research article

Dietary iodine intake, therapy with radioiodine, and anaplastic thyroid carcinoma

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Background. Anaplastic thyroid cancer (ATC) is one of the most aggressive tumors. The aim of the study was to determine the correlation between a higher dietary intake of iodine, frequency of ATC and the characteristics of ATC, and to find out how often patients with ATC had a history of radioiodine (RAI) therapy.

Patients and methods. This retrospective study included 220 patients (152 females, 68 males; mean age 68 years) with ATC who were treated in our country from 1972 to 2017. The salt was iodinated with 10 mg of potassium iodide/kg before 1999, and with 25 mg of potassium iodide/kg thereafter. The patients were assorted into 15-year periods: 1972–1986, 1987–2001, and 2002–2017.

Results. The incidence of ATC decreased after a higher iodination of salt ($p = 0.04$). Patients are nowadays older ($p = 0.013$) and have less frequent lymph node metastases ($p = 0.012$). The frequency of distant metastases did not change over time. The median survival of patients in the first, second, and third periods was 3, 4, and 3 months, respectively ($p < 0.05$). The history of RAI therapy was present in 7.7% of patients.

Conclusions. The number of patients with a history of RAI therapy did not change statistically over time. The incidence of ATC in Slovenia decreased probably because of higher salt iodination.

Key words: anaplastic thyroid carcinoma; iodination of salt; treatment, survival

Introduction

Anaplastic thyroid cancer (ATC) is one of the most aggressive tumors known in humans.[1] It is a locally widely invasive disease which progresses despite treatment and finally results in metastatic disease in the majority of patients.[2] Fortunately, ATC is a rare disease and the estimated annual incidence is about two per million of the population.[3,4] In the USA and Japan, ATC represents less than 2% of thyroid carcinomas.[5,6] On the other hand, the incidence of ATC has been stable in the last decades.[1,7]

In the literature, there are only limited data about the history of radioiodine (RAI) therapy in patients with ATC. The aim of the study was to find out how often patients had a history of RAI therapy. In one of our recent studies we compared the incidence of ATC during the periods when the intake of potassium iodide in salt was 10 and 25 mg/kg in the Republic of Slovenia.[8] It was observed that the incidence of ATC decreased with a higher iodination of salt in Slovenia.[8] Another aim of the study was to determine the correlation between a higher dietary intake of iodine, frequency of ATC and the characteristics of ATC.

Patients and methods

The data on the patients with ATC treated at the Institute of Oncology in Ljubljana in the years 1972–2017 were collected retrospectively. During this period, there were 220 patients (152 females, 68 males; median age 69 years; mean age 68 years) with ATC. The Cancer Registry of Republic of Slovenia is one of the oldest population-based

cancer registries in Europe.[9] It was founded in 1950 at the Institute of Oncology in Ljubljana as a special service for collecting and processing data on cancer incidence and cancer patients' survival. Notification of cancer has been compulsory in Slovenia since the foundation of the Registry and prescribed by law.[9] The main sources of data are notifications of cancer, gathered from all hospitals and diagnostic centers in Slovenia.[9] Furthermore, all the patients with thyroid cancer are treated at the Institute of Oncology in Ljubljana, so our data represent a population based study.

For each patient, the data on sex, age, history of treatment with radioiodine, clinical and tumor characteristics, and duration of survival were collected. Distant metastases were diagnosed by clinical examination and additional diagnostic procedures, including lung and/or bone X-ray, radionuclide investigations, ultrasonography, computed tomography, and/or nuclear magnetic resonance imaging. Data about the treatment of our patients have already been reported.[10,11]

The Protocol Review Board and Ethics Committee of the Institute of Oncology on 12th December 2018 (ERID-KSOPKR/43, OIRIKE 00448) reviewed and approved the study, which was conducted in accordance with the ethical standards prescribed in the Declaration of Helsinki. For retrospective studies, informed consent is not necessary according to the national regulations. The need for consent was waived by the Institutional Review Board and Ethics Committee of the Institute of Oncology Ljubljana.

All cases were reviewed by pathologists and cytopathologists at our comprehensive cancer center, experienced in thyroid pathology. Histological specimens were retrieved by surgical removal of the thyroid tumor, surgical biopsy, or autopsy, whereas cytological samples were obtained by fine-needle aspiration biopsy of the primary tumor or its metastases. The diagnosis of ATC was confirmed by both histology and cytology in 75 patients, by cytology alone in 97 patients, and by histology alone in 48 patients.

In Slovenia, salt was iodinated with 10 mg of potassium iodide/kg and 25 mg of potassium iodide/kg during the periods 1972–1998 and 1999–2017, respectively.[12,13] All salt that was on the market in Slovenia during the first and the second 15-year periods had the required content of iodine. Slovenia has been considered to be an area with an adequate iodine supply since 1999.[12,13] Since 2004, when Slovenia became a member of the European Union, salt with a lower content of iodine and Himalayan salt with no iodine added at all have also been available in health food stores. Furthermore, in the last decade, the use of prefabricated or frozen food became more popular in Slovenia. Fortunately, almost all households in Slovenia use salt with 25 mg of potassium iodide/kg, which is evident from epidemiological studies in schoolchildren.[12,14]

For the purposes of the present study, patients were assorted into one of three 15-year periods according to the year of diagnosis of ATC: 1972–1986, 1987–2001, and 2002–2017. The frequency of ATC during these three periods and the characteristics of the patients during these periods were compared.

The characteristics of the patients and tumors and the history of RAI therapy according to 15-year periods were statistically analyzed using contingency tables and analysis of variance. SPSS 16.0 for Windows (SPSS, Chicago, IL) was also used in Kaplan–Meier univariate analysis for the assessment of patients' survival.

Results

The incidence of ATC in Slovenia has decreased. ATC was diagnosed in the periods 1972–1987, 1988–2003, and 2004-2017 in 95, 87, and 38 patients, respectively ($p = 0.04$). The mean incidence of ATC in the periods 1972–1986, 1987–2001, and 2002–2017 was 6.3 (range 2–12), 5.8 (range 3-10), and 2.5 (range 1–10) patients per year, respectively.

The characteristics of patients and their outcomes according to 15-year periods are presented in Table 1. Patients with ATC are older now than they used to be ($p = 0.013$). During the periods 1972–1986, 1987–2001, and 2002–2017, the patients' mean age was 66 (SD ±11.8) years, 69 (SD ±8.4) years, and 72 (SD ±11.8) years. The mean tumor diameter in the three time periods was 9.1 cm, 9.9 cm, and 8.5 cm respectively. The difference was not statistically significant ($p = 0.26$). However, a tumor diameter larger than 10 cm was more frequent in patients during the 1972–2001 periods than thereafter ($p < 0.05$). Lymph node metastases were less commonly diagnosed in the last period ($p = 0.012$). However, the frequency of distant metastases did not change over time ($p = 0.65$). The median survival of patients during the first, second, and third 15-year periods was 3 months, 4 months, and 3 months, respectively ($p < 0.05$).

Cumulative yearly doses of ^{131}I applied in medicine from 1994 to 2017 in Slovenia are presented in Figure 1. Altogether, 17/220 (7.7%) of patients had a

TABLE 1. Clinical characteristics of patients and 15-year periods

Clinical characteristic	Subgroup	All patients N = 220 Number	Patients 1972–1986 N=95 Number	Patients 1987–2001 N = 87 Number	Patients 2002-2017 N = 38 Number	p-value
Gender	Male	68	27	29	12	0.77
	Female	152	68	58	26	
Age	70 years or less	124	59	49	16	0.11
	71 years or more	96	36	38	22	
History of radioiodine therapy	No	203	89	83	31	0.023
	Yes	17	6	4	7	
Previous thyroid enlargement (> 1 year)	No or no data	110	46	49	26	0.036
	Yes	110	49	38	12	
General condition	Good	92	47	33	12	0.13
	Moderate	58	25	20	13	
	Poor	70	23	34	13	
Tumor growth	≥ 3 months	173	70	72	31	0.29
	< 3 months	47	25	15	7	
Local tumor extension	Extrathyroid	199	87	78	34	0.88
	Intrathyroid	21	8	9	4	
Tumor size	< 5 cm	35	20	12	3	0.043
	5–10 cm	105	40	39	26	
	≥ 10 cm	80	35	36	9	
Tumor volume (width² x length)/2	< 50 ml	16	7	5	4	0.68
	50–99 ml	37	19	14	4	
	100–149 ml	22	6	12	4	
	150–199 ml	18	9	7	2	
	200 ml or more	127	54	49	24	
Lymph nodes metastases	No	127	45	54	28	0.012
	Yes	93	50	33	10	
Distant metastases	No	113	46	48	19	0.65
	Yes	107	49	39	19	
Presentation of anaplastic carcinoma	Incidental	8	4	4	0	0.50
	Evident	212	91	83	38	
TNM stage	IVA	17	5	9	3	0.73
	IVB	96	41	39	16	
	IVC	107	49	39	19	
Thyroid surgery	Without surgery	130	48	52	30	0.029
	Biopsy	23	13	10	0	
	Subtotal thyroidectomy	13	10	3	0	
	Extracapsular lobectomy with isthmusectomy	17	9	7	1	
	Total or near-total thyroidectomy	37	15	15	7	
Residual tumor after surgery	Biopsy or no surgery	153	61	62	30	0.55
	R0	32	18	10	4	
	R1	18	9	6	3	
	R2	17	7	9	1	
Lymph node dissection	No	211	90	83	38	0.36
	Yes	9	5	4	0	
External beam irradiation	No	37	22	11	4	0.087
	Yes	183	73	76	36	
External beam irradiation	Without or ≤ 20 Gy	54	33	15	6	0.001
	> 20 Gy and 45 Gy	74	41	26	7	
	> 45 Gy	92	21	46	25	
Chemotherapy	No	81	38	24	19	0.04
	Yes	139	57	63	19	
Death because of anaplastic carcinoma	No (alive, other causes, lost from follow-up)	13	3	7	13	0.32
	Yes	207	92	80	25	

TABLE 2. Clinical characteristics of the patients and the history of radioiodine therapy

Clinical characteristic	Subgroup	All patients N = 220	Without history of RAI therapy N = 203	With history of RAI therapy N = 17	p-value
Gender	Male	68	66	2	0.10
	Female	152	137	15	
Age	70 years or less	124	114	10	1.00
	71 years or more	96	89	7	
Year of diagnosis	1972–1986	95	89	6	0.023
	1987–2001	87	83	4	
	2002–2017	38	31	7	
Previous thyroid enlargement (> 1 year)	No or no data	110	108	2	0.001
	Yes	110	95	15	
General condition	Good	92	85	7	0.063
	Moderate	58	57	1	
	Poor	70	61	9	
Tumor growth	≥ 3 months	173	157	16	0.13
	< 3 months	47	16	1	
Local tumor extension	Extrathyroid	199	183	16	1.00
	Intrathyroid	21	20	1	
Tumor size	< 5 cm	35	34	1	0.50
	5–10 cm	105	96	9	
	≥ 10 cm	80	73	7	
Tumor volume (width^2 x length)/2	< 50 ml	16	16	0	0.19
	50–99 ml	37	36	1	
	100–149 ml	22	20	2	
	150–199 ml	18	18	0	
	200 ml or more	127	113	14	
Lymph nodes metastases	No	127	117	10	1.00
	Yes	93	86	7	
Distant metastases	No	113	105	8	0.83
	Yes	107	98	9	
Presentation of anaplastic carcinoma	Incidental	8	8	0	0.51
	Evident	212	195	17	
TNM stage	IVA	17	16	1	0.91
	IVB	96	89	7	
	IVC	107	98	9	
Thyroid surgery	Without surgery	130	117	13	0.56
	Biopsy	23	22	1	
	Subtotal thyroidectomy	13	12	1	
	Extracapsular lobectomy with isthmusectomy	17	17	0	
	Total or near-total thyroidectomy	37	35	2	
Residual tumor after surgery	Biopsy or no surgery	153	139	14	0.32
	R0	32	32	0	
	R1	18	17	1	
	R2	17	15	2	
Lymph node dissection	No	211	194	17	1.00
	Yes	9	9	0	
External beam irradiation	No	37	30	7	0.005
	Yes	183	173	10	
Dose of radiotherapy	Without or ≤ 20 Gy	54	47	7	0.244
	> 20 Gy and ≤ 45 Gy	74	70	4	
	> 45 Gy	92	86	6	
Chemotherapy	No	81	75	6	1.00
	Yes	139	128	11	
Death because of ATC	No (alive, other causes, lost from follow up)	13	12	1	1.00
	Yes	207	191	16	

ATC = anaplastic thyroid cancer; RAI = radioiodine

history of radioiodine therapy from 4 months to 40 years before the diagnosis of ATC. The number of patients with ATC who had a history of RAI therapy did not change statistically over time, while the incidence of patients with ATC decreased over time ($p = 0.023$). Data about patients with regard to the history of RAI therapy are presented in Table 2. Previous enlargement of thyroid gland was more common in patients with a history of RAI therapy in comparison to those who received no RAI ($p < 0.001$). There was no difference in survival of patients with and without a history of RAI therapy ($p = 0.49$).

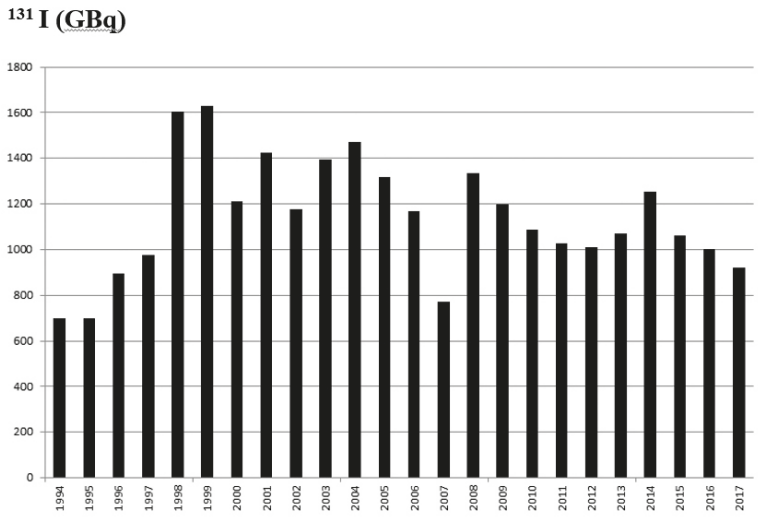

FIGURE 1. Cumulative yearly doses of ^{131}I applied in medicine from 1994 to 2017 in Slovenia.

Discussion

Salt was iodinated in Slovenia with 10 mg of potassium iodide/kg and 25 mg of potassium iodide/kg during the periods 1972–1998 and 1999–2017, respectively.[12,13] As expected and reported in other countries[15], ten years after the beginning of higher salt iodination in Slovenia, the incidence of diffuse goiter in adolescents and adults decreased.[12-14,16] Furthermore, from 1999 to 2009, the incidence of thyroid autonomy in Slovenia decreased from 32.7/100.000 to a 27 % lower value.[12] During the same time period, the baseline incidence of Graves' disease (27.8/100.000) did not change significantly.[12] On the other hand, the incidence of Hashimoto's thyroiditis (73.2/100.000 in 1999) gradually increased to levels more than twice as high as before.[12] During the same time period, the incidence of thyroid carcinoma increased from 5.1/100.000 to 7.25/100.000,[17] but the incidence of anaplastic carcinoma decreased after higher iodination of salt in Slovenia.[9] A similar observation about the incidence of ATC after higher salt iodination was reported in other endemic goiter regions, namely the Tyrol region in Austria and Argentina.[18,19]

In contrast to differentiated thyroid cancer, which often has a subtle clinical presentation and may be difficult to detect, ATC is correctly diagnosed in nearly all cases in countries with adequate health care because of rapid tumor growth and the clinical presentation.[9,20] Risk factors for ATC are: a history of goiter or a prior co-existing differentiated thyroid cancer[21-23], insufficient iodine in the diet[9,18,24,25], low level of education[21], type B blood group[21], and presence of TERT mutation in coexisting thyroid papillary carcinoma[26]. We think that the drop in ATC incidence in Slovenia was mainly caused by higher salt iodination. A lower rate of goiter in Slovenia, which was also due to higher iodination of salt, is another risk factor that contributed to a lower incidence of ATC in our country.[12,13] Other risk factors for ATC, namely the educational level of the population, the socioeconomic status of the general population, or the rate of persons with type B blood group, did not change over time in Slovenia.

RAI treatment for benign thyroid disease is considered to be a safe procedure.[27,28] A meta-analysis showed no increase in the overall cancer risk after RAI treatment for hyperthyroidism. However, there was a trend towards increased risk of thyroid, stomach, and kidney cancer.[27,28] In 1990, Venkatesh *et al*.[29] reported in a series of 121 cases with ATC that seven (6%) patients had received prior RAI treatment. Even 7.7% of patients from our present study also had a history of RAI therapy. A history of RAI therapy in patients with ATC is more frequent than the proportion of persons treated with RAI therapy in the Slovenian population. The use of ^{131}I increased in Slovenia in the 1990s and was at 1630.9 GBq in 1999. Thereafter, the use of ^{131}I has slowly been decreasing as seen in Figure 1. In 2011, a total of 531 diagnostic procedures with ^{131}I or ^{123}I for thyroid imaging with an accumulative effective dose of 2.29 manSv were done in Slovenia.[30] ^{131}I and ^{123}I were used in 48% and 52% of diagnostic procedures, which contributed to 69% and 31% of the collective effective dose for diagnostic procedures, respectively.[30] On the other hand, the therapy with ^{131}I was done in 512 patients with a benign disease and 151 patients with a carcinoma in 2014. The main difference between RAI therapy in benign thyroid disease and thyroid carcinoma is the dose

of RAI. In benign disease and thyroid carcinoma, 10–15 mCi (370–555 MBq)[28] and 50–200 mCi (1.8–7.4 GBq)[31] of RAI is used, respectively.

In 1982, Kapp *et al*.[32] reported that in two patients with a differentiated carcinoma, ATC occurred after irradiation. In one of them, the transformation to ATC occurred five years after 39.6 Gy of external beam irradiation, while in the other patient, ATC was diagnosed one year after 149 mCi of RAI. A component of differentiated thyroid carcinoma is usually identified in the primary ATC on histology examination.[22] But, the transformation of differentiated thyroid cancer to ATC may be found also in metastatic lymph nodes.[33] It was detected in two of five patients during initial surgery of primary tumor and regional lymph node dissection, while in three of five cases, the interval between treatment of differentiated carcinoma and occurrence of ATC was 46, 74, and 266 months after initial surgery. None of them had a history of RAI therapy, while one patient received external beam irradiation because of recurrent papillary carcinoma before the occurrence of ATC.[33]

In our patients, RAI therapy was applied from 4 months to 40 years before the diagnosis of ATC. For some patients with a very short interval between RAI therapy and the diagnosis of ATC, we could suspect that they already had a differentiated carcinoma and possibly a very small ATC which was not detected. Namely, in patients with Graves' disease without clinically evident nodes, a thyroid ultrasound investigation is not recommended according to the ATA Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis.[28] Furthermore, the use of thyroid scintigraphy to preselect only the cold nodules for cytology is advocated by some authors.[34] However, there are at least eight case reports in the literature about patients with a follicular variant of papillary thyroid carcinoma as autonomous functioning thyroid nodule.[35] On the other hand, ATC was also reported in a long-standing multinodular goiter or a Hürthle cell tumor following RAI therapy.[36-38]

This study has some limitations. Because it is a retrospective analysis over a very long time period, we do not have reliable data about the reasons for RAI therapy in our patients. Furthermore, diagnostic radiological methods have changed dramatically over last decades. Modern precise imaging investigations have an impact on the detection of very small regional and/or distant metastases. The detection of small distant metastases possibly influences therapeutic decisions, which might explain why a lesser proportion of patients were treated with radical surgery during the last 15-year period in comparison to prior periods.

In the literature, data on how the patients' and tumors' characteristics in ATC have changed over time are very limited.[39] We observed that, nowadays, patients are older and have less frequent regional metastases in comparison to previous periods. However, the mean tumor diameter has not changed significantly over time, and ATC was inoperable because of infiltration to the surrounding structures at the time of diagnosis in the majority of our patients. Unfortunately, the frequency of distant metastases has not changed over time. Thus, in Slovenia, the survival of patients with ATC remains short. By contrast, in South Korea where an opportunistic screening is performed in the general population for thyroid carcinoma, the proportion of cases with a differentiated thyroid carcinoma and only anaplastic foci has increased over time, while that of evident ATC has decreased from 1985 to 2013.[39] As a consequence, the survival rate is significantly higher than it used to be. Obviously, in patients with a very early ATC, lymphatic invasion was the most significant postoperative prognosticator, so the choice of ATC treatment has to be modified based on resectability and the lymphatic invasion of cancer.[39]

Conclusions

A history of RAI therapy was present in 7.7% of patients with ATC, and the number of patients with a history of RAI therapy did not change over time. The incidence of ATC in Slovenia probably decreased because of higher salt iodination. Patients are nowadays older and have less frequent lymph node metastases than in the past. The frequency of distant metastases did not change over time. The median survival of patients remains short.

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References

1. Nikiforov YE, Seethala RR. Anaplastic (undifferentiated) carcinoma. In: Nikiforov YE, Biddinger PW, Thompson LDR, editors. *Diagnostic pathology and molecular genetics of the thyroid*, 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2012. p. 263-84.

2. Besic N, Gazic B. Sites of metastases of anaplastic thyroid carcinoma: autopsy findings in 45 cases from a single institution. *Thyroid* 2013; **23**: 709-73. doi: 10.1089/thy.2012.0252

3. Untch BR, Olson JA Jr.. Anaplastic thyroid carcinoma, thyroid lymphoma, and metastasis to thyroid. *Surg Oncol Clin N Am* 2006; **15**: 661-79. doi: 10.1016/j.soc.2006.05.006

4. Ain KB. Anaplastic thyroid carcinoma: a therapeutic challenge. *Semin Surg Oncol* 1999; **16**: 64-9. doi: 10.1002/(sici)1098-2388(199901/02)16:1<64::aid-ssu10>3.0.co;2-u

5. Ain KB. Anaplastic thyroid carcinoma: behavior, biology, and therapeutic approaches. *Thyroid* 1998; **8**: 715-26. doi: 10.1089/thy.1998.8.715

6. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. Prognostic factors and therapeutic strategy for anaplastic carcinoma of the thyroid. *World J Surg* 2011; **25**: 617-622. doi: 10.1007/s002680020166

7. Hvilsom GB, Londero SC, Hahn CH, Schytte S, Pedersen HB, Christiansen P, et al. Anaplastic thyroid carcinoma in Denmark 1996-2012: a national prospective study of 219 patients. *Cancer Epidemiol* 2018; **53**: 65-71. doi: 10.1016/j.canep.2018.01.011

8. Besic N, Hocevar M, Zgajnar J. Lower incidence of anaplastic carcinoma after higher iodination of salt in Slovenia. *Thyroid* 2010; **20**: 623-6. doi: 10.1089/thy.2009.0404

9. Institute of Oncology Ljubljana. *Epidemiology and Cancer Registry.* Ljubljana: Institute of Oncology Ljubljana. [cited 2019 Aug 28]. Available at: https://www.onko-i.si/eng/sectors/epidemiology-and-cancer-registry.

10. Besic N, Auersperg M, Us-Krasovec M, Golouh, R, Frkovic-Grazio S, Vodnik A. Effect of primary treatment on survival in anaplastic thyroid carcinoma. *Eur J Surg Oncol* 2001; **27**: 260-4. doi: 10.1053/ejso.2000.1098

11. Besic N, Hocevar M, Zgajnar J, Pogacnik A, Grazio-Frkovic S, Auersperg M. Prognostic factors in anaplastic carcinoma of the thyroid-a multivariate survival analysis of 188 patients. *Langenbecks Arch Surg* 2005; **390**: 203-8. doi: 10.1007/s00423-004-0524-5

12. Zaletel K, Gaberscek S, Pirnat E. Ten-year follow-up of thyroid epidemiology in Slovenia after increase in salt iodization. *Croat Med J* 2011; **52**: 615-21. doi: 10.3325/cmj.2011.52.615

13. Gaberscek S, Zaletel K. Epidemiological trends of iodine-related thyroid disorders: an example from Slovenia. *Arh Hig Rada Toksikol* 2016; **67**: 93-8. doi: 10.1515/aiht-2016-67-2725

14. Kotnik P, Sirca Campa A, Zupancic M, Stimec M, Smole K, Mis NF, et al. Goiter prevalence and urinary iodine concentration in Slovenian adolescents. *Thyroid* 2006; **16**: 769-73. doi: 10.1089/thy.2006.16.769

15. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. *Lancet Diabetes Endocrinol* 2015; **3**: 286-95. doi: 10.1016/S2213-8587(14)70225-6

16. Bajuk V, Zaletel K, Pirnat E, Hojker S, Gaberšček S. Effects of adequate iodine supply on the incidence of iodine-induced thyroid disorders in Slovenia. *Thyroid* 2017; **27**: 558-66. doi: 10.1089/thy.2016.0186

17. Zadnik V, Primic Zakelj M. *SLORA: Slovenia and cancer.* Ljubljana: Epidemiology and Cancer Registry. Institute of Oncology Ljubljana. [cited 2018 Oct 14]. Available at: www.slora.si

18. Bacher-Stier C, Riccabona G, Tötsch M, Kemmler G, Oberaigner W, Moncayo R. Incidence and clinical characteristics of thyroid carcinoma after iodine prophylaxis in an endemic goiter country. *Thyroid* 1997; **7**: 733-41. doi: 10.1089/thy.1997.7.733

19. Harach HR, Galindez M, Campero M, Ceballos GA. Undifferentiated (anaplastic) thyroid carcinoma and iodine intake in Salta, Argentina. *Endocr Pathol* 2013; **24**: 125-31. doi: 10.1007/s12022-013-9248-9

20. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. *Thyroid Res* 2015; **8**: 8. doi: 10.1186/s13044-015-0020-8

21. Zivaljevic V, Slijepcevic N, Paunovic I, Diklic A, Kalezic N, Marinkovic J, et al. Risk factors for anaplastic thyroid cancer. *Int J Endocrinol* 2014; **2014:** 815070. doi: 10.1155/2014/815070

22. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. *Clin Oncol (R Coll Radiol)* 2010; **22**: 486-97. doi: 10.1016/j.clon.2010.03.013

23. McIver B, Hay ID, Giuffrida DF, Dvorak CE, Grant CS, Thompson GB, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery* 2001; **130**: 1028-34. doi: 10.1067/msy.2001.118266

24. Belfiore A, La Rosa G, Padova G, Sava L, Ippolito O, Vigneri R. The frequency of cold thyroid nodules and thyroid malignancies in patients from an iodine-deficient area. *Cancer* 1987; **60**: 3096-102. doi: 10.1002/1097-0142(19871215)60:12<3096::aid-cncr2820601240>3.0.co;2-v

25. Bakiri F, Djemli FK, Mokrane LA, Djidel FK. The relative roles of endemic goiter and socioeconomic development status in the prognosis of thyroid carcinoma. *Cancer* 1998; **82**: 1146-53. doi: 10.1002/(sici)1097-0142(19980315)82:6<1146::aid-cncr20>3.0.co;2-5

26. Oishi N, Kondo T, Ebina A, Sato Y, Akaishi J, Hino R, et al. Molecular alterations of coexisting thyroid papillary carcinoma and anaplastic carcinoma: identification of TERT mutation as an independent risk factor for transformation. *Mod Pathol* 2017; **11**: 1527-37. doi: 10.1038/modpathol.2017.75

27. Hieu TT, Russell AW, Cuneo R, Clark J, Kron T, Hall P, et al. Cancer risk after medical exposure to radioactive iodine in benign thyroid diseases: a metaanalysis. *Endocr Relat Cancer* 2012; **19**: 645-55. doi: 10.1530/ERC-12-0176

28. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* 2016; **26**: 1343-421. doi: 10.1089/thy.2016.0229

29. Venkatesh YS, Ordonez NG, Schultz PN, Hickey RC, Goepfert H, Samaan NA. Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases. *Cancer* 1990; **66**: 321-30. doi: 10.1002/1097-0142(19900715)66:2<321::aid-cncr2820660221>3.0.co;2-a

30. Skrk D, Zontar D. Estimated collective effective dose to the population from nuclear medicine examinations in Slovenia. *Radiol Oncol* 2013; **47**: 304-10. doi: 10.2478/raon-2013-0048

31. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016; **26**: 1-133. doi: 10.1089/thy.2015.0020

32. Kapp DS, LiVolsi VA, Sanders MM. Anaplastic carcinoma following well-differentiated thyroid cancer: etiological considerations. *Yale J Biol Med* 1982; **55**: 521-8. PMID: 7183024

33. Ito Y, Higashiyama T, Hirokawa M, Fukushima M, Inoue H, Yabuta T, et al. Prognosis of patients with papillary carcinoma showing anaplastic transformation in regional lymph nodes that were curatively resected. *Endocr J* 2008; **55**: 985-9. doi: 10.1507/endocrj.k08e-148

34. Verburg FA, Aktolun C, Chiti A, Frangos S, Giovanella L, Hoffmann M, et al. Why the European Association of Nuclear Medicine has declined to endorse the 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 2016; **43**: 1001-5. doi: 10.1007/s00259-016-3327-3

35. Shahbaz A, Fransawy Alkomos M, Mahendhar R, Nabi U, Riaz M, Sachmechi I. Follicular variant of papillary thyroid carcinoma presented as autonomous functioning thyroid nodule: a case report and review of literature. *Cureus* 2018; **7**: e3014. doi: 10.7759/cureus.3014

36. Maatouk J, Barklow TA, Zakaria W, Al-Abbadi MA. Anaplastic thyroid carcinoma arising in long-standing multinodular goiter following radioactive iodine therapy: report of a case diagnosed by fine needle aspiration. *Acta Cytol* 2009; **53**: 581-3. doi: 10.1159/000325388

37. Villa ML, Mukherjee JJ, Tran NQ, Cheah WK, Howe HS, Lee KO. Anaplastic thyroid carcinoma with destructive thyrotoxicosis in a patient with preexisting multinodular goiter. *Thyroid* 2004; **14**: 227-30. doi: 10.1089/105072504773297902

38. Mai DD, Mai KT, Shamji FM. Fine needle aspiration biopsy of anaplastic thyroid carcinoma developing from a Hürthle cell tumor: a case report. *Acta Cytol* 2001; **45**: 761-4. doi: 10.1159/000328300

39. Lee DY, Won JK, Lee SH, Park DJ, Jung KC, Sung MW, et al. Changes of clinicopathologic characteristics and survival outcomes of anaplastic and poorly differentiated thyroid carcinoma. *Thyroid* 2016; **26**: 404-13. doi: 10.1089/thy.2015.0316