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Original Paper

Trends in Treatment and Long-term Survival of Thyroid Cancer in Southeastern Netherlands, 1960–1992

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Thyroid cancer (TC), comprising less than 1% of all cancers in the Netherlands, has a good prognosis in general. Controversy still remains on the extent of surgical treatment and the indication for additional Iodine-131 (^{131}I) therapy in the management of differentiated TC. The aim of this study was to describe (changes in) the treatment of TC and to determine independent prognostic factors for crude and relative survival of differentiated TC diagnosed in general hospitals. This population-based, retrospective study was based on data from the Eindhoven Cancer Registry, Comprehensive Cancer Centre South (I.K.Z.), Eindhoven, the Netherlands. Data were collected on all 343 TC patients diagnosed from 1 January 1960 to 31 December 1992. All available information on treatment (initial and additional) and survival (on 1 April 1994) were recorded. Initial surgical treatment was defined as limited or extended. Multivariate analysis of crude and relative survival to determine prognostic factors for differentiated TC was performed. Mean follow-up was 7.6 years. The proportion of patients with differentiated TC increased from 60% in 1960–1972 to 84% in 1985–1992. TC patients were treated in all hospitals in the region, approximately 2–4/year. Ninety per cent of all TC patients initially underwent surgical treatment; the extended procedures increasing from 27% in 1960–1974 to 61% in 1985–1992. ^{131}I was also administered increasingly (from 18–44%) to patients with differentiated TC. The relative 5, 10 and 20 year survival rates for all TC were 80, 75 and 75%, respectively. In the first 5 years after diagnosis the crude death ratio was higher with the rise of age and for the follicular type and after 5 years for males and advanced disease. After inclusion of surgical treatment into the model, the estimates of the other death ratios did not change. Patients treated with ^{131}I did better only during the first 5 years. Although the prognosis for TC patients treated in general hospitals in Southeastern Netherlands was similar to that found for patients treated in referral centres, concentration of treatment should be considered.

Key words: thyroid cancer, population-based, treatment, survival, general hospitals, ^{131}I
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INTRODUCTION

THE INCIDENCE of thyroid cancer (TC) is low in the Netherlands, in 1993 340 new patients (96 male, 244 female) were registered by the Dutch Cancer Registry (0.5% of all cancer cases). The European standardised incidence rates were 1.3 and 2.7 per 100 000 inhabitants per year for men and women, respectively [1]. In general, 80% of newly diagnosed TC are differentiated (papillary or follicular) tumours which have a relatively good prognosis.

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A consensus conference on the management of differentiated TC in the Netherlands (1987) developed guidelines for the diagnostic strategy and for surgical and additional Iodine-131 (^{131}I) therapy [2]. However, controversy remained on the extent of surgical treatment both in the Netherlands and abroad [2–5]. Some authors promote total thyroidectomy with or without (modified) neck dissection [3, 6–8]; others state that patients subjected to less extensive surgery (e.g. lobectomy including ishtmusectomy) have a similar prognosis with fewer complications (postoperative hypoparathyroidism, vocal cord paralysis) [9, 10]. Three recent studies of patients with papillary and/or follicular TC concluded that more extensive forms of surgery followed by ^{131}I ablation led to a better long-term prognosis [5, 8, 11], although the optimal dose for ^{131}I ablative therapy is unknown [5, 12].

Multivariate analysis has shown that crude and/or relative survival are related to age at diagnosis, histological type and cellular differentiation and stage [5, 8, 11, 13–22]; gender was only found to be related to survival in five studies of mainly differentiated TC [5, 11, 14, 21, 22]. Various forms of extended or radical surgery were related to better prognosis, but the results were not conclusive [5, 8, 11, 20, 21]. Few studies are population-based [20, 22], whereas most studies stem from large referral centres and introduced selected patients.

The objectives of this study are to describe the (changing) pattern of treatment, also in relation to the recommendations of the 1987 consensus meeting and to determine factors related to long-term survival of differentiated TC.

PATIENTS AND METHODS

The data used for this study came from the Eindhoven Cancer Registry, which was founded in 1955 and became part of the Comprehensive Cancer Centre South in 1983. The registry covered a growing area, between 1960 and 1969 it consisted of 15 municipalities with approximately 300 000 inhabitants, since then it has increased to encompass 51 municipalities with approximately 1 million inhabitants in an area covering 2500 km^2. All hospitals are served by the Radiotherapy Institute as well as the cancer registry. Data on histological type of the tumour, stage and initial and following therapy were obtained from copies of the pathologist's reports and from the patient records of the hospitals and the Radiotherapy Institute, which also provided ^{131}I treatment.

The records of all 343 patients with a tumour originating from the thyroid diagnosed from 1 January 1960 to 31 December 1992 were studied, the 6 patients with a non-Hodgkin's lymphoma (NHL; 1 male, 5 females, age 40–83 years) were excluded from analysis because of the different nature and therapy of this malignancy, leaving 337 patients.

The pathological classification was in accordance with the recommendations of the World Health Organization: papillary, follicular, medullary (C-cell) and anaplastic carcinoma and others (including NHL) [23].

Postoperative stage could be classified according to the recommendations of the Union Internationale Contre le Cancer [24], except for 88 patients who were mostly diagnosed before 1975. Initial surgical treatment was classified as limited (excision of the tumour or surgical biopsy, lobectomy, subtotal thyroidectomy) or extended (total thyroidectomy with or without lymph node dissection); initial external radiotherapy or chemotherapy was also reported. Additional treatment consisted of radioactive iodine ablation (^{131}I), radiotherapy, other (surgery, chemotherapy) or none.

A teaching hospital was presumed to have training facilities for residents in surgery and/or internal medicine, 'other hospitals' were hospitals outside the region, mainly referral centres.

Information about vital status up to 1 April 1994 was obtained for 327 patients (95.3%), 16 patients (4.7%) were lost to follow-up.

Analysis

8 TC patients (4 males, 4 females aged 63–85 years) who died within 1 month of diagnosis were excluded from survival analysis. Survival (time from diagnosis) was calculated as crude and relative survival, the latter being the ratio of the crude rates to the expected rates [25]. Expected survival rates for the regional population were calculated from life tables (supplied by the Netherlands Statistics) compiled according to gender, age and period of diagnosis (1960–1974, 1975–1984, 1985–1992) for the regional population. Crude survival curves were calculated using the Kaplan–Meier method. Comparisons between groups were made by means of the log-rank test. Cox's proportional hazard regression model was used to assess the prognostic value (calculated as rate ratio (RR) and 95% confidence interval (95% CI)) of several factors simultaneously for crude and relative survival. Relative survival was modelled with the Relsurv program (version 1.0 n) which uses Cox's proportional hazard approach [26]. Possible interaction terms expected to have influence on survival and interaction terms possibly related to treatment were investigated in the model of crude survival. None of these were significant, possibly also as a result of low numbers. The Cox model assumes that the various factors have a proportional effect on the outcome. This assumption was checked graphically as well as by adding the covariates as time-dependent factors to the model. Since the assumption of proportionality appeared to be violated when the total follow-up time after diagnosis was considered, separate analyses were performed for the first 5-year interval and after 5 years. For the first interval patients were censored at 5 years. For the second interval only patients who were still alive at the beginning of the next period were considered. The landmark of 5 years was chosen on the basis of an observed shift in survival around the 5-year follow-up point. We were not able to calculate RR using the Relsurv program for the period after 5 years because few events occurred. The factors introduced in the main model were period of diagnosis, age, age category (< 45, 45–60, > 60 years), gender, histological type (papillary or follicular; the other histological types were excluded because the numbers were small) and stage. The model was extended with initial and additional treatment.

RESULTS

The mean follow-up of the 337 patients was 7.6 years (range 1.3–34 years), 30% of patients were followed for ≥ 10 and 10% ≥ 20 years. The clinical characteristics of the patients are listed in Table 1. The male/female ratio was 0.4. The mean age at diagnosis for papillary, follicular, medullary or anaplastic TC, which was 43 (range 5–83), 55 (13–85), 43 (16–61) and 67 years (43–87), respectively, remained stable for all histological types during the entire period.

The percentage of patients with papillary or follicular TC increased from 37 and 23% in 1960–1974 to 50 and 34% in 1985–1992, respectively. Medullary TC was diagnosed in 12

Table 1. *Clinical characteristics* (n = 337) *and* 5-, 10- *and* 20-*year crude and relative survival (excluded* 8 *patients dying* < 1 *month;* n = 329*) of patients with thyroid cancer in Southeastern Netherlands,* 1960–1992

	No. of pts (%)	% 5-year survival (SE) crude	% 5-year survival (SE) relat.	% 10-year survival (SE) crude	% 10-year survival (SE) relat.	% 20-year survival (SE) crude	% 20-year survival (SE) relat.
Total	337 (100)	71 (3)	80 (3)	62 (3)	75 (7)	52 (4)	75 (7)
Gender							
Males	102 (30)	64 (5)	76 (5)	54 (6)	72 (6)	42 (7)	70 (7)
Females	235 (70)	73 (3)	81 (3)	64 (4)	78 (4)	56 (5)	77 (5)
Age							
< 45 years	135 (40)	94 (2)	95 (3)	92 (3)	94 (4)	83 (5)	94 (7)
45–60 years	73 (22)	71 (6)	74 (6)	57 (7)	67 (7)	43 (8)	67 (16)
> 60 years	129 (38)	45 (5)	53 (6)	32 (5)	43 (7)	22 (7)	43 (21)
Histological type							
Papillary	149 (44)	89 (3)	95 (3)	79 (4)	94 (3)	68 (6)	94 (4)
Follicular	111 (33)	70 (5)	82 (5)	59 (5)	80 (6)	53 (6)	79 (8)
Medullary	12 (4)	81 (12)	87 (17)	58 (16)	85 (19)	45 (17)	84 (22)
Anaplastic	28 (8)	3 (4)	5 (4)	0	0		
Other	37 (11)	44 (9)	52 (11)	44 (9)	47 (10)	34 (8)	45 (10)
Stage							
I–II	172 (51)	90 (2)	97 (2)	88 (3)	96 (2)	83 (4)	95 (3)
III-IV	77 (23)	43 (6)	43 (6)	14 (5)	28 (7)	0	0
Unknown	88 (26)	59 (6)	77 (6)	53 (6)	68 (7)	39 (6)	65 (8)
Period							
1960–1974	82 (24)	67 (5)	79 (5)	60 (6)	76 (6)	50 (6)	76 (7)
1975–1984	115 (34)	66 (4)	74 (5)	59 (5)	70 (5)	–	–
1985–1992	140 (42)	77 (4)	85 (4)	–	–	–	–
Hospital category							
Teaching	179 (53)	68 (4)	78 (4)	61 (4)	74 (5)	47 (6)	73 (6)
Non-teaching	134 (40)	73 (4)	80 (4)	62 (5)	77 (5)	58 (6)	76 (5
Other	24 (7)	75 (9)	88 (8)	65 (10)	86 (9)	53 (11)	85 (10)
Therapy							
Limited surgery	146 (43)	67 (4)	79 (4)	61 (4)	75 (5)	57 (5)	74 (6)
Extended surgery	163 (48)	80 (3)	88 (3)	68 (5)	85 (4)	46 (10)	85 (6)
Other/none	28 (8)	30 (10)	29 (10)	14 (8)	22 (9)	0	0

SE, standard error.

patients (4%); 3 patients had a familial form of medullary TC. The percentage of patients with medullary or anaplastic TC remained stable; the percentage of patients with TC classified as 'others' decreased. For 249 patients the stage was known. Papillary TC patients had more stage I–II disease compared with follicular TC patients: 83 versus 61%. Anaplastic TC was classified as stage IV according to the recommendations of the UICC. The percentage stage I–II disease increased from 77 to 85% for papillary and from 50 to 67% for follicular TC in 1975–1984 and 1985–1992, respectively.

Treatment

TC patients were treated in all hospitals in the region, approximately 2–4 per year. The initial diagnosis of 47% of the TC patients was made by an internist, 48% by a surgeon. Initial treatment is summarised in Table 2. 9 out of 10 patients underwent surgery, the proportion initially receiving limited surgery decreased from 63% in 1960–1974 to 34% in 1985–1992; whereas the proportion subjected to extended surgery increased from 27% in 1960–1974 to 61% in 1985–1992. Extended surgery was performed increasingly in all age groups (< 30 years: 39 versus 58%; 30–59 years: 32 versus 72%; ≥ 60 years: 36 versus 51% in 1960–1974 versus 1985–1992). Papillary (49%), follicular (62%) and medullary (67%) TC patients received more extended surgery compared with anaplastic (29%) TC patients. External radiotherapy was prescribed predominantly for anaplastic TC patients, both initially and during follow-up. Patients treated in teaching hospitals underwent more extended surgery compared with non-teaching hospitals (57 versus 49%).

The initial and additional treatment of differentiated TC patients only is illustrated in Figure 1. ^{131}I therapy was available in the region during the whole study period: 46 papillary and 39 follicular TC patients were treated with ^{131}I after surgical therapy. ^{131}I therapy was administered relatively more often to follicular than to papillary TC patients (35

Table 2. *The initial treatment of* 337 *patients with thyroid cancer in the region of the Eindhoven Cancer Registry,* 1960–1992 *(*6 *patients with non-Hodgkin's lymphoma were excluded)*

	1960–1974 *n* = 82	1975–1984 *n* = 115	1985–1992 *n* = 140
	%	%	%
Surgery			
Excision of the tumour/biopsy	24	15	11
Lobectomy	22	18	18
Subtotal/near total thyroidectomy	17	8	4
Total thyroidectomy (± lymph node dissection)	27	49	61
External radiotherapy	4	3	2
Chemotherapy	1	–	–
None/unknown	5	7	4

versus 31%), more often to female than male patients (36 versus 22%) and more often to younger than older patients (< 30 years: 31%; 30–59 years: 38%; ≥ 60 years: 23%). There was no association with stage or type of initial surgical therapy. In teaching hospitals patients received ^{131}I therapy more frequently than in non-teaching hospitals.

Survival

Figure 2 shows the crude and relative survival for the whole study group. It is clear that after 10 years there was no excess mortality. In Table 1 crude and relative survival are related to putative prognostic factors. In the univariate analysis, better survival was related to female sex, age < 45 years, papillary type of tumour and stage I–II disease.

Papillary TC had the best prognosis, followed by follicular and medullary TC (log-rank test: $P = 0.004$) (Figure 3). Differentiated TC patients treated with ^{131}I did better than those not treated with ^{131}I (log-rank test: $P = 0.046$).

The results of multivariate analysis of crude survival for patients with differentiated TC are shown in Table 3. In the first 5 years the observed death rate was related to increasing age and the follicular type of tumour. Introduction of treatment into the model did not influence the other factors, patients who were not treated with ^{131}I exhibited an increased RR (Table 3). After 5 years females exhibited a decreased and patients with stage III–IV disease had an increased death rate. After 5 years the effects of age and histological type declined and introduction of treatment into the model resulted only in a decreased risk of dying for patients treated in 1975–1984. The RR of patients treated with ^{131}I became similar to those not treated with ^{131}I.

Table 3 also shows the results of multivariate analysis for the relative survival of differentiated TC patients. The results for the first 5 years were similar to those for crude survival. However, the RR for patients initially treated with radiotherapy increased to 15.

DISCUSSION

The present study indicates that patients with differentiated TC admitted to general hospitals in our area received therapy as recommended by a consensus conference in 1987 and that the prognosis of these patients was similar to those treated in large referral centres. The mean ages and male/female ratios for the different histological types were in accordance with other European studies [13, 16, 17, 19, 27], whereas differentiated TC patients were younger in studies originating from the U.S.A. [5, 8, 11, 22]. Compared to other population-based studies the proportion with papillary TC was lower (Table 1): 44 versus 60–74% [20, 22, 28].

At a consensus conference on the management of differentiated TC (1987) hemithyroidectomy was considered acceptable for treatment of well-differentiated papillary or follicular TC confined to one lobe, with no lymph node metastases (or only on the side of the tumour in papillary TC) and no distant metastases and total thyroidectomy was to be performed in all other cases [2]. Stable percentages for

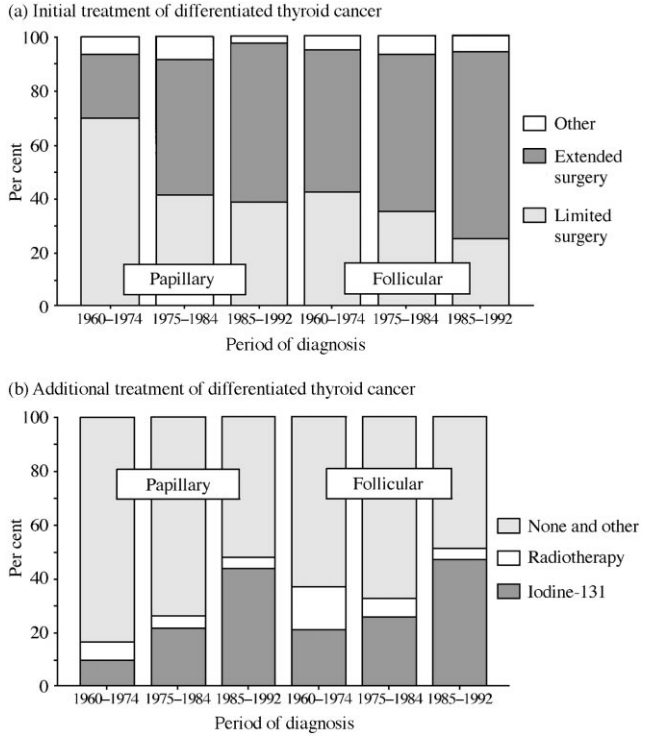

Figure 1. Trends in initial and additional treatment for differentiated (papillary or follicular) thyroid cancer in Southeastern Netherlands, 1960–1992. ($n = 260$). (a) initial treatment, limited surgery: biopsy, excision of tumour, lobectomy or subtotal thyroidectomy; extended surgery: total thyroidectomy with/without lymph node dissection; other: radiotherapy, chemotherapy, none or unknown. (b) additional treatment: radioactive iodine ablation (^{131}I), radiotherapy, other/none.

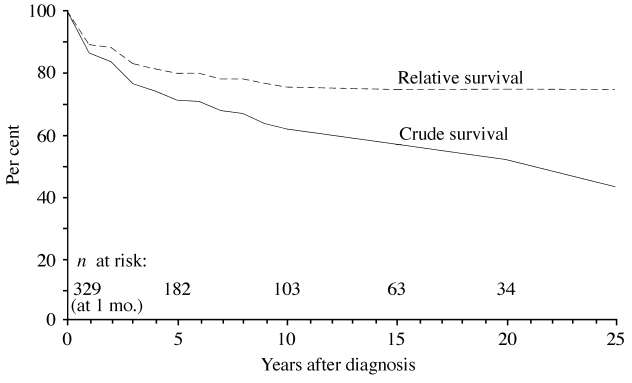

Figure 2. Crude and relative survival of 329 patients with thyroid cancer, 1960–1992. Patients who died <1 month and/or with non-Hodgkin's lymphoma were excluded.

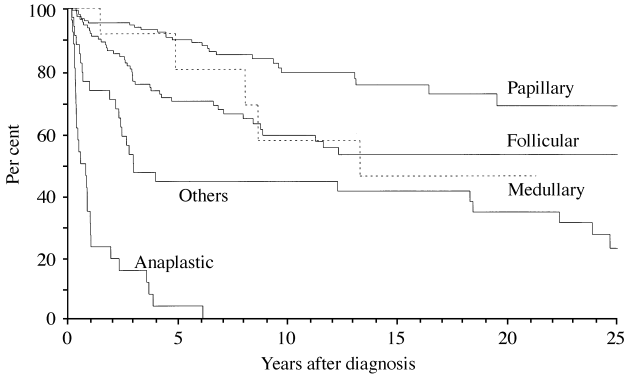

Figure 3. Crude survival of 329 patients with thyroid cancer according to histological type, 1960–1992. Patients who died <1 month and/or with non-Hodgkin's lymphoma were excluded.

lobectomy and increasing percentages for total thyroidectomy (extended surgery) were found, especially among those with differentiated TC (Table 2, Figure 1). It appeared that the recommendations of the consensus meeting were already common practice in the region during the period 1975–1984.

A total-body scan with ^{131}I was performed in the majority of cases 6–8 weeks after surgery and patients with a positive scan then received an ablation dose of 50 mC ^{131}I. The increasing percentage of patients who received ^{131}I (Figure 1) was also in accordance with the recommendations of the

Table 3. Rate ratio (95% CI) for 257 patients with differentiated thyroid cancer 1960–1992 before and after 5 years of follow-up

	Follow-up ≤ 5 years Without treatment	Follow-up ≤ 5 years With treatment	Follow-up > 5 years Without treatment	Follow-up > 5 years With treatment
Crude survival				
Age (years)				
< 45	1	1	1	1
45–59	6.4 (1.7–25)*	6.5 (1.7–25)*	3.5 (0.24–49)	1.8 (0.13–25)
> 60	12 (3.5–43)*	10 (3.0–39)*	4.2 (0.30–59)	1.9 (0.13–28)
Gender				
Male	1	1	1	1
Female	0.73 (0.38–3.9)	0.93 (0.44–2.0)	0.22 (0.09–0.57)*	0.29 (0.09–0.94)*
Histology				
Papillary	1	1	1	1
Follicular	2.0 (1.0–3.9)*	2.4 (1.2–4.8)*	1.1 (0.45–2.6)	0.84 (0.32–2.2)
Stage				
I–II	1	1	1	1
III–IV	1.3 (0.59–3.1)	1.3 (0.54–3.3)	19 (2.2–> 100)*	28 (2.7–> 100)*
Unknown	0.69 (0.23–2.1)	0.65 (0.21–2.0)	2.1 (0.16–29)	4.1 (0.29–57)
Period of diagnosis				
1960–1974	1	1	1	1
1975–1984	0.99 (0.36–2.7)	1.1 (0.39–3.1)	0.22 (0.05–1.1)	0.14 (0.03–0.73)*
1985–1992	0.44 (0.13–1.6)	0.62 (0.17–2.3)	0.47 (0.06–3.8)	0.47 (0.05–4.2)
Initial therapy				
Limited surgery		1		1
Extended surgery		0.87 (0.44–1.7)		1.5 (0.54–4.3)
Other/none		1.3 (0.36–4.7)		17 (2.9–> 100)*
Follow-up therapy				
Iodine-131		1		1
Radiotherapy		5.6 (1.4–22)*		0.76 (0.10–5.6)
None		4.6 (1.5–14)*		0.31 (0.10–1.02)
Relative survival				
Age (years)				
< 45	1	1		
45–59	6.4 (0.94–45)*	9.4 (1.6–55)*		
> 60	10.0 (1.7–63)*	12 (2.4–57)*		
Gender				
Male	1	1		
Female	0.76 (0.26–2.3)	1.1 (0.32–3.8)		
Histology				
Papillary	1	1		
Follicular	2.1 (0.70–6.2)	2.7 (0.97–7.2)*		
Stage				
I–II	1	1		
III–IV	1.7 (0.44–6.6)	1.2 (0.33–4.1)		
Unknown	0.71 (0.13–3.8)	0.44 (0.10–2.0)		
Period of diagnosis				
1960–1974	1	1		
1975–1984	0.90 (0.22–1.5)	1.1 (0.26–4.4)		
1985–1992	0.22 (0.04–1.5)	0.62 (0.06–2.1)		
Initial therapy				
Limited surgery		1		
Extended surgery		0.72 (0.29–2.0)		
Other/none		1.1 (0.17–6.9)		
Follow-up therapy				
Iodine-131		1		
Radiotherapy		15 (1.6–> 100)*		
None		5.9 (0.85–41)*		

Values calculated by Cox regression, without and with treatment in the model. *$P < 0.05$.

consensus meeting and other authors: ^{131}I should be given to all patients with follicular and advanced papillary TC to ablate remaining normal or neoplastic tissue and metastases [2, 29, 30]. A 1993 Dutch Health Council report on the quality of care in oncology recommended a certain degree of regional concentration of care for TC patients and quality improvement could be achieved by regional agreements between specialists [31]. The differences in treatment between teaching and non-teaching hospitals in our region with only general hospitals were small but none the less not negligible. The small number of TC patients per hospital and the decreasing number of thyroid operations in The Netherlands may be an argument for regional concentration because the results and postoperative complications of thyroidectomy depend upon the experience of the surgeon [4, 6, 8, 32].

The results of the univariate analysis of survival (all histological types) were comparable with those of studies from both referral centres and cancer registries. The relative 5- and 10-year survival was 76 and 72% for males and 81 and 78% for females, respectively. In a population-based study from Norway (1970–1985), 5- and 10-year survival (only TC deaths) was 76 and 66% for males and 82 and 79% for females, respectively, while in a study from Denmark (1978–1982), 5- and 10-year relative survival was relatively low: 52 and 48% for males and 65 and 59% for females, respectively [20, 33]. In the population-based SEER program in the United States (1973–1991), 5- and 10-year relative survival was 93 and 93% for males and 96 and 95% for females, respectively [22]. The good results are likely to be explained by the greater proportion of papillary TC (74%), possibly also due to overdiagnosis.

In our study relative survival was related to age at diagnosis, histological type and stage (Table 1), as in other studies [13, 16, 20, 22, 33].

The fact that patients who underwent extended surgery did slightly better compared with patients who underwent limited surgery (Table 1) can largely be explained by selection (patients with differentiated TC received more extended surgery compared with the other histological types which have a worse prognosis).

The multivariate analysis was performed only for differentiated TC. In most other studies independent factors related to the prognosis were age, histological type and cell differentiation and extent of disease (stage) [5, 8, 13–22]; gender was related to prognosis in studies with relatively long-term follow-up [5, 11, 14, 21, 22]. In the present study the effect of these prognostic factors was clearly different in the first 5 years (when younger patients, patients with papillary TC and those treated with ^{131}I did better) compared with later years (when females and patients with stage I–II disease did better). This may also explain the differences in outcome between studies.

Inclusion of initial and follow-up treatment in the multivariate analysis did not affect the other prognostic factors. A favourable effect on prognosis for differentiated TC patients undergoing more extended forms of surgery was found in three studies of selected patient groups, moreover with different definitions of extended surgery [5, 8, 11]. In this study the extent of surgical therapy was not related to a better prognosis (Table 3).

Patients treated with ^{131}I had a better prognosis compared with patients without this treatment only in the first 5 years. The latter group, however, most likely consisted of patients without indications for ^{131}I treatment (negative diagnostic scans) or patients who were not referred for a diagnostic scan and eventual treatment (patients with all stages of disease; some of these patients can be considered as 'undertreated', mainly in the period before 1984, Figure 1). Initially more advanced disease (e.g. metastases on the diagnostic scan) and/or the development of second tumours may be explanations for the fact that the long-term prognosis of patients treated with ^{131}I did not differ from those not treated with ^{131}I.

The results of multivariate analysis for crude and relative survival were more or less identical in the first 5 years (Table 3), because correction for expected death has only a limited effect among relatively young patients with a good prognosis (see also Table 2: relative survival for papillary and follicular TC).

In conclusion, the prognosis for unselected TC patients treated in general hospitals in Southeastern Netherlands was similar to that for selected series of patients treated in referral centres. The prognosis of patients with differentiated TC was, in the first 5 years of follow-up, better for younger patients and papillary type of tumour and after 5 years better for females and stage I–II disease. Additional ^{131}I treatment was related to a favourable prognosis only in the first 5 years. Regional cooperation (e.g. by developing regional guidelines for diagnostic procedures and therapy) of endocrinologists, pathologists, surgeons and radiotherapists may further improve the results of treatment.

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