

Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis

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Abstract

In differentiated thyroid carcinoma 10-year survival rates amount to 80–95%. Because age at diagnosis varies widely, these survival rates strongly depend on age at presentation. The aim of the present study was to analyse the attributable risk factors, including therapy *per se*, on survival in thyroid cancer after proper adjustment for the baseline mortality rate in the general population and to elucidate the adverse treatment effects on survival. Initial treatment in 504 patients consisted of thyroidectomy and ¹³¹I ablation. High-dose ¹³¹I was administered for residual disease. Patients in complete remission underwent an annual physical examination and thyroglobulin measurements during TSH suppression. Survival time was studied after transformation to standardised survival time to adjust for the baseline mortality rate in the general population.

Median follow-up since diagnosis was 9 years. The 10-year overall survival was 83% and disease-specific survival 91%. After initial treatment, persistent disease occurred in 75 patients (15%). In univariate analysis, T4, N1, M1 status and Hürthle cell type were prognostic for persistent and recurrent disease. Age was not prognostic for recurrent disease in multivariate analysis. The standardised survival time was not altered in disease-free patients. However, patients with persistent disease had a median standardised survival time of only 0.60 (95% confidence interval 0.47;0.72), ranging from 0 to above 1, independent of initial tumour status or age. The cumulative proportion of persistent disease was at least 20% of the whole group.

Disease-free patients after thyroid carcinoma have a normal residual life span. In contrast, in cases of persistent disease the life expectancy ranges widely with its median being reduced to 60%. Overall, treatment including radioiodine is safe but unsuccessful in 20% of the patients. Age is not a disease-specific risk factor and should not be used as an independent factor in treatment algorithms.

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Introduction

Patients with differentiated thyroid carcinoma have an excellent 10-year survival ranging between 80 and 95% (Schlumberger 1998, Sherman 2003). This illustrates that the natural course of the disease is relatively mild and that treatment of this tumour type, which consists of thyroidectomy followed by high-dose radioiodine and life-long thyroid hormone therapy, is highly successful. Nonetheless, it is still not known whether

this treatment adversely affects the residual life span. Standard survival curves express survival in years alive irrespective of age. However, in order to determine life expectancy, age at diagnosis must also be taken into account. This is even more important as age at presentation of thyroid cancer occurs throughout all decades of life.

When disease-specific mortality is low and age at diagnosis varies considerably, long-term survival should be properly adjusted for the baseline mortality

rate in the general population. Statistical analysis on survival should, therefore, include methods of age adjustment. Nonetheless, the graphical presentation of survival data remains problematic as long as survival is expressed in years. Ten-year cumulative proportions of survival, both disease specific and overall, decrease with advancing age at diagnosis and should be reported separately for several age categories within the sample. By analogy, visual presentation as, for example, by Kaplan–Meier plots should include survival curves for each age category. Relative risks or hazard ratios calculated after adjustment for age only represent their mean value in the sample. A shortcoming of this risk assessment is that it does not provide insight into their variance and could easily miss a small proportion of the diseased population with a highly deviating risk.

As an alternative, we have used a newly developed method which combines proper adjustment for age at diagnosis with the capacity of graphical presentation of the risk distribution unbiased by age to study survival. For this method, we introduced a new parameter of survival: the standardised survival time.

This method also provides a new insight into survival as it enables the effect of treatment from ‘prolonging life with as many years as possible’ to ‘regaining a normal residual life span’ to be studied. The aim of this study was to apply this method to a cohort of 504 thyroid carcinoma patients in whom the residual life span was analysed.

Patients and methods

Patients

The University Hospital Groningen is the major referral centre in the northern part of The Netherlands for treatment with ^{131}I of patients with differentiated thyroid carcinoma. From January 1978 through September 2000, all 504 consecutive patients with differentiated thyroid carcinoma who were referred for treatment with ^{131}I were included in this analysis.

Treatment regimen

Initial treatment consisted of near total or total thyroidectomy. Lymph node biopsies were performed and this procedure was followed by a lateral modified radical neck dissection in cases of lymph node metastases. After surgery, patients were staged according to the post-operative TNM classification as recommended for thyroid cancer (Brierley *et al.* 1997).

Post-surgical treatment with ^{131}I was given according to our standard protocol (van Tol *et al.* 2003); this

is largely comparable with the subsequent published guidelines of the British Thyroid Association (www.british-thyroid-association.org).

Follow-up was started by measuring thyroglobulin (Tg) under thyroxine suppression therapy after a negative post-therapy whole body scan (WBS), with a frequency of two to three times annually and once a year thereafter.

Evidence of thyroid cancer disease was defined as (1) the presence of a clinically detectable differentiated thyroid cancer, (2) a positive diagnostic or post-therapy ^{131}I WBS or detectable serum Tg after thyroid hormone withdrawal and (3) detectable Tg during thyroid hormone medication. Persistent disease after initial therapy was defined as evidence of thyroid cancer disease found at any visit after ablation. Patients without persistent disease after initial therapy were considered to be in remission after ablation. Recurrent disease was defined as tumour recurrence indicated by newly detectable Tg during suppression therapy or evidence of disease detected by any other technique. After recurrence, a post-therapy ^{131}I 150 mCi scan was obtained after discontinuation of thyroid hormone therapy. Ultrasonography or magnetic resonance imaging of the neck and mediastinum and computed tomography scanning was performed depending on clinical suspicion. Patients in remission were considered to be disease free as long as recurrent disease was absent. Persistent disease after recurrence was defined in analogy with persistent disease after initial therapy.

Laboratory methods

From 1978 until 1984 serum Tg was measured by a home-made RIA. From 1984 until 1989 a commercially available RIA (Cis Bio International, Gif-sur-Yvette, France) with a lower detection limit of 3.0 ng/ml was used. From 1989 onwards the detection limit was set as 1.5 ng/ml. A validated conversion factor $((\text{old}-40)/2 = \text{new})$ was used for serum for old serum Tg levels measured before 1984 to enable comparison with the new serum Tg concentrations. In cases of undetectable serum Tg, the presence of Tg antibodies was evaluated by recovery of added standard Tg. Tg antibodies were considered to be absent if recovery was $>85\%$.

Statistical analysis

The standardised survival time was calculated as the ratio between the observed survival time of an individual and the median residual life span of

individuals with the same age in the general population in the year of diagnosis. The median residual life span was derived from gender-specific reports provided by the Dutch Central Office of Statistics (www.CBS.nl). This method provides an age adjustment of survival in each individual, enabling direct comparison between groups. Further, it directly compares a (sub)sample with the general population by the 95% confidence interval (CI) of its median standardised survival time.

Data are expressed as means \pm s.d. unless stated otherwise. Differences in various parameters were tested using the chi-square test with continuity correction or the Mann–Whitney U test, as appropriate. Survival curves were constructed according to the Kaplan–Meier method. Differences in standardised survival time were tested by log rank test, with relative risks calculated as the quotient of the ratio of observed events and extent of exposure. Patients were censored at the end of follow-up, unless an event occurred before that date. Events were defined as death for overall survival, death due to thyroid cancer for disease-specific survival and (re)occurrence of disease or death for the disease-free interval. Cox regression analysis was performed to study age as an independent risk factor.

The patients were grouped into four strata, representing quarters of ranked residual life span at diagnosis. In all tests, a two-sided *P* value <0.05 was considered to be significant and 95% CI are given when appropriate.

Results

Patient characteristics

Characteristics of the 504 patients are given in Table 1. Age at diagnosis ranged from 7 to 87 years with a median of 46 years. The quarters of life expectancy ranged from 4 to 72 years with quartiles from young to old of 72–47.3, 47.3–34.5, 34.5–21.4 and 21.4–4 years. Follow-up since diagnosis was 23 (median 9) years.

Overall and disease-free survival

Overall 10-year survival in the whole group of 504 patients was 83%; the disease-specific survival was 91% (Fig. 1). After 10 years, 75% of the patients were alive and disease free. The 10-year overall survival in the stratified quarters of ranked life expectancy was, from young to old, 100, 94, 86 and 53% respectively (Fig. 2). For disease-specific survival, these figures were 100, 95, 93 and 77% respectively.

Table 1 Characteristics of the study group

	All patients	
	No.	%
All	504	
Sex		
Male	129	26
Female	375	74
Age (in years)		
<40	185	37
40–59	180	36
≥ 60	139	28
Tumour histology		
Papillary	306	61
Follicular	170	34
Hürthle	28	6
Tumour stage		
T0–T3	377*	75
T4	78*	16
N0	354	70
N1	150	30
M0	466	93
M1	38	8

*Of 49 patients (9.7%) no data were available on initial tumour size.

Persistent disease after initial treatment

Seventy-five patients had persistent disease. Univariate analysis indicated that the odds ratios (OR) for risk factors regarding persistent disease indicated that age (below or above the median (OR=4.09 95% CI 2.32;7.26), T4 (OR=7.71 95% CI 4.39;13.5), M1 (OR=35.1 95% CI 15.2;81.1), N1 (OR=2.34 95% CI 1.42;3.86) and Hürthle cell carcinoma (OR=4.92 95% CI 2.22;10.9) were highly associated with persistent disease.

Recurrence after complete remission

A tumour recurrence was detected in 35 patients during follow-up. Recurrence occurred after a median of 54 months (range 14–257 months) since diagnosis. Recurrences were detected with serum Tg during suppression therapy in 26, a palpable neck lesion in seven (in two of them serum Tg also turned out to be detectable) and by imaging techniques in the two other patients. In the 26 patients with raised Tg only, 13 patients had a local recurrence in the neck, of whom two also had lung metastases, two patients showed mediastinal metastases and two patients had only pulmonary metastases. Despite an extensive diagnostic approach, an anatomic substrate for the serum Tg rise was never found in the remaining nine patients who all had Tg values off thyroid hormone treatment below 15 ng/ml.

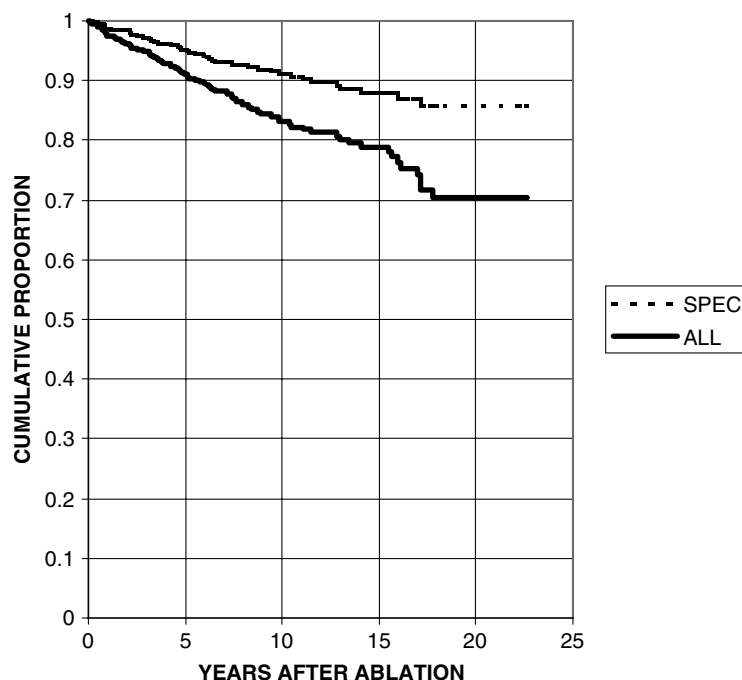


Figure 1 Disease-specific (SPEC) and overall (ALL) Kaplan–Meier survival curves.

No additional therapy was given (no anatomical substrate or patient refusal) in ten of the 35 patients with recurrent disease. Treatment of the localised recurrences included high-dose ^{131}I ($n=19$), surgery of the neck ($n=15$) and external radiotherapy to the neck and mediastinal structures ($n=7$). Most patients received more than one form of treatment. A second complete remission was achieved in 14 of the 35 patients.

Death from other causes

Thirty-eight patients died from causes other than thyroid cancer. Two died from another pre-existing primary tumour and nine (23%) from a cardiac cause. The two patients who died from another pre-existing primary tumour suffered from chronic lymphatic leukaemia and acromegaly respectively and belonged to a group of 26 patients with a history of a primary tumour diagnosed before thyroid carcinoma. Ten of these 38 patients had evidence of persistent thyroid cancer at their latest visit.

Life expectancy in differentiated thyroid carcinoma

A Kaplan–Meier plot of the cumulative proportion of deaths, both overall and disease specific, against

standardised survival time is shown in Fig. 3. The expectation for the age- and gender-matched (median life expectancy of 34.5 years in 1990) general population is also shown. The median standardised survival time in the whole cohort was 0.88 (95% CI 0.76;0.99).

The cumulative proportion of death at half standardised survival time was 0.165 (95% CI 0.124;0.213), which is above the proportion of maximally 0.10 in the age-matched general population. At a standardised survival time of 1, two-thirds of all patients had died, about half of them from thyroid cancer. Of those still alive, some had persistent disease.

In order to visualise the impact of persistent disease and of the treatment *per se* on life expectancy, the patients were divided into those with persistent disease at the latest visit and those without such evidence. Plots of proportion of death (overall and disease specific) against standardised survival time are given for both groups in Fig. 4. The expected curves for a median life expectancy of 38 years in the year 1990 (as in the patient group without persistent disease) for both genders of the general population are indicated for comparison.

Median standardised survival time was 0.60 (95% CI 0.47;0.72) in persistent disease and about 80% of these patients died from thyroid cancer. The standardised survival time ranged from 0 to above 1.

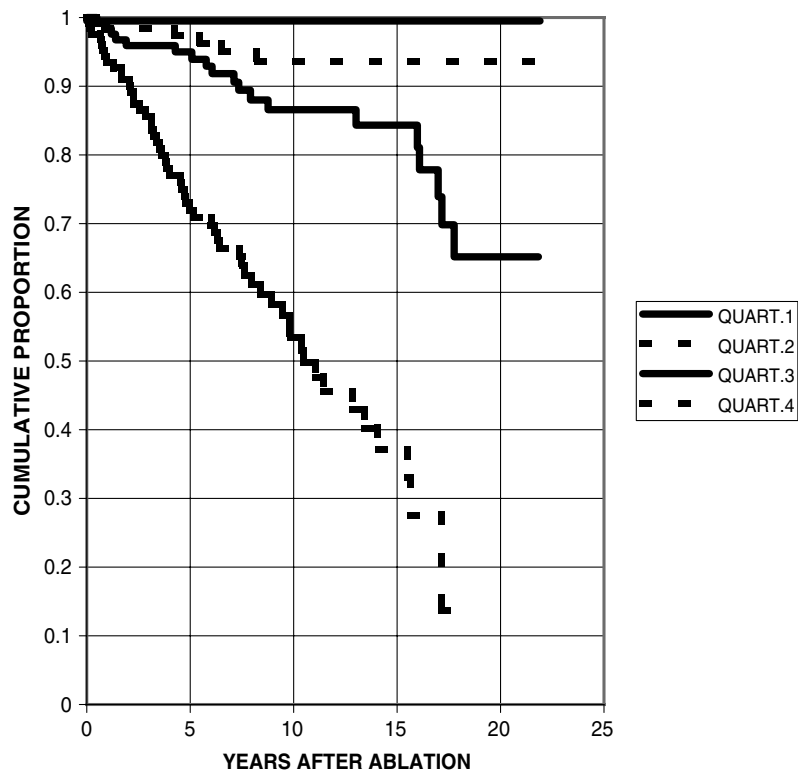


Figure 2 Overall survival (Kaplan–Meier) according to categories of life expectancy. Quarters (QUART.) 1–4: quarters of ranked life expectancy from young to old: 47.3–72 years (quartile 1), 34.5–47.3 years (quartile 2), 21.4–34.5 years (quartile 3) and 4–21.4 years (quartile 4).

The survival pattern of those without persistent disease was similar to that of the whole Dutch population, with a proportion of death below 0.10 up to a standardised survival time of 0.5, and a median standardised survival time of 1.19 (95% CI 0.85;1.53).

Prognostic factors

The univariate relative risks regarding TNM status and presence of Hürthle cell carcinoma regarding disease-free interval are given in Table 2. With multivariate regression analysis, age was not a prognostic factor ($P=0.68$) for recurrent disease. Univariate relative risks for overall survival in the total cohort and those with persistent disease at the latest visit are also provided in Table 2. These data reflect the well-known association of T4, N1, M1 and Hürthle cell carcinoma with diminished disease-free and overall survival. Within the group of patients with persistent disease, TNM status and Hürthle cell carcinoma were not significantly associated with a shorter standardised survival. Within this group, the standardised survival

time in patients with a life expectancy at diagnosis above the median of 34.5 years was not different from those with an expectancy below the median (RR=0.85, 95% CI 0.31;2.34, $P=0.76$).

Discussion

This study has shown that patients in remission after treatment for thyroid carcinoma have a survival pattern that is similar to that of the general Dutch population. We also showed that in this group the cumulative proportion of death was below 0.10 up to a standardised survival time of 0.5, and that the median standardised survival time was normal, indicating that the treatment *per se* is safe. Thus, not only was median survival unaffected by the use of radioiodine, as reported earlier (Berthe *et al.* 2004), but there was no indication that any small subgroup of patients might be harmed by radioiodine. In a large series, an increase in the incidence of several tumours in association with the dose of radioiodine was found (Rubino *et al.* 2003). Although the incidence in several tumours was

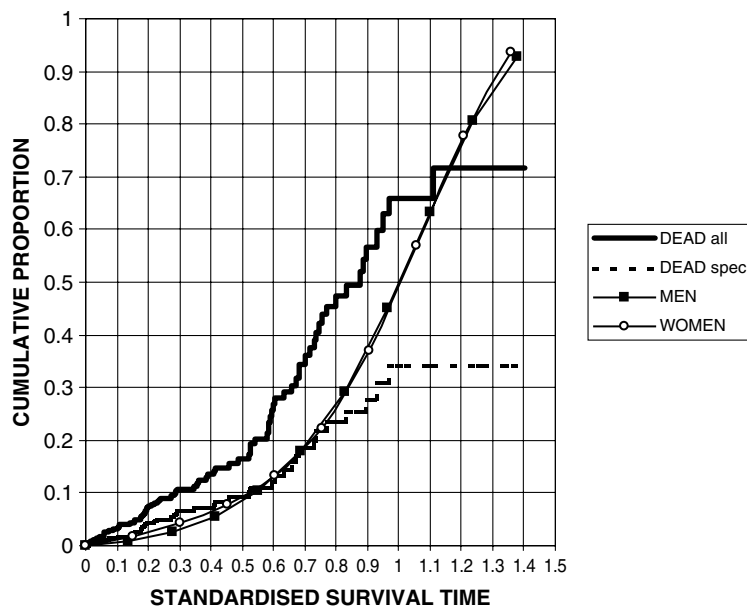


Figure 3 Cumulative proportions of death, both overall and disease specific, against standardised survival time. DEAD all=overall deaths, DEAD spec=death from thyroid cancer and MEN and WOMEN=expected deaths for men and women with an expectancy of 34.5 years in 1990.

increased, they remain too low to result in any detectable excess mortality.

In our group comprising the 38 deaths from other causes, two out of 26 patients died from a pre-existing tumour other than thyroid cancer. An increased incidence of secondary tumors in thyroid cancer has been previously recognized, but this elevated risk has not been found to be associated with the use of radioiodine and has not been found to affect median overall survival (Berthe *et al.* 2004, Kim *et al.* 2004). If life-long thyroid medication is harmful, we would have expected to find an excess mortality and an increased relative incidence of deaths from cardiac disease. We did not find excess mortality and found that 23% of deaths from other disease has a cardiac cause, as compared with 20% in 2002 in the whole Dutch population (www.CBS.nl). This finding indicated that life-long thyroid hormone medication is, in general, not accompanied by excess mortality.

Patients with persistent disease had a clear reduction in the standardised survival time. A worse TNM status and Hürthle cell carcinoma, with an increased prevalence at higher age at diagnosis, but not the age itself, are prognostic for initially persistent disease and recurrence. However, these factors did not influence the standardised survival time of patients who cannot be cured in the initial or successive treatment

procedure. In addition, age at diagnosis did not affect the standardised survival time in cases of persistent disease. This is very remarkable, because it means that the increase in death rate is proportional to the age-dependent death rate in the general population. The almost straight Kaplan–Meier plot (Fig. 4) for persistent cases indicates that their standardised survival times show an almost Gaussian distribution pattern. The wide range in standardised survival time, ranging from 0 to above 1, illustrates the variance in progression of disease, and is compatible with a wide range in dedifferentiation of the metastatic tissue.

How can we explain the absence of disease-specific risk of age in the standardised analysis? If it is supposed that the comparison of two age groups (young and older) from the general population shows that the younger group has a life expectancy twice that of the older group, when the vital strength of the younger group may be considered to be twice that of the older one. When both groups live in the same environment with the same threats, the median survival in the younger group is indeed twice that of the older group upon follow-up. However, in both groups the median survival is equal to expectancy, making median standardised survival 100% in both groups. Performing a subgroup analysis on those who were newly diagnosed to have some specified severe disease at the

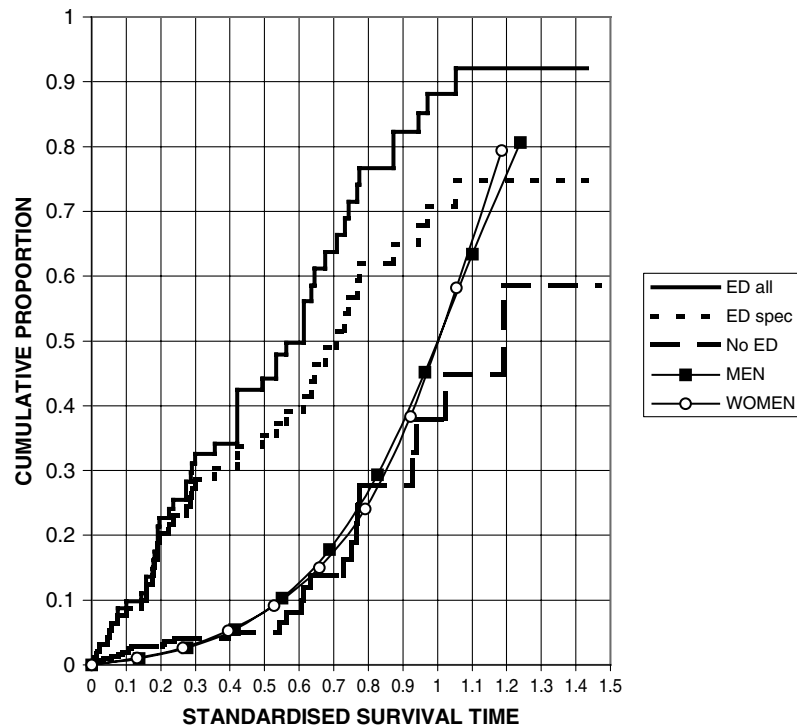


Figure 4 Cumulative proportions of death against standardises survival time in patients with and without persistent disease. ED all=overall deaths in patients with evidence of persistent disease, ED spec=disease-specific deaths in patients with evidence of persistent disease, No ED=overall deaths in patients without evidence of persistent disease and MEN and WOMEN=expected deaths for men and women with an expectancy of 38 years in 1990.

start of follow-up, it would not be surprising to find a shortened median survival in these patients as compared with the median survival of their own age group, taking the excess probability of death of that specific disease into probability. It should not be surprising either to find the shortened median survival in the younger patients to still be twice the shortened median survival in the older patients, as the vital strength of the younger patients was selected to be twice that of the older patients.

In the patients with persistent thyroid cancer, we found a reduced standardised survival, which was indeed independent of age. In these patients, the proportional increase in the age-dependent death rate in the general population is quite understandable, as the death rate in the general population is the inverse of the age-dependent vital strength.

Age as an independent disease-specific risk factor, as used in the prognostic systems based on conventional multiple regression analysis (European Organization

Table 2 Relative risks of prognostic factors

Comparison	Disease-free interval RR (95% CI)	Overall survival Total cohort RR (95% CI)	Overall survival Persistent disease RR (95% CI)
T4 vs T0–3	4.15 (2.88;5.96)	2.17 (1.35;3.51)	1.29 (0.73;2.27)
M1 vs M0	6.83 (4.79;9.74)	3.77 (2.29;6.21)	1.68 (0.96;2.93)
N1 vs N0	2.00 (1.38;2.89)	1.46 (0.89;2.38)	1.10 (0.64;1.90)
H vs PTC+FTC	3.47 (2.11;5.70)	2.10 (1.02;4.32)	0.72 (0.33;1.59)

RR=Relative risk, 95% CI=95% Confidence interval, FTC=follicular thyroid cancer, PTC=papillary thyroid cancer, H=Hürthle cell carcinoma.

for Research and Treatment of Cancer, TNM, etc.), is therefore not present in the standardised data presented here and should not, in our opinion, be used in treatment criteria. This new statistical approach underlines the prognostic value of the above-mentioned risk factors and the urgent need for initial curative therapy in these high-risk groups, irrespective of age.

However, about 20% of deaths in cases with persistent disease is not due to thyroid cancer and some have a standardised survival time above 1. This illustrates the mild course in several of them.

During our follow-up regimen, which consisted of Tg measurements during suppression therapy and neck palpation, evidence of recurrence was found in only 35 patients. The tumour could not be localised in nine, when Tg off thyroxine suppression treatment was below 15 ng/ml. Approximately half of the recurrences reached a second remission. Our recurrence rate is in the lower range of the numbers that are mentioned in other studies, varying between 5 and 23%, and in low-risk group analysis even lower (Schlumberger 1998, Cailleux et al. 2001, Mazzaferri & Kloos 2001, Hay et al. 2002). Most studies describe a follow-up period which starts before serum Tg measurements are available and consequently remission was only defined with a negative ^{131}I scan and in the absence of signs of clinical disease, so it is likely that many patients were falsely considered to be in remission.

With a maximal follow-up in our study of 23 years the estimation of the proportion of persistent disease is more than 20%. In cases where recurrences continue to occur after more than two decades, the proportion of persistent disease will grow even further. However, as the prevalence of a tumour with a poor prognostic status is lower in younger patients, the ultimate proportion of disease-specific deaths will probably remain well below a third, which is the interim estimation at this moment as indicated in Fig. 3.

In summary, this study has shown that age is not a disease-specific risk factor and should therefore not be used as an independent factor in treatment decisions. We have also shown that treatment *per se* (thyroidectomy, high-dose radioactive iodine and thyroid hormone medication) is safe and does not shorten life expectancy. Nonetheless, it remains important to realise that patients with persistent disease have a median standardised survival time of only 60%, independent of age. This underlines the urgent need for new therapeutic approaches to patients with persistent disease, rather than concentrating all one's efforts on diagnosing the recurrence of the disease as early as possible.

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References

- Berthe E, Henry-Amar M, Michels J-J, Rame J-P, Berthet P, Babib E, Icard P, Samam G, Galateau-Sallé F, Mahoudeau J & Bardet S 2004 Risk of second primary cancer following differentiated thyroid cancer. *European Journal of Nuclear Medicine and Molecular Imaging* **31** 685–691.
- Brierley JD, Panzarella T, Tsang RW, Gospodarowicz MK & O'Sullivan B 1997 A comparison of different staging systems predictability of patient outcome: thyroid carcinoma as an example. *Cancer* **79** 2414–2423.
- British Thyroid Association 2002 *Guidelines for the Management of Thyroid Cancer in Adults*. www.british-thyroid-association.org. British Thyroid Association and Royal College of Physicians.
- Cailleux AF, Baudin E, Travagli JP, Ricard M & Schlumberger M 2001 Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? *Journal of Clinical Endocrinology and Metabolism* **86** 949–950.
- Dutch Central Office of Statistics www.CBS.nl CBS. Voorburg/Heerlen, The Netherlands.
- Hay ID, McConahey WM & Goellner JR 2002 Managing patients with papillary thyroid carcinoma: insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. *Transactions of the American Clinical and Climatological Association* **113** 241–260.
- Kim S, Wei JP, Braveman JM & Brams DM 2004 Predicting outcome and directing therapy for papillary thyroid carcinoma. *Archives of Surgery* **139** 390–394.
- Mazzaferri EL & Kloos RT 2001 Current approaches to primary therapy for papillary and follicular thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **86** 1447–1463.
- Rubino C, de Vathaire F, Dottorini ME, Hall P, Schwartz C, Couette JE, Dondon MG, Abbas MT, Langlois C & Schlumberger M 2003 Second primary malignancies in thyroid cancer patients. *British Journal of Cancer* **89** 1638–1644.
- Schlumberger MJ 1998 Papillary and follicular thyroid carcinoma. *New England Journal of Medicine* **338** 297–306.
- Sherman SI 2003 Thyroid carcinoma. *Lancet* **361** 501–511.
- van Tol KM, Jager PL, de Vries EG, Piers DA, Boezen HM, Sluiter WJ, Dullaart RP & Links TP 2003 Outcome in patients with differentiated thyroid cancer with negative diagnostic whole-body scanning and detectable stimulated thyroglobulin. *European Journal of Endocrinology* **148** 589–596.