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ORIGINAL ARTICLE

Lobectomy versus total thyroidectomy in children with post-Chernobyl thyroid cancer: a 15 year follow-up

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Abstract In 1994, 21 Belarus children presenting papillary thyroid cancer (PTC) diagnosed after the Chernobyl disaster, and already submitted to subtotal surgery, underwent thyroid re-operation and post-operative radioiodine (131^I) therapy. All were re-evaluated after a 15-year follow-up, to evaluate the results of partial versus total thyroidectomy. Nineteen out of 21 children (mean age 9.2 years) had previously undergone a lobectomy. All cases underwent re-operation in 1994. Histology revealed a PTC in the residual lobe in three cases, three had lymph node metastases. After surgery, 20 patients underwent 131^I therapy. The post-131^I whole body scan was negative in seven cases, showed neck node metastases in five, lung metastases in three, multiple associated metastases in six. The follow-up was performed with rhTSH-stimulated serum thyroglobulin (Tg) evaluation and ultrasonography. Twenty patients showed Tg <1 ng/ml and negative ultrasonography; the patient who refused 131^I therapy showed a thyroid remnant and a Tg of 32 ng/ml. Chi-square analysis showed significantly higher prevalences of residual cancer in the neck or lung, lymph node metastases, and re-operations (before completion) in patients who had undergone lobectomy than in those who had undergone completion thyroidectomy and 131^I therapy. The surgical complications after lobectomy were similar to those after completion thyroidectomy. A less-than-total thyroidectomy should not be indicated in patients with radiation-induced PTC, due to the high risk of residual cancer in the thyroid left in situ. The results of this study favor total thyroidectomy as the initial treatment for thyroid cancer in children exposed to fallout radiation.

Keywords Thyroid cancer · Childhood · Chernobyl · Radiation · Thyroidectomy · Complications

Introduction

In 1994, our department had the opportunity to evaluate the clinical conditions of a cohort of 47 children who had already been operated on in Belarus for papillary thyroid cancer (PTC) following the Chernobyl accident. All the patients came from the same area (the Gomel region). After a careful evaluation, the decision was made (according to the most widely used treatment schedules for this kind of patient) to re-operate on 21 children between September and October 1994 [1, 2], and the extent of completion surgery was complete bilateral central compartment resection of both residual thyroid tissue and/or lymph nodes. In fact, there was a high prevalence of residual disease, which was confirmed in 61% of the cases [1] both by histological specimen examination and whole body scan (WBS).

Fifteen years later (October 2008–January 2009), all the patients underwent a full workup in our hospital. We then decided to compare the results of lobectomy with those of total thyroidectomy combined with radioiodine treatment in the same patients.

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Materials and methods

Patients

We evaluated 21 Belarusan consenting children suffering from PTC [F/M, 14/7, mean age 9.2 years, mean age at presentation of PTC 9.6 years (range 4–14)], who had already been submitted to surgery in other surgical units of the former Soviet Union.

According to the final histology after the first surgery (that was obtained for every patient), the tumors were classified as follows, according to the DeGroot's Classification: Class 1, $n = 7$ (36%); Class 2, $n = 12$ (55%); Class 3, $n = 2$ (9%); Class 4, $n = 0$ (see also Table 1). Tumor size increased from 1.3 cm in the De Groot's Class I, to 1.9 cm in the Class II, to 2.4 cm in the Class III. Multifocality was present in 10/21 (48%) of patients.

Of these PTCs, 11/21 (52%) showed RET rearrangements; 8/11 (73%) of them a PTC 3 type, and 3/11(27%) PTC1 type (PTC2 was missing), with a prevalence similar to that found in other studies [3].

In neck ultrasonograms, all 21 children showed residual tissue in the thyroid bed (Fig. 1a, b). Nineteen children in this group had previously undergone an ultrasonographically confirmed total lobectomy, and five of them (25%) also demonstrated neck node metastases (Fig. 1c). In the two other children, who were previously subjected to total thyroidectomy, surgery was performed because of the presence of neck node metastases.

The pre-operative evaluation also revealed that five (26%) of the 19 patients who had undergone a hemithyroidectomy had unilateral recurrent nerve palsy. In the same group, two patients (10.5%) had permanent hypoparathyroidism.

The mean period from the first operation to our first observation was 2 years, and the surgical approaches at the first and at the re-operations are summarized in Table 1, together with the DeGroot's Classification of the tumors after the re-operations.

After the second surgery, hypoparathyroidism developed in four (21%) out of the 19 patients who underwent a completion total thyroidectomy, and unilateral laryngeal nerve palsy developed in one (5.2%) of these 19 patients.

Histological examinations were positive for residual PTC in six patients (28.6%): (a) in three cases (14.3%), other PTC foci were found in the thyroid remnant; (b) in three other cases (14.3%), lymph node metastases were found. Fifteen patients did not have any residual disease.

All the patients but one (who refused ^{131}I therapy) remained off thyroid hormone supplementation following completion thyroidectomy in order to obtain high levels of circulating TSH (higher than 50 μU/ml), and they underwent radioiodine treatment and a post-therapy WBS using a variable dosage of ^{131}I (from 30 to 80 mCi in relation to the body weight, surface area, thyroid bed radioiodine uptake, etc.: the dose varied from 2 to 7 MBq/kg) from 4 to 6 weeks after operation. WBSs were performed 5–10 days after the administration of ^{131}I [4, 5].

After the re-operation, on the basis of the results of the post-^{131}I therapy WBSs, this was the evaluation of the patients, according the starting DeGroot's classification (Table 2): De Groot's Class 1: five free of disease (free), one lung metastasis (lung), one lymph node + lung + bone metastases; Class 2: one free, four lymph node metastases, two lung and five lymph node + lung metastases; Class 3: one free, one lymph node metastasis.

Following the ^{131}I therapy, all patients were maintained on thyroid hormone, and the dose of thyroid hormone was adjusted with the aim to obtain low levels of TSH (<0.07 μU/ml). Fourteen patients were further treated with ^{131}I therapy [median number of two ^{131}I treatments per patient (range 1–3)].

Table 1 Staging and type of first surgery and re-operation in 21 children operated on for PTC, following both the UICC/AJCC [23] and the DeGroot's classifications

TNM UICC/AJCC	De Groot's class	First operation			Re-operation			
		TL	TT	Total	CT	ND	CT + ND	Total
T1N0 ($n = 6$)	I	6	1	7	1	1	5	7
T2N0 ($n = 1$)								
T1N1 ($n = 9$)	II	11	1	12	9	1	2	12
T2 N1 ($n = 3$)								
T3N0 ($n = 2$)	III	2	0	2	0	0	2	2
	Total	19	2	21	10	2	9	21

TL total lobectomy, *TT* total thyroidectomy, *CT* completion thyroidectomy, *ND* neck node dissection. DeGroot's classification: *Class I* tumor limited to the thyroid gland, *II* neck node metastases, *III* tumor extending outside the thyroid gland, and *IV* distant metastases. No patient was De Groot's stage IV. Lymphadenectomy was performed at initial operation in 12 patients

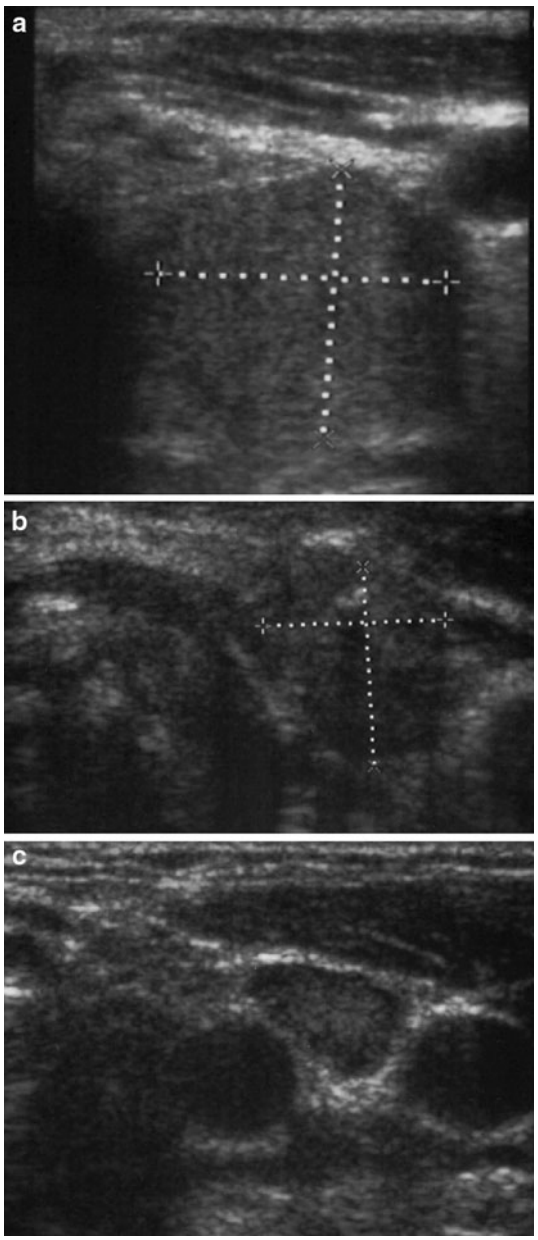

Fig. 1 Examples of neck ultrasound images of residual tissue (**a**, **b**) in the thyroid bed after surgery, and of lymph node metastasis (**c**). **a** Residual tissue between trachea and carotid. **b** Residual tissue with calcification between trachea and carotid. **c** Lymph node metastasis between carotid and jugular vein

Patient re-evaluation in 2008–2009

Study design

The study design consisted of serum thyroglobulin (Tg) measurements and ^{131}I WBSs under rhTSH stimulation during L-T4 suppressive therapy. Patients received one injection of rhTSH (0.9 mg, im; Thyrogen, Genzyme Corp., Cambridge, MA) for two consecutive days. Serum samples for TSH and Tg measurements were collected before the first rhTSH injection and during the following days, up to the fifth day [6]. All patients also underwent neck ultrasonography, and suspicious neck masses or lymph nodes were submitted to fine needle aspiration cytology (FNAC) [7], and they all gave their signed consent for the treatment of their clinical data.

Methods

Sequential serum Tg and TSH determinations were run in the same assay. Serum Tg was measured using a commercial immunometric assay (Diagnostic Products, Los Angeles, CA) with a lower detection limit of 0.2 ng/ml and a functional sensitivity of 0.9 ng/ml. The assay was standardized against certified reference material for human Tg (CRM 457) from the Community Bureau of Reference of the European Commission [6].

In our laboratory, the intra- and inter-assay coefficients of variation of the method were 4.3 and 7.0%, respectively. Based on the functional sensitivity of the assay (0.9 ng/ml), we selected 1 ng/ml as the cut-off value discriminating undetectable from detectable Tg levels. Anti-Tg autoantibodies (AbTg) were measured in all sera by an immunoradiometric assay method (ICN Pharmaceuticals, Inc., Beerse, Belgium). A concentration of AbTg <5 U/ml was considered negative. Serum TSH was measured using an ultrasensitive commercial immunometric assay (Diagnostic Products).

Statistical analysis

The results are expressed as means ± SD and the given range. The Chi-square and the Mantel–Haenszel tests were used to compare the same patients in their different situations, to obtain a contingency table analysis, as indicated in the results.

Results

Results of the long-term follow-up

In October 2008–May 2009 (after 15 years), all 21 patients were re-evaluated by neck ultrasonography and rhTSH-stimulated serum Tg. All patients had a concentration of AbTg <5 U/ml, which is considered negative.

In 20 cases, neck ultrasonography confirmed the absence of residual tissue and of images suspicious for neck lymph node metastasis, and rhTSH-stimulated serum Tg was <1 ng/ml.

The remaining one patient (the same who refused ^{131}I therapy) showed residual thyroid tissue on the left side in

Table 2 Comparison of the results of initial lobectomy with those of completion thyroidectomy in the 19 children with a residual thyroid lobe

	Presence of residual cancer in the neck or distant metastases (sum of results of histology and post-therapy WBS)	Absence of residual cancer in the neck and distant metastases
Post-lobectomy	14	5
Post-completion thyroidectomy and ^{131}I	0	19
Chi-square test, Mantel–Haenszel = 21.6, $P = 0.000$		

	Re-operation	No re-operation
Post-lobectomy before completion thyroidectomy	5	14
Post-completion thyroidectomy and ^{131}I	0	19
Chi-square test, Mantel–Haenszel = 5.6, $P = 0.018$		

	Complications (recurrent nerve palsy or hypoparathyroidism)	No complications
Post-lobectomy	7	12
Post-completion thyroidectomy	5	14
Chi-square test, Mantel–Haenszel = 0.474, $P = 0.49$		

neck ultrasonography without nodules or images suspicious for lymph node metastasis. FNAC of the left thyroid tissue confirmed the presence of normal thyroid tissue. The patient had a basal Tg value of 2 ng/ml, which increased to 32 ng/ml after rhTSH stimulation.

Lobectomy (2-year follow-up) versus completion thyroidectomy (15-year follow-up)

Chi-square and contingency table analysis showed a significantly higher prevalence of residual disease in patients after lobectomy than after completion thyroidectomy and ^{131}I therapy (Table 2). This result is particularly important considering the length of the follow-up period (15 years) after the completion thyroidectomies relative to that after the one after the lobectomies (mean 2 years).

After lobectomy and before completion thyroidectomy, five patients had undergone other operations (mainly lymphadenectomy), while no patient was re-operated on after completion thyroidectomy and ^{131}I therapy ($P < 0.05$). The rate of complications (recurrent nerve palsy and hypoparathyroidism) after lobectomy was similar to that after completion thyroidectomy (Table 2).

Discussion

In spite of its excellent prognosis, PTC in children implies a rather aggressive primary surgical treatment, consisting at least of a total thyroidectomy [8–11]. The removal of the entire gland allows the therapeutic use of ^{131}I with an excellent cure rate [12–14]. Furthermore, neck ultrasonography and serum Tg measurement guarantee the most successful and least invasive follow-up for these patients [15]. For this reason, this treatment protocol was advocated for children presenting with PTC due to exposure to nuclear radiation after the Chernobyl accident [1, 16, 17]. In the early phase of the treatment, however, total thyroidectomy was not the initial surgical approach in Belarus and Ukraine [16, 17], the two countries where most of the thyroid carcinomas in children were registered. Since, the aggressiveness of the disease seemed to us to be higher than in similar groups of children, where this was also in agreement with other clinical observations [2, 17–19], the problem arouse as to whether to re-operate on these patients to perform a completion thyroidectomy. In fact, it was readily apparent that a heavy involvement of lymph nodes, venous spread, and lung and bone metastasis was occurring in these children [17, 18]. However, recent studies seem to demonstrate that the possible increased aggressiveness of these tumors was due not only to the radiation exposure, but also to the iodine deficiency of these populations [20].

The results of the present crossover study (initial lobectomy vs. completion thyroidectomy and ^{131}I) show that after a 15-year follow-up, none of the patients treated with total thyroidectomy and ^{131}I therapy has experienced a recurrence or metastasis, while a high prevalence of residual cancer and metastasis was present in the 2-year follow-up after the initial lobectomies; however, further studies are necessary to evaluate the optimal treatment of radiation-induced thyroid cancer in children. After

lobectomy and before completion thyroidectomy, a significantly higher number of local recurrences required a second or third operation in several patients, whereas no patient had to undergo further surgery after total thyroidectomy. This finding is also in agreement with results obtained in patients not exposed to nuclear irradiation [21]. Moreover, the complication rate (recurrent nerve palsy and even hypoparathyroidism) after lobectomy was similar to that after thyroidectomy (no statistically significant difference). Surprisingly, two cases of hypoparathyroidism were registered after a single lobectomy performed in Belarus; this complication is generally absent after a hemithyroidectomy. The only explanation might be that a contemporary wide exploration on the opposite side was carried out that might have affected the blood supply to the parathyroid glands. Our surgical results after the completion thyroidectomy might also be regarded as disappointing, but a 5.3% rate of unilateral recurrent nerve palsy is consistent with other reports [16, 22], and this percentage corresponds to only one lesion out of 19 cases of completion thyroidectomy.

A specific reason to report on the long-term outcome of this group of patients resides in the fact that they are a homogeneous cohort; in fact, all the children came from a relatively small and compact area (Gomel) where the exposure was both high and uniform. Furthermore, the clinical evaluation and the surgical and nuclear medical procedures were all performed in a very short time and with homogeneous methods. This homogeneity in the patient cohort and their treatment distinguishes this study from most (if not all) other studies where the duration of data collection lasted for decades and uniform methods were not used. However, further studies are necessary.

Disclosure All the authors declare that no competing financial interests exist for the present study.

References

1. P. Miccoli, A. Antonelli, C. Spinelli, M. Ferdeghini, P. Fallahi, L. Baschieri, Arch. Surg. **133**, 89 (1998)
2. N.W. Thompson, in *Proceedings of a Workshop*, Bethesda, MD, 10–11 September 1992, p. 77
3. H.M. Rabes, E.P. Demidchik, J.D. Sidorow, E. Lengfelder, C. Beimfohr, D. Hoelzel, S. Klugbauer, Clin. Cancer Res. **6**(3), 1093 (2000)
4. M. Luster, S.E. Clarke, M. Dietlein, M. Lassmann, P. Lind, W.J. Oyen, J. Tennvall, E. Bombardieri, Eur. J. Nucl. Med. Mol. Imaging **35**(10), 1941 (2008)
5. S.I. Sherman, E.T. Tielens, S. Sostre, M.D. Wharam, P.W. Ladenson, J. Clin. Endocrinol. Metab. **78**, 629 (1994)
6. F. Pacini, E. Molinaro, M.G. Castagna, L. Agate, R. Elisei, C. Ceccarelli, F. Lippi, D. Taddei, L. Grasso, A. Pinchera, J. Clin. Endocrinol. Metab. **88**, 3668 (2003)
7. A. Antonelli, P. Miccoli, M. Ferdeghini, G. Di Coscio, B. Alberti, P. Iacconi, V. Baldi, P. Fallahi, L. Baschieri, Thyroid **5**, 25 (1995)
8. J.K. Harness, N.W. Thompson, M.K. McLeod, J.L. Pasieka, A. Fukuuchi, World J. Surg. **16**, 547 (1992)
9. A. Antonelli, P. Miccoli, V.E. Derzhitski, G. Panasiuk, N. Solovieva, L. Baschieri, World J. Surg. **20**, 867 (1996)
10. C. Ceccarelli, F. Pacini, F. Lippi, R. Elisei, M. Arganini, P. Miccoli, A. Pinchera, Surgery **104**, 1143 (1988)
11. C. Spinelli, A. Bertocchini, A. Antonelli, P. Miccoli, J. Pediatr. Surg. **39**, 1500 (2004)
12. M. Schlumberger, F. De Vathaire, J.P. Travagli, G. Vassal, J. Lemerle, C. Parmentier, M. Tubiana, J. Clin. Endocrinol. Metab. **65**, 1088 (1987)
13. E.L. Mazzaferri, R.T. Kloos, J. Clin. Endocrinol. Metab. **86**, 1467 (2001)
14. B. Cady, R. Rossi, Surgery **104**, 947 (1988)
15. A. Antonelli, P. Miccoli, P. Fallahi, S.M. Ferrari, M. Grosso, G. Boni, P. Berti, Surgery **140**, 1035 (2006)
16. Y.E. Demidchik, E.P. Demidchik, C. Reiners, J. Biko, M. Mine, V.A. Saenko, S. Yamashita, Ann. Surg. **243**, 525 (2006)
17. S.J. Rybakov, I.V. Komissarenko, N.D. Tronko, A.N. Kvachenyuk, T.I. Bogdanova, A.E. Kovalenko, M.Y. Bolgov, World J. Surg. **24**, 1146 (2000)
18. M.D. Tronko, T.I. Bogdanova, I.V. Komissarenko, O.V. Epstein, V. Oliynyk, A. Kovalenko, I.A. Likhtarev, I. Kairo, S.B. Peters, V.A. LiVolsi, Cancer **86**, 149 (1999)
19. S. Naing, B.J. Collins, A.B. Schneider, Thyroid **19**, 479 (2009)
20. E.D. Williams, A. Abrosimov, T. Bogdanova, Thyroid **18**, 847 (2008)
21. E.L. Mazzaferri, S.M. Jhiang, Am. J. Med. **97**, 418 (1994)
22. T.S. Reeve, L. Delbridge, P. Brady, P. Crummer, C. Smyth, World J. Surg. **12**, 449 (1988)
23. *AJCC Cancer Staging Manual*, 6th edn. (Springer, New York, 2002), XIV