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.³,⁷

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. 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. The main sources of data are notifications of cancer, gathered from all hospitals and diagnostic centers in Slovenia. 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.

The Protocol Review Board and Ethics Committee of the Institute of Oncology on 12th December 2018 (ERID-KSOPKR/43, OIRKE 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 cytotechnologists 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. 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. Since 2004, when Slovenia became a member of the European Union, 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.

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
| Clinical characteristic                  | Subgroup          | All patients N = 220 | Patients 1972–1986 N=95 | Patients 1987–2001 N = 87 | Patients 2002-2017 N = 38 | 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 radiiodine 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**                   |                   |                     |                         |                           |                           |         |
| Male                                    | 92                | 47                  | 33                      | 12                        |                           |         |
| Female                                  | 152               | 68                  | 58                      | 26                        |                           |         |
| **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                         |                           |         |
| 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                         |                           |         |
| 50–99 ml                                | 37                | 19                  | 14                      | 4                         |                           |         |
| 100–149 ml                              | 22                | 6                   | 12                      | 4                         |                           | 0.68    |
| 150–199 ml                              | 18                | 9                   | 7                       | 2                         |                           |         |
| ≥ 200 ml                                | 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                         |                           |         |
| Evident                                 | 212               | 91                  | 83                      | 38                        |                           | 0.50    |
| **TNM stage**                           |                   |                     |                         |                           |                           |         |
| IVA                                     | 17                | 5                   | 9                       | 3                         |                           |         |
| IVB                                     | 96                | 41                  | 39                      | 16                        |                           | 0.73    |
| IVC                                     | 107               | 49                  | 39                      | 19                        |                           |         |
| **Thyroid surgery**                     |                   |                     |                         |                           |                           |         |
| Without surgery                         | 130               | 48                  | 52                      | 30                        |                           |         |
| Biopsy                                  | 23                | 13                  | 10                      | 0                         |                           |         |
| Subtotal thyroidectomy                  | 13                | 10                  | 3                       | 0                         |                           |         |
| Extracapsular lobectomy with isthmsectomy| 17            | 9                   | 7                       | 1                         |                           | 0.029   |
| Total or near-total thyroidectomy       | 37                | 15                  | 15                      | 7                         |                           |         |
| **Residual tumor after surgery**        |                   |                     |                         |                           |                           |         |
| Biopsy or no surgery                    | 153               | 61                  | 62                      | 30                        |                           |         |
| R0                                      | 32                | 18                  | 10                      | 4                         |                           | 0.55    |
| 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                        |                           |         |
| **Chemotherapy**                        |                   |                     |                         |                           |                           |         |
| No (alive, other causes, lost from follow-up) | 13  | 3 | 7 | 13 |                           | 0.32    |
| Yes                                     | 207               | 92                  | 80                      | 25                        |                           |         |
| **Death because of anaplastic carcinoma**| No or no data   | 110                 | 46                      | 49                        | 26                        | 0.036   |
|                                         | Yes               | 110                 | 49                      | 38                        | 12                        |         |
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                                  |         |
|                                         | 1987–2001                 | 87                   | 83                                     | 4                                  | 0.023   |
|                                         | 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                                  |         |
|                                         | Moderate                  | 58                   | 57                                     | 1                                  | 0.063   |
|                                         | 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                                 |         |
|                                         | Intrathyroid              | 21                   | 20                                     | 1                                  | 1.00    |
| Tumor size                              | < 5 cm                    | 35                   | 34                                     | 1                                  |         |
|                                         | 5–10 cm                   | 105                  | 96                                     | 9                                  | 0.50    |
|                                         | ≥ 10 cm                   | 80                   | 73                                     | 7                                  |         |
| Tumor volume (width² x length)/2       | < 50 ml                   | 16                   | 16                                     | 0                                  |         |
|                                         | 50–99 ml                  | 37                   | 36                                     | 1                                  |         |
|                                         | 100–149 ml                | 22                   | 20                                     | 2                                  | 0.19    |
|                                         | 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                                  |         |
|                                         | IVB                       | 96                   | 89                                     | 7                                  | 0.91    |
|                                         | IVC                       | 107                  | 98                                     | 9                                  |         |
| Thyroid surgery                          | Without surgery           | 130                  | 117                                    | 13                                 |         |
|                                         | Biopsy                    | 23                   | 22                                     | 1                                  |         |
|                                         | Subtotal thyroidectomy    | 13                   | 12                                     | 1                                  | 0.56    |
|                                         | Extracapsular lobectomy   | 17                   | 17                                     | 0                                  |         |
|                                         | with isthmusectomy        | 37                   | 35                                     | 2                                  |         |
| Residual tumor after surgery            | Biopsy or no surgery      | 153                  | 139                                    | 14                                 |         |
|                                         | R0                        | 32                   | 32                                     | 0                                  | 0.32    |
|                                         | 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                                  |         |
|                                         | > 20 Gy and ≤ 45 Gy       | 74                   | 70                                     | 4                                  | 0.244   |
|                                         | > 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
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.\textsuperscript{12,13} As expected and reported in other countries\textsuperscript{15}, ten years after the beginning of higher salt iodination in Slovenia, the incidence of diffuse goiter in adolescents and adults decreased.\textsuperscript{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.\textsuperscript{12} During the same time period, the baseline incidence of Graves’ disease (27.8/100,000) did not change significantly.\textsuperscript{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.\textsuperscript{12} During the same time period, the incidence of thyroid carcinoma increased from 5.1/100,000 to 7.25/100,000,\textsuperscript{17} but the incidence of anaplastic carcinoma decreased after higher iodination of salt in Slovenia.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9,20} Risk factors for ATC are: a history of goiter or a prior co-existing differentiated thyroid cancer\textsuperscript{21-23}, insufficient iodine in the diet\textsuperscript{24,25}, low level of education\textsuperscript{21}, type B blood group\textsuperscript{21}, and presence of TERT mutation in coexisting thyroid papillary carcinoma\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{27,28} In 1990, Venkatesh et al.\textsuperscript{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 \textsuperscript{131}I increased in Slovenia in the 1990s and was at 1630.9 GBq in 1999. Thereafter, the use of \textsuperscript{131}I has slowly been decreasing as seen in Figure 1. In 2011, a total of 531 diagnostic procedures with \textsuperscript{131}I or \textsuperscript{123}I for thyroid imaging with an accumulative effective dose of 2.29 manSv were done in Slovenia.\textsuperscript{30} \textsuperscript{131}I and \textsuperscript{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.\textsuperscript{30} On the other hand, the therapy with \textsuperscript{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) and 50–200 mCi (1.8–7.4 GBq) of RAI is used, respectively.

In 1982, Kapp et al. 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. But, the transformation of differentiated thyroid cancer to ATC may be found also in metastatic lymph nodes. 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.

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. Furthermore, the use of thyroid scintigraphy to preselect only the cold nodules for cytology is advocated by some authors. 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. On the other hand, ATC was also reported in a long-standing multinodular goiter or a Hürthle cell tumor following RAI therapy.

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. 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. 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.

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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