients had lymph node metastases, including 26 patients with stage N_{1b}, bilateral metastases. Follicular carcinomas gave mostly distant metastases (to the bone and lungs), in 10.4% of our patients.

38 patients died of the primary disease in the group of 386 papillary patient group. 3 of these patients had stage T₄M₁ tumors, 6 had distant metastases (T₁₋₃M₁), and another 18 had extrathyroideal (T₄M₀) tumors. In the follicular group, 16 patients died of the 106. Of these, 4 had T₄M₁ stage. Another 5 had known distant metastases (T₂₋₃M₁) at the time of surgery, and 3 patients had stage T₄M₀. In the follicular cancer group all cancer related deaths occurred in the first decade of the follow-up.

Based on the Kaplan-Meier survival curves, age over 40 years, distant metastases, extrathyroidal invasion, lymph node involvement, and infiltrating versus encapsulated form of tumor had negative influence on survival. Multifocality, gender, type of surgery (total or near-total thyroidectomy vs. less than near-total thyroidectomy), and lymphocytic infiltration did not influence survival (**Table 1**).

Table 1 Survival factors of papillary and follicular cancer patients (Kaplan-Meier curves - p value)

	Papillary cancer	Follicular cancer
Gender	0.28	0.20
Age	<0.0001	0.046
Size	0.48	0.20
T₁₋₂₋₃₋₄	<0.0001	<0.0001
Met.	<0.0001	<0.0001
Node	0.01	0.046
Infiltr	0.37	0.29
Surg	0.47	0.11
Multif	0.47	0.6
Encaps	0.05	0.08
Iodine	0.66	0.7

Gender - sex of patient; **Age** – age of patient over 40; **Size**- tumour size if no extrathyroidal invasion present; **T₁₋₂₋₃₋₄** - tumor size (intrathyroidal v.s. extrathyroidal tumor); **Met** - distant metastasis; **Node** - lymph node metastasis present; **Infiltr** - lymphocytic infiltration present; **Surg**- extent of surgery (total or near total thyroidectomy vs. less than near total thyroidectomy); **Multif** - multifocal tumour; **Encaps** – encapsulated form of tumor v.s. infiltrative; **Iodine** - iodine intake

Patients with stage T₄ tumors, spreading beyond the anatomical borders of the thyroid gland, had significantly worse survival curves than those with T₁, T₂, or T₃ stage tumors, both in the papillary and in the follicular groups. Patients with stage T₄ tumors often had only palliative operations. If we exclude patients with stage T₄ tumors from the analysis, there is no significant difference between the survival of stage T₁, T₂ and T₃ patients. 13 patients with papillary carcinomas and 11 in the follicular group had distant metastases at the time of diagnosis. 9 of these patients died during the follow-up period in each group. Distant metastases meant significantly worse survival chances in both groups. The presence of lymphocytic infiltration accompanied a slightly better prognosis in both the papillary and the follicular group, but this difference was not significant.

Of the 386 patients with PTC, 96 underwent total, and 166 near-total thyroidectomy. Less radical operations were performed on 121 patients. Of the 42 stage T₄ patients, 15 had palliative operations, another 3 had only biopsy for histology. 27 total and 34 near-total thyroidectomies were performed in the patients with FTC. Another 45 of the patients in this group had only lobectomy or subtotal resection, 2 underwent palliative operation, and 1 had only biopsy. Analyzing the survival curves, we found no significant difference, but total and near-total thyroidectomy yielded better long-term survival in follicular carcinoma cases. We found multifocal appearance of the tumor in 128 patients (33.2%) with papillary, and in 19 patients (18.0%) with follicular carcinoma. Multifocality did not show significantly worse survival in either group. In 28 of the 128 patients with multifocal papillary carcinomas, we performed completing operations due to the stage of the tumor. In 17 of these cases, histology revealed residual tumors. On the other hand, 52 completing operations were performed for the 258 solitary tumors; among these cases only 7 residual tumors were found. This finding highlights a significant difference, which supports the importance of a radical operative approach. Iodine intake (calculated from the iodine levels of the drinking water near the patients' residence) did not influence survival significantly in either the papillary (p=0.66) or in the follicular (p=0.70) cases. Increasing iodine intake, however, significantly increased the relative frequency of papillary carcinomas, with a relative decrease in follicular carcinomas.

Those factors that significantly influenced survival were also examined by Cox regression analysis. This analysis found that in PTC age over 40 years old, pT₄ stage tumor, distant metastases, and lymph node metastases, while in patients with FTC, age, extrathyroidal growth, and distant metastases were significant prognostic factors (**Table 2**).

Table 2 Prognostic risk factors: Cox regression analysis (p)

	Papillary cc.	Follicular cc.
Age	0.002	0.011
pT4	<0.0001	0.003
Met	<0.0001	<0.0001
Node	<0.0001	0.171

Age - age of patient, **pT4** - tumour size if extrathyroidal invasion present **Met** - distant metastasis; **Node** - lymph node metastasis present

During the time period our study covered, the absolute number and relative frequency of PTC cases in the past decade increased, as opposed to the decreasing ratio of FTC among all cases. This extent is due to the increasing number of patients we treat at our hospital from Eastern Hungary for primary or completing operations. Among patients with FTC, the proportion of early T₁ and T₂ stage cases has been increasing, while in the group of PTC patients no such trend could be seen. Among PTC patients, the frequency of lymph node metastases decreased from 40.7% to 30.9%, whereas distant metastases became less frequent in both groups.

Changes following the Chernobyl nuclear accident

To study the effects of the accident at the nuclear reactor, we analyzed cases in two years prior (1981 and 1985), and two years after (1989 and 1995) the accident. Data for a total of 1226 patients who underwent operations for benign or malignant thyroid lesions were analyzed. The incidence of carcinomas did not increase significantly following the disaster (from 9.9% to 11.2%), but the frequency of PTC cases increased significantly, from 54.5% to 77.7% with a

simultaneous decrease of FTC cases from 30.9% to 13.2%. The proportion of childhood and juvenile carcinomas has increased. Since the nuclear accident, papilla formation, oncocytic transformation and lymphocytic infiltration have significantly increased among the benign thyroid abnormalities.

4. Discussion

The survival of differentiated thyroid carcinoma is also influenced by several factors other than those evaluated by the commonly accepted TNM classification (tumor size, lymph node metastases, and distant metastases). Various scoring systems have been created based on the results of retrospective studies. In **Table 3**, we compare our data to those factors that are considered major influencing factors by most authors. The two types of differentiated carcinomas have to be examined separately due to their different biological behavior in our opinion. The patient's age at the time of diagnosis is the most important prognostic factor in both the PTC and FTC patient groups, with both recurrence and mortality rates increasing after age 40. In older patients, recurrence appears earlier, and death also occurs sooner after recurrence, indicating faster tumor growth and mitosis rate. Furthermore, these tumors are less differentiated, and ^{131}I isotope uptake is lower by both the primary tumors and their metastases.

Our results indicate a continuous increase in patient numbers, with increased proportion of papillary carcinomas, and more frequent presence of early stage tumors during the time period of our study. All these correlate well with foreign statistics. Improved diagnostic techniques, especially the more widespread use of ultrasound imaging and its increasing use as a screening technique is a reason for these findings.

Table 5 Prognostic factors influencing survival

Author	Type	N	Gender	Size	pT4	Met	Node	Multif	Infiltr	Surg	Iodine
Byar (1979)	All	507	M		M	M					
Cady (1988)	DTC	755		M	M	M					
Sanders (1998)	DTC	1019		M	M	M	n.s.			n.s.	
Mazzaferrri (1994)	DTC	1355	M	M	M	M	M	M		M	
Sellers (1992)	DTC	212	n.s.	M	n.s.	M	M	n.s.		n.s.	
Simpson (1987)	PTC	1074	n.s.	n.s.	M	n.s.	n.s.	n.s.		n.s.	
Hay (1987)	PTC	860	n.s.	M	M	M	n.s.		n.s.		
Hay (1993)	PTC	1779	n.s.	M	M	M	n.s.	n.s.	n.s.	M	
Akslen (1993)	PTC	173	M	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	
Kashima (1998)	PTC	1533	n.s.	n.s.	n.s.		M	n.s.	M		
Present study	PTC	386	n.s.	n.s.	M	M	M	n.s.	n.s.	n.s.	n.s.
Simpson (1987)	FTC	504	n.s.	M	M	M	M			M	
Mueller-G. (1990)	FTC	149	n.s.		n.s.	M	n.s.				
Shaha (1995)	FTC	228	n.s.	M	M	M	n.s.				
Present study	FTC	106	n.s.	n.s.	M	M	n.s.	n.s.	n.s.	n.s.	n.s.

All - all types of thyroid cancer; **DTC** - differentiated thyroid cancer; **FTC** - follicular cancer; **Infiltr** - lymphocytic infiltration present; **Iodine** - iodine intake; **Met** - distant metastasis; **Multif** - multifocal tumour; **N** - Number of patients; **Node** - lymph node metastasis present; **n.s.** - non significant; **pT4** - tumour size if extrathyroidal invasion present; **PTC** - papillary cancer; **Gender** -sex of patient; **Size**- tumour size if no extrathyroidal invasion present; **Surg**- extent of surgery (total or near total thyroidectomy vs. less than near total thyroidectomy); **M** - significant (p< 0.05)

Cancer patients undergo surgery at earlier stages because fine needle biopsy and ultrasound-guided aspiration cytology has become ever more widespread during the past two decades. Yet with the increase in the number of patients with papillary carcinomas, the proportion of stage T₄ cases did not decrease. This might be explained by the relatively high number of patients admitted to our department as a designated center for Eastern Hungary who were seen with advanced stage tumors during this time period. On the other hand, unfortunately

it still happens, primarily among the elderly, that patients go to the doctor after the tumor has already persisted for 10-15 years.

The most common operation for an endocrine disease is performed for multinodular goiter or for a solitary node in the thyroid gland. It is important to exclude the possibility of malignancy during the treatment of patients with a node in the thyroid gland, as best survival is achieved when thyroid carcinoma is operated on at an early stage. Cytology has an important role in the evaluation of dominant nodes and can basically influence the surgical plan. For cases (C3-C5) where preoperative cytology proves or raises the suspicion of malignancy, we follow the following operative procedures at our clinic: The first step is the removal of the thyroid lobe containing the node, together with the isthmus, preserving the recurrent laryngeal nerve and the parathyroid glands. The lobe is then sent for intraoperative frozen section.

- If the quick-frozen sample indicates malignancy, we go on with the operation, extending the surgery to total thyroidectomy (or to near-thyroidectomy if the surgeon is unsure whether the recurrent laryngeal nerve was preserved).
- If the result of the frozen section is uncertain, or if the opinions of the two pathologists are contradictory, and the diagnosis can only be established from the final section, the operation is finished as a lobectomy, and the other side is only palpated. It is rare but may occur that we find a lesion, a node, undetected by imaging techniques, which is then removed. If the final histology later proves malignancy, we operate the patient, performing a so-called “completing” operation. The initial lobectomy removed the lobe of the thyroid gland containing the tumor, therefore now only the other, yet untouched side needs to be operated on. Under these conditions, the recurrent laryngeal nerve and the parathyroid glands can be identified with certainty, which is important in order to avoid the two most severe complications (paresis of the recurrent laryngeal nerve and

hypoparathyroidism) that might persist for the rest of the patient's life. Stage T₁, solitary papillary carcinomas without metastases require no completing operations.

We performed primary radical operations on 181 PTC patients in our hospital during the study period: 70 total and 103 near-total thyroidectomies, and 8 lobectomies. 85 patients needed completing operations. 36 patients had their first operation at another hospital, and based on their histology results, they were referred to us for the second operation. Of the other 49 cases, 18 patients had intraoperative frozen section which could not rule out malignancy, or resulted in false negative (benign) diagnosis. The completing operations were total thyroidectomies in 24 cases, near-total thyroidectomies in 59 cases, and 2 lobectomies. Residual tumors were found in the removed thyroid tissue in 23 cases (27%). During the study period, 101 patients underwent only lobectomy or subtotal resection, which are not considered radical enough according to present therapeutical guidelines. This relatively high number is explained by the patients' refusal to a second operation.

Total (in 14 patients) or near-total (15 patients) thyroidectomy was performed in 29 patients with FTC as the first operation. 32 patients underwent completing operations. Among these patients, 14 were referred to us from another hospital following their first operation. Of the other 18 cases, histological examination found residual tumors in 6 of the specimen removed during 13 total and 19 near-total thyroidectomies. Paresis of the recurrent laryngeal nerve occurred in 2.2-3.4% and lasting hypoparathyroidism in 2.2-7.1% among the groups.

The frequency of lymph node metastases is between 35-60% in PTC, and significantly lower (15-20%) in FTC patients based on the literature. In childhood-PTC cases, its prevalence can be as high as 80%. They can also accompany papillary "microcarcinomas" – tumors smaller than 1 cm, they can

even be the first clinical symptom of the disease, leading to the diagnosis. Among our 386 PTC patients, 134 had lymph node metastases (34.7%). An even higher prevalence (48.0%) was found in our childhood and juvenile population. Cervical lymph node enlargement was the first clinical sign in 57 PTC patients, and the subsequent histological analysis of the removed lymph node established the diagnosis of PTC. Ultrasound imaging of the thyroid gland should be part of the routine diagnostic examination in cases of cervical lymphadenomegaly nowadays, followed by cytology if necessary (ultrasound-guided, if needed). This approach could decrease the number of patients who are first biopsied, and later, based on the result of histology, have to undergo a second operation to bring a final surgical solution to the tumor of the thyroid itself.

The surgical treatment of cervical lymph node metastases can either be local dissection (LD), or modified radical neck dissection (MRND) with therapeutic or prophylactic goal in mind. Proponents of the less radical LD argue that lymph node metastases don't affect survival. Proponents of neck dissection argue that prophylactically performed MRNDs reveal lymph node metastases in up to 70% with negative palpation findings. Only the lymph nodes on the side of the thyroid cancer are involved in most cases. We performed 89 LDs and 44 MRNDs in our PTC patients. In 3 cases the metastatic cervical lymph nodes adhered to neighboring organs, and only their palliative removal was possible. Subsequent operations for recurrent lymph node involvement was performed in 63 patients. 34 patients needed one, 19 patients needed two further operations, and 5 patients required three and another 5 required four subsequent operations. The number of patients with re-operations for recurrent lymph node involvement was 17 following LDs, and 16 after MRNDs. In 30 patients (11.9%) who were categorized to be in stage N₀ by imaging techniques and histology at the time of the diagnosis of the tumor, follow-up examinations revealed lymph node metastases. We found no worse relapse rate in patients with only LDs than in those patients who underwent MRNDs, yet we changed

our approach during the past 10 years, and we recommend performing MRNDs, in line with the recommendations of the literature.

The scientific literature is divided on the prognostical significance of the autoimmune response to thyroid carcinoma. Some authors consider high antibody levels against TSH or the thyroid gland itself a promoter of malignant transformation. Others found more favorable outcomes for those cases when papillary carcinoma was accompanied by Hashimoto thyroiditis or lymphocytic infiltration. The results of clinical and immunological studies of differentiated thyroid carcinomas support the fundamental role that the immune system plays in keeping the disease under control. We have established an animal model previously, where SCID (severe combined immune deficient) mice were transplanted with human thyroid carcinoma with and without the autologous human immune system present. Our results supported the importance of the role of the immune system.

Among the patients with PTC, those with lymph node metastases had evident lymphocytic infiltrations more often than those without metastases. Tumor cells reaching the regional lymph nodes promotes a more pronounced lymphocytic infiltration by the direct sensitization of the lymphocytes in the lymph nodes. This may be the possible explanation for this phenomenon in PTC cases.

The presence of lymphocytic infiltration showed a somewhat better prognosis in both PTC and FTC cases in our patients during the study period, though it did not result in a significant difference.

Another reason for the need to carefully plan the extent of operations, keeping the various prognostic factors in mind, is the spread of minimal invasive operation in the thyroid surgery.

Since the Chernobyl nuclear disaster, several research groups have been trying to quantify the extent of the damage the radiation had caused in the large number of exposed people. It is well known that the nuclear cloud contained a

high concentration of iodine isotopes, primarily ^{131}I . Researchers therefore are examining the change in the prevalence of thyroid gland diseases, primarily that of carcinomas. By now there is a consensus among the majority of the publications that there is an increase in the number of thyroid cancer cases, especially in the papillary type, mostly in children and juveniles, that follows an aggressive course, and is accompanied by autoimmune thyroiditis. We examined the patient population operated for thyroid disease in two selected years prior and after the Chernobyl disaster. This comparison found a significant increase in the number of cases with papillary formation, oncocytic transformation, and the frequency of chronic thyroiditis. Furthermore, papillary carcinomas became more numerous, especially in the younger segment of the population.

5. Summary, new conclusions

The clinical course of papillary and follicular thyroid carcinomas is relatively favorable. They have low tumor-related mortality, and survival rates have been increasing during the past 10-15 years as the result of modern diagnostic and therapeutic protocols. Determining and applying the prognostic factors of survival gives us a chance to design an individualized surgical plan concerning the extent of the surgical intervention, the need for follow-up treatment, the frequency and extent (invasiveness, cost) of follow-up care visits.

The demographic parameters of the population we studied with differentiated thyroid carcinomas were similar to those previously published from other geographic areas. Cox regression analysis found that in papillary carcinoma cases, age over 40 years, pT₄ stage tumor, distant metastases, and lymph node metastases, while in patients with follicular carcinoma, age, extrathyroidal growth, and distant metastases are significant prognostic factors. Lymphocytic infiltration indicated somewhat better prognosis in both the

papillary and follicular group of patients, but with no significant difference. Iodine intake did not significantly influence survival either among patients with papillary or follicular carcinomas. But the increase in iodine intake resulted in a significant increase in the frequency of papillary carcinoma cases as compared to that of follicular carcinoma cases.

Comparing the time periods between 1971-1984 and 1985-1998, we found an increase in the number and in the proportion of earlier stage, less advanced cases. The increasing use of ultrasound imaging as a screening tool, and cytological analysis play important roles in this finding. Primarily definitive operations are known to have the lowest incidence of complications (recurrent laryngeal nerve paresis, and hypoparathyroidism), yet the question of completing re-operations cannot be avoided, as pre- and intraoperative diagnostic methods are no one hundred percent reliable, either separately, or in combination. Ultrasound imaging of the thyroid gland should be part of the routine diagnostic examination in cases of cervical lymphadenomegaly nowadays, followed by cytology if necessary (ultrasound-guided, if needed). This approach could decrease the number of patients who are first biopsied, and later, based on the result of histology, have to undergo a second operation to bring a final surgical solution to the tumor of the thyroid itself.

Changes after the Chernobyl nuclear accident, and the increase in the number of papillary carcinomas, especially in the younger age groups, underline the importance of early, careful diagnostic approach for nodular lesions in the thyroid gland in the endangered age groups. In the histology specimen of these patients, focal papillary structures and oncocytic transformations are more frequent, making cytological diagnosis much more difficult. For these cases, only surgery and a definitive histological analysis can bring a final solution.

New conclusions

1. Based on long-term follow-up data on patients with papillary thyroid carcinomas and follicular thyroid carcinomas, we found by Cox regression analysis that in papillary carcinoma cases, age over 40 years, pT₄ stage tumor, distant metastases, and lymph node metastases, while in patients with follicular carcinoma, age, extrathyroidal growth, and distant metastases are significant prognostic factors. In this latter population, the effect of lymph node metastases was not significant. The unfavorable prognosis in patients over 40 is in line with data from the literature.
2. Prognosis is not affected by lymphocytic infiltration in either the papillary or the follicular carcinoma group of patients.
3. Iodine intake does not influence significantly survival either among patients with papillary or follicular carcinomas. But the increase in iodine intake resulted in an increase in the frequency of papillary carcinoma cases as compared to that of follicular carcinoma cases.
4. No statistically significant difference could be found in the survival of patients who underwent radical (total or near-total thyroidectomy) versus less radical operations (lobectomy, subtotal resection).
5. The multifocal appearance of papillary carcinomas (present in 33.2% of our cases) did not influence survival significantly, but significantly more residual tumors were found during completing operations performed for multifocal carcinomas than in those performed for solitary carcinomas. This justifies a radical surgical approach in papillary carcinomas.

6. Prognostic factors need to be weighed carefully when patients are chosen for minimally invasive operations.

7. Comparing the time periods between 1971-1984 and 1985-1998, we found an increase in the number and in the proportion of earlier stage, less advanced cases. The increasing use of ultrasound imaging as a screening tool, and cytological analysis play important roles in this finding.

8. We found no worse relapse rate in patients undergoing local lymph node dissection (LD) when compared to those patients who had modified radical neck dissection (MRND). Nevertheless, in line with the recommendations in the scientific literature, we recommend performing MRNDs, until our data are verified in larger number of patients, or corroborated by other researchers.

9 Following the accident at the Chernobyl nuclear reactor,

- The number of childhood and juvenile carcinoma cases increased. No such change was found in the population aged over 30.
- There was an increase in the frequency of lymphocytic infiltrations and Hashimoto thyroiditis.
- Papilla formation and oncocytic transformation were also found in significantly higher numbers, which make cytological diagnosis much more difficult.

These changes might explain the increase in those primarily younger patients after the Chernobyl accident, who were seen in our hospital with concomitant thyroiditis or suspicious (C3) cytology results. For these patients, only surgery and the histology can give a final answer concerning malignancy and bring the definitive therapeutic resolution.

PUBLICATIONS

a. Publications related to the thesis

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b. Other publications related to thyroid gland

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