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Incidence and Clinical Characteristics of Thyroid Carcinoma After Iodine Prophylaxis in an Endemic Goiter Country

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ABSTRACT

Iodized salt prophylaxis has been performed in Austria since 1963. Through this approach, mean urinary iodine excretion has been normalized to 144 ± 23.5 μg/g creatinine per day. Thus Tyrol is no longer an endemic goiter area. We have analyzed the impact of iodized salt prophylaxis on thyroid cancer (TC) comparing data from the early 1960s with those corresponding to the period 1986 to 1995, when iodine supply was normalized. The study included 439 patients from Tyrol and Southern Tyrol. The incidence of TC in Tyrol has risen during the past decades from 3.07 between in 1957 and 1970 to 7.8 between 1990 and 1994 (CR/100000/year). We observed a rise in the percentage of differentiated adenocarcinomas (56% to 91.5%) with a predominance of papillary TC (54.4%) along with a decrease of anaplastic TC. In addition to these histological features, a shift to less advanced TNM stages, eg, T1-3, N0-1a, M0, was obvious, increasing from 29% to 72.2%, whereas advanced tumors, ie, T4 or N1b or M1, decreased from 71% to 28%. These changes have significantly improved prognosis. The current 5-year survival rate is 90.7% as compared with a rate of 73% in the 1960s; the values for 7-year survival are 89% and 48%, respectively. The marked effects of age, tumor stages, and histology on prognosis were confirmed with the Kaplan-Meier method. We conclude that together with normalization of iodine supply in an endemic goiter region the epidemiological profile of TC has changed. Even though the incidence of TC has risen, prognosis has significantly improved due to a shift towards differentiated forms of TC that are diagnosed at earlier stages.

INTRODUCTION

THYROID CARCINOMA (TC) is a rare tumor type in comparison with other malignancies (1,2). While it can produce dramatic clinical pictures in some patients, it behaves almost like a benign tumor in others. These differences have been attributed to histological patterns, distribution of tumor stages, age, and sex (3–5). Iodine deficiency has been discussed in relation to the incidence and clinical course of the disease for decades (6–8). As chronic thyrotropin (TSH) stimulation of thyrocytes can produce thyroid tumors (9), one would expect that this mechanism could be related to tumor growth in regions with iodine deficiency, influencing the incidence of TC. However, the highest incidence rates are found in areas where iodine intake is high (1,2,10). Therefore the development of TC does not seem to be related to iodine deficiency per se. On the other hand, the prognosis of TC is worse in endemic goiter regions than in countries with adequate iodine supply (6,7) due to frequently advanced tumor stages at the time of diagnosis and a predominance of more aggressive histological types. Our institution has had the rare opportunity to study changes in epidemiology of TC during three decades in the Austrian province of Tyrol, where iodine deficiency was present. Within this setting, previous investigations have documented a gradual decrease of iodine deficiency by the mandatory introduction of iodized salt with 10 mg potassium iodide (KI) per kg salt in 1963 (11). During previous years goiter prevalence in schoolchildren was 45.9% (7,12) and iodine excretion was about 35.9 μg/g creatinine. Five years later, goiter prevalence in this age group decreased to 18.8%

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(12), and iodine excretion in 1982 was still low with 42–75 μg/g creatinine (13). Goiters in adults were still frequent (up to 35% [13]). In order to eradicate iodine deficiency completely, the Austrian Health Authorities increased the amount of iodine supplementation to 20 mg KI/kg salt in 1992 (14). At the present time mean urinary excretion is normalized, reflected by a mean value of 144.7 ± 23.5 μg I/g creatinine (13,15) together with a significantly lower goiter prevalence in school children of 3.0% to 5.0%. In view of these changes, we designed this study in order to compare epidemiological, histological, and clinical data concerning TC as observed during early years of this supplementation program (6,7,16–19) with the present situation (1986 to 1995).

MATERIALS AND METHODS

Patients and settings, diagnostic, and therapeutic procedures

Diagnostic procedures in order to detect small thyroid malignancies included routinely performed ultrasound of the neck, thyroid scanning with technetium 99m ^{99m}Tc and fine-needle biopsy for more than 25 years (7). The frequency of routinely performed fine-needle biopsies at our Thyroid Clinic remained quite constant during the past decades with a total of 15,152 biopsies between 1970 and 1984 (7), and 13,778 in the time period between 1986 and 1996.

Our institution is the only medical center that has the capability of carrying out high-dose radioactive iodine (^{131}I) therapy for TC in the province of Tyrol (Austria) and Southern Tyrol (Provincia di Bolzano, Italy), including a population of 1,063,395 inhabitants (1991 data). Medical management of TC patients has been carried out in an uniform manner for three decades, thus allowing us to compare our current data with previous figures. Between 1986 and 1995, 613 patients with TC were seen at our institution. Complete data files were available for 439 Tyrolean patients (110 males, 329 females). A retrospective, detailed analysis of these patients was carried out by reviewing their medical records. We emphasize that we were able to see every patient who had TC proven by surgery, due to a very strong interdisciplinary cooperation between our department and the departments of surgery and pathology. TC was histologically verified in all cases and classified according to the current WHO criteria (20–22). All 439 patients underwent total or near-total thyroidectomy, if possible, and neck dissection, if necessary.

Postsurgical treatment and follow-up

After surgery, thyroid remnant ablation was carried out with a calculated dose of 500 Gy (23), corresponding to 1.1–3.7 GBq ^{131}I in the majority of patients (n = 369), except those having either medullary carcinoma or microcarcinoma or sarcoma. Then, patients were given thyroxine (T_4) treatment in order to suppress circulating thyrotropin (TSH) levels. Patients older than 50 years, or with tumor stage T4 had additional radiotherapy of the thyroid bed (500 Gy). Follow-up was done routinely every 4 months during the first 2 years, then every 6 months, and after 5 years, once a year. If there was no clinical, biochemical (thyroglobulin [Tg] levels), radiological and sonographic, or scintigraphic evidence (whole-body scans done either with 74-111 MBq ^{131}I or 555 MBq ^{99m}Tc Cardiolite-MIBI; ELSCINT-HELIX dual head camera, high-energy parallel hole collimator for ^{131}I, LEAP collimator for ^{99m}Tc-MIBI) of recurrence or metastasis during the whole observation period, patients were classified as tumor free. In cases of scintigraphic or radiological suspicion of progression, or rising Tg levels, ^{131}I therapy was performed. In patients with metastases, 5.5–7.4 GBq ^{131}I was given in intervals of 4 to 6 months. Radiotherapy was used in patients presenting localized metastases with low ^{131}I uptake (40 Gy). Patients with aggressive tumors and poor ^{131}I uptake received α-interferon therapy (2–4 million units, adjusted individually) 2 to 3 times weekly.

Data analysis

The variables included in this evaluation were: histological classification, TNM stages, age, and sex. (Considering the individualized multimodal therapy, no analysis of different treatment modalities was performed). Disease extension according to TNM stages (21,22) at initial diagnosis was classified into two groups: group A (n = 302) included stages T1-3 (tumor limited to the thyroid: T1 ≤1 cm, T3 >4 cm), N0-1a (no or ipsilateral lymph node metastases), M0 (no distant metastases) in which patients were considered as potentially "curable" by local surgery. Group B (n = 116) included patients with either T4 (tumor exceeding thyroid) or N1b (mediastinal lymph nodes) or M1 (distant metastases present), in whom no radical cure seemed possible by surgery (21,22). In order to calculate survival rates, December 31, 1995 was chosen at the end point of the observation period. Information concerning possible death up to this date was obtained from the Tyrolean Cancer Registry and by contacting involved physicians. Mean length of follow-up period of patients last known to be alive, was 47.5 months. Survival curves were calculated according to prognostic parameters. Only mortality due to TC was taken into account. In order to show survival in relation to age, Cox regression analysis was done. For clearer presentation, patients were subdivided into age group younger than 55 years vs. those older than 55 years. The age limit was used, taking into account the lack of mortality in patients younger than 50 years, which would have complicated the Kaplan-Meier survival analysis when a lower age limit would have been used. The prognostic findings were compared with previous reports from our institution (6,7,16–19) as well as with data from other countries; moreover, current TC incidence data were analyzed and compared with previous data (18,24,25). We tried to relate tumor incidence and tumor type to the respective situation of iodine supplementation.

Statistics

Survival was analyzed using the Kaplan-Meier method (26). The log-rank test was used to check for significant differences between groups. No adjustments for multiple comparisons were made, because the increase of the type-2 error caused by such an adjustment has to be considered as more serious than the loss of control over the signifi-

cance level of the universal null hypothesis that all statements bearing the label "statistically significant" are simultaneously true (27). The simultaneous impact of several prognostic variables (TNM stages, histology, age, sex) on survival was investigated using Cox regression (26).

RESULTS

Incidence of thyroid cancer in Tyrol

The total incidence rates for TC have shown a constant rise during past decades. This is demonstrated by the mean crude incidence rates of 3.07 for the period 1960 to 1970 (18,24), and of 3.98 from 1971 to 1980 (25). The current incidence figures are almost twice as high as those observed previously (Table 1).

Age

The results are presented in Table 2. Patients with "curable" tumor stages (group A), were significantly younger than patients with advanced tumor stages in group B (T4 or distant metastases or mediastinal lymph nodes). This difference could be shown for both papillary- and follicular-type TC. Patients with papillary TC were younger at the time of diagnosis than patients with follicular carcinoma ($p < .01$) or anaplastic cancer.

Sex

The overall female-to-male (f/m) ratio was 2.9/1. No significant difference in the female-to male-ratios was found between group A and B, nor between papillary and follicular TC, nor when comparing age group younger than 55 years with age group older than 55 years. The f/m ratio for anaplastic carcinoma was 1.2/1.

Distribution of histology and TNM stages

As shown in Table 3, papillary carcinoma was the predominant tumor type (54.4%), followed by follicular carcinoma. Anaplastic carcinoma was seen in 4.5%, and medullary TC in 2% of patients. We were able to observe a shift to a higher proportion of well-differentiated tumor types during the last decades (Table 4). A marked shift towards less advanced tumor stages could be seen: 72.2% belonged to the "curable" group A (T 1-3, N 0-1a, M 0); 27.7% had either tumor stage T4; or N1b, or distant metastases (group B) (Table 5). Distant metastases were present in 17.9% of all patients and in 14.1% already at diagnosis. The proportion of cases presenting metastases according to the histological classification was 7.5% for papillary TC; 22.6% for follicular TC; 33% for medullary TC: and 75% for anaplastic TC.

TABLE 1. CURRENT INCIDENCE RATES IN TYROL*

	Crude incidence rate (CR)		
	1980 to 1984	*1985 to 1989*	*1990 to 1994*
Male	3.23	2.52	4.25
Female	13.01	7.72	11.45
Mean	8.1	5.1	7.8
	Age standardized incidence rate (SIR)		
	1980 to 1984	*1985 to 1989*	*1990 to 1994*
Male	2.76	2.27	3.53
Female	11.0	5.97	8.68
Mean	6.8	4.12	6.11

*Per 100,000/year. Data obtained from the Cancer Registry of Tyrol.
Periods were chosen rather than single years in order to describe incidence trends more accurately.

Death due to TC during follow-up

Forty-nine of 439 patients died during the evaluation period. In 33 cases, death could be attributed to TC, ie, in 7.5% of all cases. In the remaining 16 cases, the cause of death was either cardiovascular disease or an additional tumor. In 5 cases information concerning the cause of death was not available. Mortality according to the histological type was 2% for papillary TC; 6.1% for follicular TC; 33.3% for medullary, TC; and 65% for anaplastic TC. Most patients who died, showed either follicular or anaplastic TC (69%) and a predominance of advanced tumor stages. None of the deceased patients was younger than 50 years and no patient with an original stage T1 died.

Kaplan-Meier survival analysis

The current overall survival rate for all patients is shown in Figure 1. Patients in group A showed a significantly better survival than patients in group B within differentiated TC ($p < .001$) (Table 6). The survival rate of patients with papillary carcinoma was better than patients with follicular TC, in case that no adjustment was made for tumor stage ($p = .025$; Table 6). However, if the comparison of survival in patients with papillary and follicular TC was made within the respective, stage-adjusted subgroups (group A and B), survival did not differ significantly, as shown in Figure 2. Survival of patients with distant metastases, and survival according to sex is shown in Table 6. Survival for patients with an age of 55 years or less was significantly better than for older patients ($p < .001$) (Table 6); this could be shown for both papillary ($p = .002$) and follicular TC ($p = .025$), confirming the results of the Cox Regression.

Simultaneous impact of variables on prognosis by multivariate Cox regression analysis

Considering the prognostic impact of age, sex, histological type (papillary and follicular), and tumor stage (group A and B), only the parameters age ($p = .005$) and stage ($p < .001$) remained statistically significant. Sex and histological type no longer showed a significant impact on survival within differentiated TC.

DISCUSSION

Incidence of thyroid carcinoma

Many risk factors for TC are well known, such as radiotherapy (28,29), especially in childhood (30), and pos-

TABLE 2. MEAN AGE OF PATIENTS (IN YEARS ± SD) WITH THYROID CARCINOMA AT TIME OF DIAGNOSIS. RELATION TO PROGNOSTIC PARAMETERS

Variable	*n*	*Mean age*	
All patients	439	54.1 ± 16.3	
Male	110	54.6 ± 16.3	
Female	329	53.9 ± 16.4	
Curable by surgery[a,*]	305	50.8 ± 15.6	
Only palliative surgery possible[b,*]	115	62.2 ± 15.3	
No metastases	370	52.9 ± 16.5	
Metastatic disease[#]	68	60.8 ± 13.8	
Death due to TC	33	69.4 ± 9.3	
Papillary TC[°,+]	239	51.4 ± 16	curable by surgery[a,§]: 49.7 ± 15 only palliative surgery[b,§]: 56.6 ± 18.4
Follicular TC[°]	163	56.1 ± 16.3	curable by surgery[a,i]: 51.9 ± 16.6 only palliative surgery[b,i]: 66.8 ± 9.9
Anaplastic TC[+]	20	64.7 ± 11.2 g	curable by surgery[a,$]: 67.0 ± 11.3 only palliative surgery[b,$]: 64.4 ± 11.5

[a]Patients presenting a tumor stage T1-3, or N0-1a, or M0 (group A).
[b]Patients presenting either a tumor stage T4 or N1b or M1 (group B).
*$p < 0.001$ comparing patients with curative vs. palliative stages.
#$p < 0.001$ comparing patients with and without metastases.
°$p < 0.01$ comparing papillary vs. follicular type.
+$p < 0.001$ comparing papillary vs. anaplastic type.
§$p \neq 0.015$ when comparing group A and B within papillary thyroid carcinoma.
i$p < 0.01$ when comparing group A and B within follicular carcinoma.
$$p$ = n.s. when comparing group A and B within anaplastic carcinoma.

sibly chronic TSH stimulation (9). Other mechanisms of carcinogenesis have been discussed, such as high levels of ionizing radiation from rocks or volcanic soil (31), or due to nuclear weapon tests (32), even different ethnic patterns (33), as well as environmental and genetic factors (31) were investigated. For women, additional risk factors such as miscarriage (34), have been postulated. In spite of these observations, no conclusive data exist concerning a possible further influence of different levels of iodine supply on the risk of TC. Some authors described a trend toward an increased risk for residents in iodine deficient endemic goiter areas (8,35), especially at a young age (8). Other authors observed a higher risk associated with iodine-rich food (34), and still others suggested a protective effect of iodine-rich food (seafood, vegetables [36]). However, the incidence of TC is known to be high in the iodine-rich and goiter-free areas of Hawaii and Iceland (1,2), whereas endemic goiter countries with iodine deficiency (Germany, Slovakia, Israel, Yugoslavia) show incidence data in a lower range (1,2). However, there are no reports about high incidence figures in other iodine rich countries, such as Japan. This observation is an argument against a possible causative relation between high iodine intake and the high TC incidence figures reported from Hawaii and Iceland. In these countries, many other factors have been investigated as well, such as volcanic activity (31), socioeconomic, and ethnic reasons (38), but no conclusion can be drawn so far. Moreover, local variations in incidence pattern may also occur within a country, as reported for Colombia, where despite sufficient and uniform iodine supply throughout the whole country, endemic goiter, along with an associated higher TC incidence rate, was shown to be present in some Colombian valleys, possibly being related to mechanisms other than iodine supply (37).

As for Tyrol, TC incidence was increasing during the past decades, when iodine supply was improving. A simi-

TABLE 3. DISTRIBUTION AND CHANGES OF THE HISTOLOGICAL TYPES OF THYROID CARCINOMA IN THE TYROL AREA DURING THE PAST DECADES. DATA FROM THE DEPARTMENT OF PATHOLOGY, UNIVERSITY INNSBRUCK

Histology	*1986 to 1995 (present data)*	*1952 to 1975**
	% (n)	% (n)
Papillary	54.4 (239)	21 (94)
Follicular	37.1 (163)	37.8 (169)
Medullary	2.0 (9)	0.7 (3)
Anaplastic	4.6 (20)	28.6 (128)
Angiosarcoma	0.7 (3)	2.9 (13)
Lymphoma	0.2 (1)	1.4 (6)
Pure oxyphilic	0.7 (3)	/
Unknown/others	0.2 (1)	7,6 (34)
Total	100 (439)	100 (447)

*(Ref. 17).

TABLE 4. PERCENTAGE OF DIFFERENTIATED THYROID ADENOCARCINOMA IN TYROL SINCE 1957

Period	*Undifferentiated thyroid cancer*	*Differentiated adenocarcinoma*
1957 to 1970*	28.4%	56.2%
1952 to 1975§	28,6	58,8
1971 to 1978*	19.2%	68.3%
1979 to 1983*	6.1%	86.3%
1986 to 1995°	4.9%	91.5%

*(Ref. 19).
§(Ref. 17).
°present data.

TABLE 5. COMPARISON OF DISTRIBUTION OF TUMOR STAGES DURING THE PAST DECADES IN TYROL (1957 TO 1995)

	Curable by surgery (%)[a]	*Only palliative surgery possible (%)*[b]
Tyrol, 1957 to 1970*	29	71
Tyrol, 1971 to 1981*	52.3	47.7
Tyrol, 1986 to 1995°	72.2 (n = 302)	27.7 (n = 116)

[a]Patients presenting a tumor stage T1–3, NO–1a, MO (group A).
[b]Patients presenting either a tumor stage T4 or N1B or M1 (group B).
21patients excluded because of insufficient data.
*(Ref. 17).
°present data.

lar trend, but without any relation to the extent of iodine supply, was observed in other countries. (United Kingdom, Norway, Switzerland and others [32,39,40]). This could partly be due to the continuous improvement of diagnostic techniques, including fine-needle biopsy (41), methods that were able to narrow the gap between tumors found in ordinary thyroid glands at autopsy (up to 30% of all examined thyroids [42]) and the incidence of clinically assessed TC (43). However, because of the early use and the constant frequency of routinely performed fine-needle biopsies during the past decades in our hospital (7), it seems unlikely, that the increase and the high TC incidence figures in Tyrol are merely due to the increased performance of fine needle biopsies.

Strikingly, our current incidence data are among the highest reported worldwide (Table 1) (1,2); however, we have no conclusive explanation for this observation up to now. No excessive natural radiation has been found in Tyrol (44). However, one may only speculate about a possible relation between the improvement of iodine supply and the rise in incidence rates. In areas with sufficient iodine supply, scintigraphically cold thyroid nodules should be evaluated more carefully than in endemic goiter regions, as they may more often be cancer, and not only simple goiter (in 5% to 20% cancer vs. about 3% in endemic goiter areas [7,45]).

The low frequency of TC in children in our study (5 patients younger than 20 years), which did not even allow statistical analysis in this age group, should also be stressed. TC incidence is quite low in children (46) and has been described as stable throughout the past decades (47), whereas others have observed a slow but steady increase during the last 20 years in Denmark (48) and England (49). Currently, the effects of the Chernobyl disaster on TC incidence in children are being investigated (50).

Changes in the presentation of thyroid cancer in a former endemic goiter area

Histological changes. Since iodized salt prophylaxis was introduced in 1963, the proportion of differentiated adenocarcinomas increased markedly during improvement of iodine supply, while anaplastic carcinoma decreased significantly (Table 4). A predominance and increase of papillary carcinoma was obvious (Table 3) (17,19), an observation that was also reported from other countries with previous iodine deficiency (51–53), especially from those

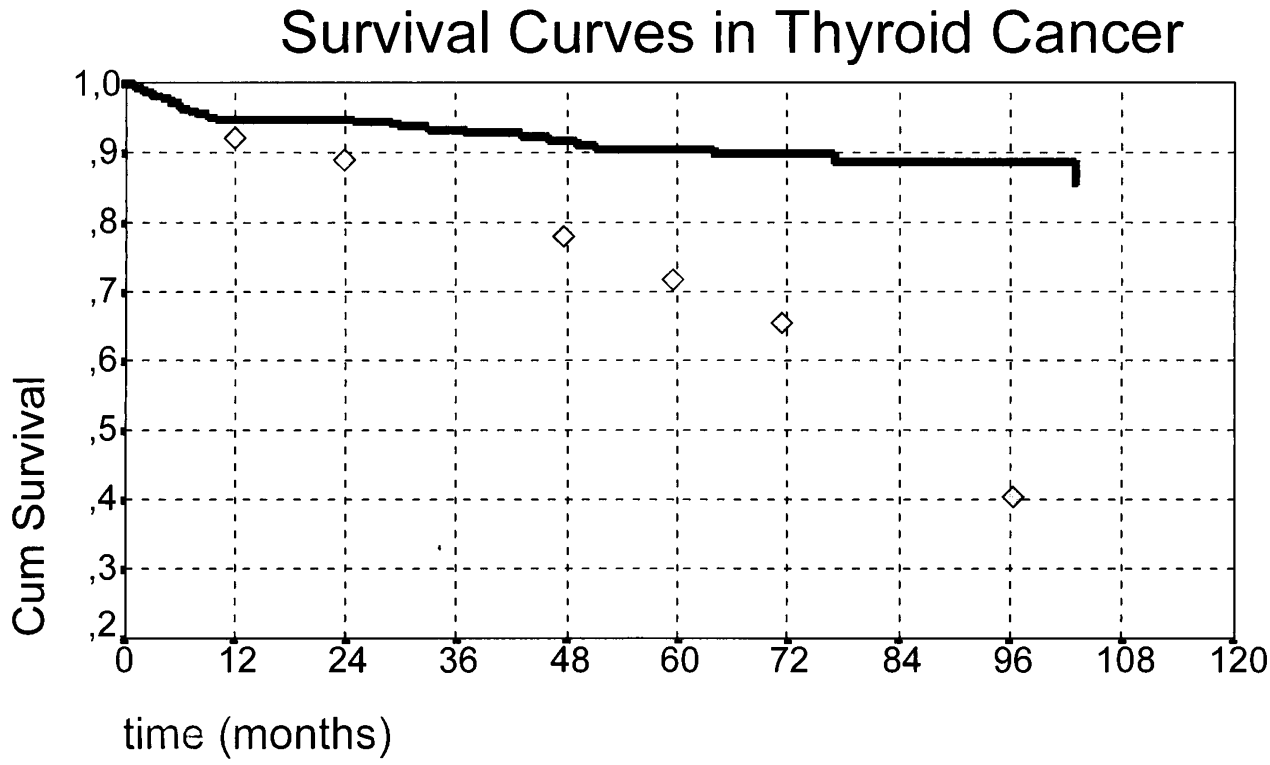

FIG. 1. Overall survival for patients with thyroid cancer. Only deaths caused by thyroid cancer are reported. The bold Kaplan-Meier curve represents survival of patients from the time period 1986 to 1995: 1-year survival: 94.9% ± 1.1%; 93.4% ± 1.3% at 3 years; 90.7% ± 1.7% at 5 years, and 88.8% ± 2.2% at 7 years. The rhombic symbols show the survival curve from the time period 1962 to 1969[7] (evaluation was done using timetable method).

TABLE 6. SURVIVAL RATES ACCORDING TO PROGNOSTIC PARAMETERS 1986 TO 1995 (IN %)

Criteria	*Variable*	*1 year*	*3 years*	*5 years*	*7 years*
Papillary Tumor	"Curable" by surgery[a,§]	100	100	100	100
	Only palliative surgery[b,§]	97.9 ± 2	97.9 ± 2	75.0 ± 11.8	75.0 ± 11.8
	Both groups	99.1 ± 0.6	99.1 ± 0.6	96.2 ± 1.8	96.2 ± 1.8
Follicular Tumor	Curable by surgery[a,$]	100	100	100	100
	Only palliative surgery[b,§]	92.6 ± 4.1	85.6 ± 6.1	68.9 ± 10.3	61.3 ± 11.7
	Both groups	98.2 ± 1.1	95.8 ± 1.9	92.8 ± 2.8	87.3 ± 4.7
Anaplastic Tumor		35.0 ± 10.2	35.0 ± 10.2		
Age at diagnosis*	Younger than 55 yr.	99.0 ± 0.7	99.0 ± 0.7	99.0 ± 0.7	97.7 ± 1.5
	Older than 55 yr.	90.4 ± 2.1	87.3 ± 2.5	81.1 ± 3.6	78.5 ± 4.3
Sex°	male	90.5 ± 2.9	90.5 ± 2.9	88.2 ± 3.6	85.2 ± 4.6
	female	96.4 ± 1.1	94.4 ± 1.4	91.6 ± 2.0	90.2 ± 2.4
Metastases	survivors after metastatic disease	76.3 ± 5.1	66.9 ± 6.0	56.7 ± 7.5	49.6 ± 9.3

[a]Patients presenting a tumor stage T1-3, or N0-1a, or M0 (group A).
[b]Patients presenting either a tumor stage T4 or N1b or M1 (group B).
*$p < 0.001$ when comparing the age groups < 55 years vs. > 55 years.
°$p = 0.114$ (Breslow-test: $p = 0.046$); male vs. female.
§$p < 0.001$ when comparing "curable" vs. "palliative" within papillary TC.
$$p < 0.001$ when comparing "curable" vs. "palliative" within follicular TC.

where controlled iodized salt prophylaxis is now done, eg, Switzerland (52). These findings suggest that as long as endemic goiter is a frequent feature in a population, patients are not worried about goiter growth until serious symptoms occur. By that time, initially well-differentiated TC may have changed into anaplastic cancer. This phenomenon of late dedifferentiation has been shown in isolated cell lines of papillary TC (54), in animal studies (55), and in humans (56). The current pattern of histological distribution in our study was shown to be similar to that of other countries with no or only mild iodine deficiency (Norway, United Kingdom, Spain) (3,4,53). Nevertheless, the percentage of papillary tumors in Tyrol is not yet as high as in really iodine-rich countries, where papillary TC is shown to be by far the most common thyroid malignancy (70% to 80%), eg, in Japan or Iceland (10,57). In Japan, where people were reported to have a mean urinary iodine excretion of up to 1500 μg/g creatinine (57), the proportion of papillary TC has always been high, without any shift observed (57). The proportion of follicular carcinoma in our study decreased only slightly, when compared with previous studies (Table 3) (17).

Changes of TNM-stages

Marked changes were observed when the impact of iodine prophylaxis on the distribution of tumor stages was analyzed. Currently, the majority of patients belong to the "curable" group A. The current relation between patients belonging to group A and the "palliative" group B shows a nearly inverse pattern, when compared with the distribution of tumor stages observed before and at the onset of iodine prophylaxis (Table 5) (7).

Evaluation of the prognostic impact of variables that have changed under iodine supplementation

The influence of TNM stages and histological distribution on prognosis is well known (58,59) and was confirmed by our study: Patients with advanced tumor stages had a significantly poorer prognosis than patients in the potentially "curable" group A, even in differentiated TC (Table 6). One could conclude from the results of the Cox regression analysis, and from the absence of a significant difference in survival between papillary and follicular TC within the stage-adjusted subgroups A and B (Fig. 2), that within differentiated TC, the impact of histology on prognosis is not as marked as the influence of tumor stages. Nevertheless, anaplastic carcinoma showed a poor survival of only 35% at 1 year, this figure remaining unchanged for the following years.

Due to the changes of histological pattern, ie, the marked decrease of anaplastic TC and of the distribution of tumor stages that occured during improvement of iodine supply, the survival rate has improved significantly (Fig. 1). Current overall 5-year survival rate is 90.7%, compared with 73% for the period from 1962 to 1969; 7-year survival for our patients improved from 45% to 50% (1962 to 1969) to 88.8% (7). Only 7.5% of all TC patients died because of their tumor in our study, which is a remarkably low figure in comparison with other reports coming from countries with insufficient as well as with sufficient iodine supply (Switzerland, Norway, United States, United Kingdom, Japan, mortality of TC ranging from 8.2% to 16%) (3,52,58,60,61). Apart from the impact of improved iodine supply, our current better survival data may be partly explained by the fact that other authors used collective mortality over longer observation time-spans for evaluation, including patients from the early 1960s up to the 1980s or 1990s. Therapeutic techniques were not as refined as they are today, thus leading to a bias when prognosis is evaluated. Moreover, our rigorous and continuous follow-up program may have further contributed to this improvement in survival.

Distant metastases in this study were quite rare in papillary cancer (7.5%), in agreement with other reports (59), but often present in follicular and medullary TC (62), and

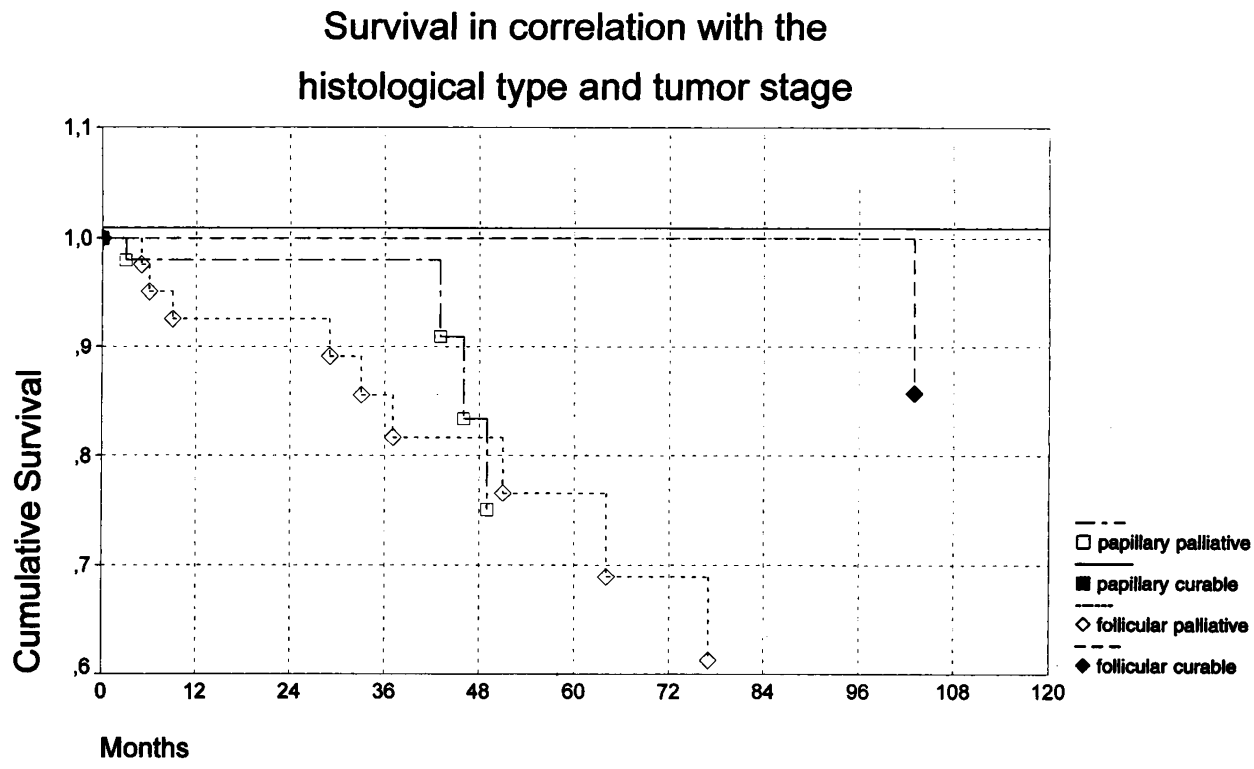

FIG. 2. Survival in correlation with the histological type and tumor stage (1986 to 1995). Papillary vs. follicular: $p = 0.025$; Group A (= curable, solid symbols) vs. group B (= palliative, open symbols): $p < 0.01$. Papillary (□,■) vs. follicular ◇,◆ within subgroups (curable, palliative): n. s.

most of all in anaplastic carcinoma. However, about 50% of patients with metastases were still alive after 7 years (Table 6).

Prognostic impact of age and sex

A trend toward a worse survival in men could be observed (Table 6), probably being due to a relatively higher proportion of anaplastic carcinomas in male patients (f/m ratio: 1.2/1), whereas no predominance of advanced tumor stages was seen in men. The difference in survival was marked especially in the first years after diagnosis, confirming the report of Noguchi et al. (61). Patients with anaplastic thyroid carcinoma seem most likely to die within the first few years after diagnosis, a fact that would fit well into this theory. Other authors were not able to observe any significant difference in survival between men and women (58). The strong impact of age on prognosis of patients with TC, as reported by many authors (3,5), was also confirmed by this study (Table 6).

CONCLUSION

Obviously, improved iodine supply in a former iodine-deficient goiter area has a strong impact on survival rate and prognosis of TC patients due to an increased percentage of highly differentiated TC as well as of potentially curable tumor stages. In areas with sufficient iodine supply and adequate medical care, well-differentiated TC will be detected before spreading to surrounding tissue or lymph nodes. Both age and TNM-stages are the most important prognostic factors within differentiated TC. We were not able to find a convincing explanation for the rising incidence of TC during improvement of iodine supply. However, because current TC incidence rates in Tyrol are high, further investigations into possible mechanisms of carcinogenesis seem necessary.

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