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Survival in Thyroid Cancer in Sweden From 1999 To 2018

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Introduction: Thyroid cancer (TC) is diagnosed in several histological types which differ in their clinical characteristics and survival. We aim to describe how they influence TC survival in Sweden.

Methods: Cancer data were obtained from the Swedish cancer registry between years 1999 and 2018, and these were used to analyze relative survival.

Results: Relative survival for all TC improved when analyzed in 10-year periods, and female survival improved more than male survival. Female survival advantage appeared to be present also for specific histological types, although case numbers were low for rare types. Female 5-year relative survival for TC was 100% for follicular, 95.1% for oncocytic, 93.4% for papillary, 89.7% for medullary, and 6.1% for anaplastic cancer. Among the clinical TNM classes, only T4 and M1 stages were associated with decreased survival compared to T1-3 and M0. Anaplastic cancer presented most often at high T and M1 stages, in contrast to other TC. Curiously, the diagnostic age for anaplastic M1 patients was lower than that for M0 patients. Both anaplastic and medullary cancers did not show age-dependent increases in the probability of metastases, in contrast to the main histological types. This could indicate the presence of several types of anaplastic and medullary cancers.

Conclusion: The poor survival for anaplastic TC is an extreme contrast to the excellent survival of differentiated TC. As less than 20% of anaplastic cancer patients survived one year, urgent diagnosis and initiation of treatment are important. Facilitated treatment pathways have been instituted in Denmark resulting in improved survival. Anaplastic cancer should be a target of a major research focus.

Keywords: prognosis, relative survival, anaplastic cancer, metastasis, trends

Introduction

The thyroid gland constitutes two connected lobes and with a weight of 20 to 30 g it is among the largest endocrine glands in humans.[1] Various types of thyroid lesions may be present at a prevalence of 4% to 7%, and most are asymptomatic without affecting hormone secretion of the gland.[1] Thyroid cancer (TC) is the most common endocrine tumor. The incidence of TC is higher in females compared to males, particularly in well-differentiated, undifferentiated and medullary TC.[2,3] Differentiated TC includes the most common papillary, less common follicular and rare oncocytic (Hurthle) types.[3,4] However, large changes have been introduced in the 2022 World Health Organization (WHO) classification of TC which will have implications for future studies.[5] The new classification will help to sort out the

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current problem areas of follicular neoplasms, dividing them into benign, low-risk and malignant neoplasms and subtyping papillary TC according to histomorphologic features.[5] Undifferentiated TC and anaplastic TC are characterized by with high mortality.[3,6] A special biological feature of anaplastic TC is that it often arises after a previously diagnosed or concomitant differentiated TC.[7] Medullary thyroid cancer may have a hereditary background in one-fourth of cases, as manifestation of the multiple endocrine neoplasia type 2 syndrome.[3,8,9] Papillary TC carries the best and anaplastic TC the worse overall prognosis.[10] The incidence of TC has increased in large parts of the world, and particularly in countries of East Asia, mainly because of increased diagnosis of small papillary tumors.[2,11,12] In the Nordic countries with a tradition of cancer registration, the 60-year increase in TC incidence has been about 4-fold for women and 3-fold for men.[2,12] No TC screening has been conducted in the Northern countries.[13]

Overdiagnostics has been considered an essential reason for the observed increase in incidence of TC, as recent screening methods have been conducted by sensitive imaging tools, such as ultrasonography, computed tomography and magnetic resonance imaging.[3,11] Overweight has become an increasingly important risk factor for TC.[14] TC also manifests in the common autoimmune diseases Graves and Hashimoto, which interfere with endocrine functions of the gland.[15,16] Non-medullary TC exhibits a high familial risk.[17] In Sweden, table salt has been iodinated since 1936.[18] Historically, treatment for TC has been surgery, which is currently assisted by cervical ultrasonography imaging to define tumor spread;[10] whether a total or partial thyroidectomy is conducted is still the matter of debate.[19] Concerns about overdiagnosis have led to recommendations for not biopsying thyroid nodules of less than 1 cm and applying validated criteria for interpreting biopsy results.[3,20,21] Similarly, in response to worries about overtreatment, low-risk patients may be subjected to active surveillance and minimally invasive interventions.[3] For metastatic cases, several systemic therapies are available, including radio-iodide, targeted therapies and immunotherapies.[22–24]

We analyzed recently relative survival in TC in the Nordic countries based on the NORDCAN register and could demonstrate improvement in survival without interruptions through 50 years.[12] However, 1-year survival remained low in a small proportion of cases which we presumed to be related to anaplastic cancer. This was not based on our own data (NORDCAN lacks histological and clinical data) but rather on the available limited literature.[24–26] Here we access data from the Swedish cancer registry and aim to define the main factors influencing relative survival in TC, including histology, stage, age and sex. We also consider conditional relative survival, which enables a better definition of critical survival periods after diagnosis.[27–29]

Methods

Cancer data were obtained from the Swedish population-based cancer registry from two 10-year periods, from 1999 through 2018 although most analyses were focused on the latter 10-year period. The coverage of cancer registration is practically complete in Sweden, and 98% of cancers are microscopically verified.[30] The quality indicators collected by the Cancer Incidence in Five Continents have been internationally in the top class.[31] The population of Sweden was obtained from the total population register. The linkages between the different registers were done using the personal identification number, assigned to each resident in Sweden, and replaced by a serial number to preserve people's integrity.

TC classification in the current period was based the third edition of the WHO classification as the new 2017 WHO classification was introduced in Sweden in 2019. In the Swedish annual quality register for TC, the new entities, such as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and follicular tumor of uncertain malignant potential, appear first from 2019 onwards with about 5 annual cases for each of a total of 600 TCs (https://cancercentrum.se/globalassets/cancerdiagnoser/skoldkortel/kvalitetsregister/arsrapport_2021_tyreoidea.pdf). The individual TC patients were identified using an ICD-based classification system in the cancer registry. The histological types were defined based on SNOMED ICD-0-2 classification labels, which were complete throughout the study period. The code 80203 is used for undifferentiated and 80213 for anaplastic cancer.[6]

For stage- specific analyses, patients were included based on the availability of tumor-node-metastasis (TNM) classification. The TNM data were available from 2002. In total, 3143 TC cases were included in 1999–2008 and 5209 TC cases in 2009–2018 for which period most analyses were performed. The 7th edition of the TNM classification of malignant tumors was used until the end of the present study period (new TNM version 8 system was started

1.1.2019).[13] In Sweden, the TNM classification for anaplastic cancer has been the same as for other TCs, and now also in the TNM version 8.

Survival analysis was restricted to patients >14 years old; young patients were treated in pediatric clinics. Patients were excluded from survival analyses if they were diagnosed with multiple TCs assigned with distinct SNOMED labels, if the tumor was detected at the autopsy, if diagnosis date and date of death were identical or in the absence of residence status at date of diagnosis. If there were multiple entries with same type label for a same patient within studied period, only the earliest tumor was considered.

Data analysis was performed on SAS and R. The association between metastatic status, sex and diagnostic age was evaluated using the generalized additive models with logit link function. To allow for the non-linear effect of age, we used thin plate regression splines from *mgcv* package in R.[32] We set k = 5 as a parameter controlling maximal degrees of freedom. The patients were classified based on the status of distant metastases at diagnosis (M1 vs M0/Mx). All the patients in period 2002–2018 with available M data were included in the analysis.

Relative survival (ie, overall survival in thyroid cancer patients compared to the matched national population) was calculated using the Pohar Perme estimator[33,34] with the custom-made R script. This estimator is considered unbiased and applicable to populations with varying mortality rates.[35] The follow-up period was divided into 5 days following the date of diagnosis and subsequent 10-day-long intervals. 1-year, 2.5-year and 5-year survival was defined as being alive 365, 915 and 1825 days following the day of diagnosis, respectively. The expected mortality was calculated based on age, sex and calendar year, using population lifetables.[36] Patients were treated as censored at the date of first emigration after diagnosis, end of follow-up or end of study period. Since incomplete follow-up information was available for the patients diagnosed in the most recent period, we used the "complete approach" for up-to-date estimate.[37] Specifically, the patients diagnosed in 2009–2018 contributed with all the available person-time until 31st December 2018. It should be noted that due to the applied survival method, the 1-year relative survival estimates are more up-to date than 5-year survival data (the most recently diagnosed patients contribute with incomplete follow-up).

Conditional relative survival was calculated by dividing the respective relative survival estimates. In conditional 5/1-year survival, patients were followed during next four years conditioned on surviving 1 year; in conditional 5/2.5-year survival, patients were followed 2.5 years after surviving initial 2.5 years. Confidence intervals (95%) of all estimators were derived by approximating variance on a logarithmic scale using the delta method.[38] The estimates with non-overlapping 95% confidence intervals were considered to be significantly different.

For parametric estimation of relative survival, we built flexible parametric model using *rstpm2* package in R.[39,40] The modelling was performed on the log cumulative hazard scale, with the baseline hazard modelled with a natural cubic spline (4 degrees of freedom) applied in log time. The model further included main effects of sex, age (natural cubic spline with 2 degrees of freedom), diagnostic year, histology type, M status (2 levels: M0 and M1) and all two-way interactions between histology type, M status and sex. Moreover, we included interaction between histology and log time (4 degrees of freedom), allowing for non-proportional hazards.

The publicly available Swedish quality register for TC was used to collect relevant diagnostic and treatment-related background data on patients (https://statistik.incanet.se/npcr/). Its coverage against the Swedish cancer registry was 85% in the past 10 years. These data were separate from the other register data used and were not individually linked. The first annual report covered year 2013. In some 60% of patients, cancer was confirmed pre-operatively enabling tailored treatment.[10] A complete TNM classification was available for over 90% of the patients, and it was largely pathological rather than clinical. Close to 80% of the patients were presented to a multidisciplinary conference, and close to 90% of patients were treated according to the existing treatment guidelines. In later years, many of these percentages had improved.

Results

Case Distribution

Table 1 shows case numbers, diagnostic ages and proportion of metastatic cases of TC diagnosed in Sweden in 2009–18, stratified by sex and histological type. There were 5368 cases in total, of which 73% were female. The mean age at diagnosis was 52.1± 0.3 for females and 56.9 ± 0.45 for males. The highest diagnostic ages were observed for poorly

Table 1 Summary of Thyroid Cancer in Sweden (2009–2018): Case Numbers, Mean Diagnostic Age and Proportion of Cases with Distant Metastases at Diagnosis (M1/(Mx + M0+M1)) by Histology Type, All Ages Included

Tumor type SNOMED	Females			Males		
	Counts	Mean age (±SE)	M1 (%)	Counts	Mean age (±SE)	M1 (%)
Papillary 82603	2642	48.8 ± 0.3	1.7	902	54.3 ± 0.6	3.8
Follicular 83303	482	56.8 ± 0.9	8.3	183	62.8 ± 1.2	9.7
Papillary-follicular var[a]	181	48.9 ± 1.2	1.4	55	53.6 ± 2.1	7.3
Medullary 85103	104	57.2 ± 1.8	10.1	95	50.9 ± 2.1	16.2
Oncocytic 82903	80	65.3 ± 1.8	3.3	32	59.0 ± 2.5	4.3
Undifferentiated 80203	36	77.2 ± 1.8	33.3	18	69.3 ± 3.7	35.7
Anaplastic 80213	133	76.2 ± 0.9	43.0	86	70.8 ± 1.2	50.8
Other label[b]	240	57.1 ± 1.2	11.0	99	62.2 ± 1.7	14.3
All thyroid cancer	3898	52.1 ± 0.29	4.8	1470	56.9 ± 0.45	8.9

Notes: [a]SNOMED 83403; [b]Includes follicular, minimally invasive cases in women 186, papillary carcinoma, not otherwise specified 73 and 6 other designations with maximally 20 cases.

differentiated forms (anaplastic, undifferentiated), while the lowest diagnostic age was observed in papillary type for females and in medullary type for males. Curiously, the mean diagnostic age for metastatic anaplastic cancer was lower than for non-metastatic form (women 74.3 vs 76.2 years, $p = 0.5$; men 67.1 vs 72.6 years, $p = 0.21$, Wilcoxon rank-sum tests). For papillary cancer, M0 cases were diagnosed at age about 15 years below M1 cases ($p < 0.0001$, Wilcoxon rank-sum test for both sexes). The observed proportion of cases with distant metastases (M1/(Mx+M0+M1)) at diagnosis varied across histological types, from relatively low proportions in differentiated TC (papillary female 1.7%, follicular female 8.3%) to 50% in the anaplastic type. For further analysis, only the common histological types were included.

Stage distribution in 2009–18 is shown in Supplementary Table 1. We did not show stage distribution for patients diagnosed in 1999–2008 because of the large number of missing data (more than half for rare histological types). Among tumor T stages, the distributions of T classes differed by histology; T1 was the most common class for papillary and female medullary cancers and T2 for female follicular cancer and oncocytic carcinoma. T3 was the most common class for the male follicular and medullary cancers and oncocytic carcinoma. T4 was the dominant class for anaplastic cancer (80%). Nodal (N) class distributions also slightly differed by sex, N0 being dominant for all but medullary and anaplastic cancers in women, but for men, N1 was the most common class for papillary (29.4% women, 42.4% men), medullary and anaplastic cancers. While distant metastasis at diagnosis (M1) was rare in TC, they were more common than M0 for anaplastic cancer (43% of all for women and 50% for men, considering also Mx). For papillary cancer, the proportions of M1 of all cases were 1.6% for women and 3.9% for men.

Because a proportion of anaplastic cancers are known to present after or concomitantly with differentiated TC, we looked in the cancer registry file if such information was available. For 18 anaplastic (or undifferentiated) patients there was information of a prior or concomitant differentiated TC, but no further details were available.

Survival in Histological Types

Table 2 presents estimated 1-, 2.5- and 5-year relative survival and 5/1- and 5/2.5-year conditional survival of patients diagnosed in 2009–2018. For all survival metrics (except for 5/2.5-year), female survival in all TC was significantly (95% CIs did not overlap) better than that for male survival. Female (non-significant) survival advantage was also true of survival in papillary and follicular types. Relative 5-year survival was high for female papillary (97.9%) and follicular (100.0%) types, compared to the male cohort of 92.6% and 87.2%, respectively. For patients diagnosed with medullary cancer, the 5-year estimates were 89.7% in females and 84.4% in males. The diagnosis of anaplastic cancer was associated with high early mortality, with 1-year relative survival below 20%. Conditional 5/1- and 5/2.5-year relative survival was high for all but anaplastic cancer. In men, 5/1-year relative survival tended to be somewhat lower than in women. Similar patterns were observed for 5/2.5-year conditional survival. While for anaplastic cancer 1-year survival

Table 2 1-year, 2.5-year and 5-year relative survival, 5/1-year and 5/2.5-year conditional relative survival (Pohar Perme estimates with 95% confidence interval) for main thyroid cancer types in Sweden (2009–2018)

	Females	**Males**
Tumor type	1-year relative survival	
All thyroid cancer	94.9 [93.9–95.9]	90.3 [88.1–92.6]
Papillary	99.2 [98.6–99.8]	97.5 [95.7–99.2]
Follicular	97.7 [95.3–100.3]	93.7 [87.7–100.1]
Medullary	91.9 [83.9–100.7]	94.0 [86.7–101.8]
Oncocytic	99.3 [93.5–105.4]	97.8 [87.9–108.7]
Anaplastic	18.3 [11.2–29.8]	18.7 [9.9–35.2]
	2.5-year relative survival	
All thyroid cancer	94.2 [93.0–95.4]	87.6 [84.8–90.4]
Papillary	98.9 [98.0–99.8]	95.7 [93.1–98.3]
Follicular	98.7 [95.5–102.0]	90.0 [81.7–99.2]
Medullary	88.4 [78.3–99.9]	93.3 [84.5–103.0]
Oncocytic	98.6 [88.5–109.8]	96.1 [81.5–113.3]
Anaplastic	7.6 [3.0–19.1]	7.9 [2.5–24.9]
	5-year relative survival	
All thyroid cancer	93.5 [91.8–95.2]	83.9 [80.3–87.8]
Papillary	97.9 [96.3–99.4]	92.6 [88.9–96.6]
Follicular	100.0 [94.7–105.5]	87.2 [75.0–101.3]
Medullary	89.7 [78.4–102.5]	84.4 [69.5–102.6]
Oncocytic	95.1 [79.2–114.0]	92.8 [72.0–119.7]
Anaplastic	6.1 [1.7–21.3]	5.4 [1.0–29.6]
	5/1-year conditional rel. survival	
All thyroid cancer	98.5 [97.1–99.9]	92.9 [89.5–96.5]
Papillary	98.7 [97.2–100.2]	95.1 [91.6–98.7]
Follicular	102.3 [97.6–107.2]	93.0 [81.3–106.4]
Medullary	97.5 [88.4–107.6]	89.8 [75.2–107.3]
Oncocytic	95.8 [80.6–113.7]	95.0 [75.4–119.6]
Anaplastic	33.2 [10.5–105.5]	28.7 [5.9–140.4]
	5/2.5-year conditional rel. survival	
All thyroid cancer	99.3 [98.0–100.5]	95.9 [92.9–98.9]
Papillary	98.9 [97.6–100.2]	96.8 [93.8–100.0]
Follicular	101.3 [97.1–105.7]	96.8 [86.4–108.6]
Medullary	101.4 [95.9–107.1]	90.5 [76.5–107.0]
Oncocytic	96.4 [83.3–111.7]	96.6 [79.6–117.2]
Anaplastic	80.0 [34.2–186.9]	67.7 [19.0–240.8]

was 18%, 5/1-year conditional survival was about 30%. Similarly, 2.5-year survival was less than 8% compared with 5/2.5-year conditional survival of 80% (for women). Thus, the few (18%) anaplastic patients who survived the first year had a 30% chance of surviving the next 4 years, and those 8% of the (female) patients surviving the first 2.5 years had an 80% chance of surviving the second 2.5-year period. Note that in many of the above cases, the numbers are small.

In Supplementary Figure 1, we compare relative survival curves of all, papillary and follicular cancers diagnosed in 2009–2018 to corresponding cohorts diagnosed in the preceding period (1999–2008). Overall, relative survival tended to

be higher in the later period, and improvements were higher for women compared to men. The sex difference was large in follicular cancer, where male relative survival remained below 90% %, while in women, it was nearly 100%.

Stage-Specific Survival

In Table 3, we show the 1-, 2.5-, 5-year relative survival according to local tumor growth (T-staging) in 2009–18 (all included patients were without distant metastases, M0). Only T1 to T4 are shown because of rarity of T0. In relative 1- and 5-year survival for papillary and follicular types only T4 stage showed suppressed survival. Case numbers were low for the rare subtypes. For anaplastic type, 1-year survival in T4 (which was by far the most common T stage) was between 30 and 40%.

We also tested the possible association of nodal metastases (N stage) on relative survival of patients with localized disease (M0, T1-T3). Female 5-year survival for N0 papillary cancer was 101.9% (99.7–104.1, N = 267) and for N1 cancer it was 97.9% (94.4–101.6, N = 133). Male 5-year survival was 97.5% for N0 and 96.5% for N1. For follicular cancer, very few N1 cases were found. In relative survival, it is not uncommon that survival is barely over 100% (the above 95% CIs included 1.00; thus, the difference was not significant) as all-cause deaths are considered and some patient populations may have less comorbidities than the reference population.

Table 3 1-Year, 2.5-Year and 5-Year Relative Survival (Pohar Perme Estimates with 95% Confidence Interval) in Sweden (2009–2018) According T- Staging in Patients Without Distant Metastases (M0). The Case Numbers (Uncensored) in the Beginning and End of Follow-Up are Shown if Estimates Were Not Available

	Female Thyroid Cancer			
	T1	**T2**	**T3**	**T4**
Tumor type	1-year relative survival			
All thyroid cancer Papillary Follicular Medullary Oncocytic Anaplastic	100.3 [99.9–100.6] 100.2 [99.8–100.6] 100.6 [100.6–100.6] 100.8 [100.8–100.8] 101.5 [101.5–101.5] 104.8 [104.8–104.8]	99.9 [98.8–101.1] 99.8 [98.5–101.2] 100.1 [97.6–102.7] 100.9 [100.9–100.9] 101.7 [101.7–101.7] 54.8 [9.6–313.3]	99.1 [97.2–101.0] 99.5 [97.7–101.3] 101.2 [98.7–103.7] 88.2 [58.1–133.9] 102.2 [102.2–102.2] 3 0	76.0 [60.0–96.3] 88.8 [74.9–105.3] 71.7 [35.6–144.3] 101.7 [101.7–101.7] 0 0 26.4 [11.2–62.6]
	2.5-year relative survival			
All thyroid cancer Papillary Follicular Medullary Oncocytic Anaplastic	101.0 [100.5–101.6] 101.0 [100.5–101.6] 101.7 [101.7–101.7] 102.4 [102.4–102.4] 104.9 [104.9–104.9] 1 0	100.2 [98.3–102.1] 99.4 [96.9–102.0] 101.7 [99.2–104.3] 97.3 [84.0–112.7] 106.2 [106.2–106.2] 57.0 [10.0–325.7]	98.9 [95.8–102.0] 98.6 [95.1–102.2] 104.6 [100.6–108.9] 94.1 [62.0–143.0] 107.1 [107.1–107.1] 3 0	58.5 [41.6–82.1] 72.4 [51.9–100.9] 73.8 [36.7–148.5] 104.6 [104.6–104.6] 0 0 9.8 [1.7–55.3]
	5-year relative survival			
All thyroid cancer Papillary Follicular Medullary Oncocytic Anaplastic	100.4 [98.6–102.2] 100.4 [98.5–102.3] 99.5 [88.7–111.7] 98.6 [82.2–118.4] 113.9 [113.9–113.9] 1 0	101.5 [98.4–104.7] 99.9 [95.9–104.1] 102.9 [98.1–107.9] 99.0 [85.5–114.7] 98.2 [57.4–168.0] 1 0	100.5 [94.8–106.6] 99.2 [92.5–106.3] 107.7 [95.3–121.6] 102.1 [67.2–155.1] 105.6 [78.3–142.5] 2 0	59.3 [40.6–86.6] 65.2 [42.8–99.2] 78.8 [39.1–158.5] 110.7 [110.7–110.7] 0 0 8 0
	Male thyroid cancer			
	T1	T2	T3	T4

(*Continued*)

Table 3 (Continued).

	Female Thyroid Cancer			
	T1	**T2**	**T3**	**T4**
Tumor type	1-year relative survival			
All thyroid cancer	99.2 [96.9–101.5]	99.5 [97.0–102.2]	99.1 [96.1–102.2]	65.2 [50.4–84.4]
Papillary	99.3 [96.9–101.8]	100.0 [97.8–102.3]	99.7 [96.7–102.8]	83.5 [65.6–106.1]
Follicular	101.3 [101.3–101.3]	99.8 [92.9–107.2]	99.2 [92.0–107.0]	64.4 [29.4–141.0]
Medullary	100.9 [100.9–100.9]	87.6 [59.3–129.3]	100.8 [100.8–100.8]	0 0
Oncocytic	0 0	100.8 [100.8–100.8]	101.6 [101.6–101.6]	102.7 [102.7–102.7]
Anaplastic	0 0	0 0	55.3 [6.8–446.4]	41.8 [18.6–93.7]
	2.5-year relative survival			
All thyroid cancer	98.0 [94.1–102.0]	97.7 [92.9–102.8]	99.1 [94.8–103.6]	56.0 [40.8–77.0]
Papillary	98.9 [95.2–102.8]	97.4 [92.1–103.0]	100.6 [96.3–105.2]	84.3 [64.5–110.30
Follicular	77.7 [35.7–169.1]	101.4 [90.4–113.7]	97.9 [87.1–110.0]	59.9 [23.0–156.1]
Medullary	102.2 [102.2–102.2]	74.7 [40.1–139.3]	101.8 [101.8–101.8]	0 0
Oncocytic	0 0	102.3 [102.3–102.3]	105.6 [105.6–105.6]	51.3 [7.0–376.6]
Anaplastic	0 0	0 0	2 0	21.8 [4.3–111.1]
	5-year relative survival			
All thyroid cancer	92.3 [84.8–100.5]	94.5 [85.8–104.1]	97.5 [88.4–107.6]	49.1 [32.5–74.0]
Papillary	94.2 [86.9–102.2]	95.4 [86.4–105.3]	99.9 [89.3–111.7]	86.2 [62.0–120.0]
Follicular	50.0 [11.2–222.5]	92.4 [69.5–122.9]	103.6 [88.4–121.4]	36.4 [7.3–180.9]
Medullary	104.8 [104.8–104.8]	79.6 [42.7–148.5]	89.9 [57.4–140.8]	0 0
Oncocytic	0 0	105.3 [105.3–105.3]	87.8 [42.5–181.3]	54.4 [7.4–398.8]
Anaplastic	0 0	0 0	1 0	4 0

We next assessed relative survival of the patients with respect to distant spread of the tumor (M-staging, Table 4). In all TC, relative survival after 1-year was 98.2% for females and 95.5% for males without distant metastases at diagnosis (M0). In the non-metastatic female cohort, survival continued to be high and 5-year relative survival was 98.2%, significantly higher than that of males (90.5%). Five-year survival in M0 papillary and follicular cancer appeared to be equal between sexes (close to 100% in women and 90% for men). In all TC 5-year survival was significantly worse for M1 compared to M0 in women and men. In M1, 5-year survival in follicular cancer appeared to be better than that for papillary cancer in women (83.0 vs 46.0) and men (55.0 and 39.5) but 95% CIs overlapped because of few cases. Sample

Table 4 1-Year, 2.5-Year and 5-Year Relative Survival (Pohar Perme Estimates with 95% Confidence Interval) for Main Thyroid Cancer Types in Sweden (2009–2018) According M-Staging. The Case Numbers (Uncensored) in the Beginning and End of Follow-Up are Shown if Estimates Were Not Available

	Female thyroid cancer		Male thyroid cancer	
	M0	**M1**	**M0**	**M1**
Tumor type	1-year relative survival			
All thyroid cancer	98.2 [97.4–99.1]	59.3 [47.3–74.4]	95.5 [93.2–97.9]	50.5 [38.6–66.2]
Papillary	99.7 [99.2–100.3]	86.6 [70.6–106.2]	98.1 [96.1–100.2]	81.3 [61.3–107.8]
Follicular	99.6 [97.4–101.8]	84.3 [66.4–106.9]	97.0 [90.8–103.6]	88.0 [65.0–119.1]
Medullary	99.3 [94.4–104.3]	64.6 [31.4–132.7]	98.3 [91.6–105.5]	73.4 [43.9–122.8]
Oncocytic	101.9 [101.9–101.9]	103.2 [103.2–103.2]	101.6 [101.6–101.6]	100.6 [100.6–100.6]
Anaplastic	28.4 [13.8–58.2]	10.5 [2.9–38.4]	42.3 [20.1–88.9]	5.7 [0.7–43.3]

(*Continued*)

Table 4 (Continued).

	Female thyroid cancer		Male thyroid cancer	
	M0	**M1**	**M0**	**M1**
	2.5-year relative survival			
All thyroid cancer	98.2 [97.1–99.4]	49.4 [36.9–66.0]	94.1 [91.1–97.3]	35.6 [24.1–52.5]
Papillary	99.7 [98.7–100.7]	74.5 [52.4–105.9]	97.7 [94.9–100.6]	55.8 [31.3–99.7]
Follicular	101.9 [99.5–104.4]	86.6 [68.2–109.8]	95.2 [86.1–105.3]	75.6 [45.9–124.4]
Medullary	99.3 [91.9–107.3]	37.6 [10.3–137.1]	96.3 [85.8–108.0]	64.8 [33.8–124.0]
Oncocytic	106.4 [106.4–106.4]	110.5 [110.5–110.5]	92.6 [66.3–129.5]	101.7 [101.7–101.7]
Anaplastic	11.8 [2.9–47.0]	2.4 [0.1–49.2] 97.6	18.3 [3.4–97.9]	23 0
	5-year relative survival			
All thyroid cancer	98.2 [96.3–100.0]	41.7 [28.5–61.1]	90.5 [85.7–95.6]	23.4 [13.1–41.6]
Papillary	99.2 [97.4–101.1]	46.0 [20.2–104.7]	95.4 [90.5–100.4]	39.5 [16.4–94.8]
Follicular	102.4 [95.9–109.4]	83.0 [58.1–118.4]	88.7 [72.7–108.1]	55.0 [20.2–149.9]
Medullary	99.3 [88.2–111.7]	37.8 [10.4–138.0]	93.7 [76.4–114.9]	42.1 [14.4–122.8]
Oncocytic	104.3 [82.6–131.8]	127.6 [127.6–127.6]	83.3 [46.5–149.1]	1 0
Anaplastic	12 0	14 0	5 0	16 0

sizes were even more limiting for other histological types, but M1 stage appeared to be associated with lower survival than M0. For anaplastic cancer, only 4 female and 2 male M1 patient survived past year 1. We show no data for Mx (metastatic status undefined), because survival for these patients was close to M0 patients.

In Figure 1 relative survival is shown for female and male M0 and M1 TC using a parametric model. Metastatic cancer was associated with decreased survival in all histological types. For females, the differentiated TC survival for M1 decreased throughout the 5-year period. Survival was best for follicular cancer; for papillary cancer, the decrease was almost linear, and at 5 years, survival was about 60%, and for medullary cancer, it was below 50%. For female anaplastic cancer, a plateau was reached by year 2, at more than 10% for M0 and below 5% for M1. Male survival in metastatic follicular cancer at 5 years was only 50% and that for papillary cancer was no more than over 30%.

Using logistic regression analysis, we compared the probability of metastatic TC in histological types by age and sex (Figure 2). At age 65 years the predicted probability of M1 was 2% and 6% for female and male papillary cancer, it was 10% for follicular cancer of both sexes, it was 9% for female and 18% for male medullary cancer and it was close to 50% for anaplastic cancer. For papillary and follicular cancers, the probability of metastasis increased by age, in female to about 80 years and in males towards 95 years. In papillary cancer at age around 50 years the male probability of metastases was significantly higher than in females. In contrast, in follicular cancer, there was an absence of such association of metastatic status and male sex. For medullary and anaplastic cancer, the probability of metastasis appeared to decrease by age. Case numbers were few, but it may also be related to the heterogeneity of these cancers.

Discussion

The analysis of relative survival in two 10-year periods suggested improvements in total TC survival, which was larger for women than for men (Supplementary Figure 1. This was consistent with the more favorable distribution of each TNM stages in women (Supplementary Table 1). For men, early (1-year) mortality in 2009–18 was about 10% while for women it was 5% (Table 2). Early mortality for female papillary cancer was 0.9% while for men it was 2.5%; for female follicular cancer it was 2.3% compared to male mortality of 6.3%. For the rare cancers, the figures were less reliable, but for anaplastic cancer, the first-year mortality of over 80% demonstrated the exceptionally high fatality for this cancer, which is known in the literature.[7,10,25,26,41] These data on anaplastic cancer are a partial solution to the conundrum of early mortality in all TC observed by us for all Nordic countries.[12] However, the present data show that early mortality even in other types of TC, although modest, does contribute to the first-year mortality in TC. Even though early mortality

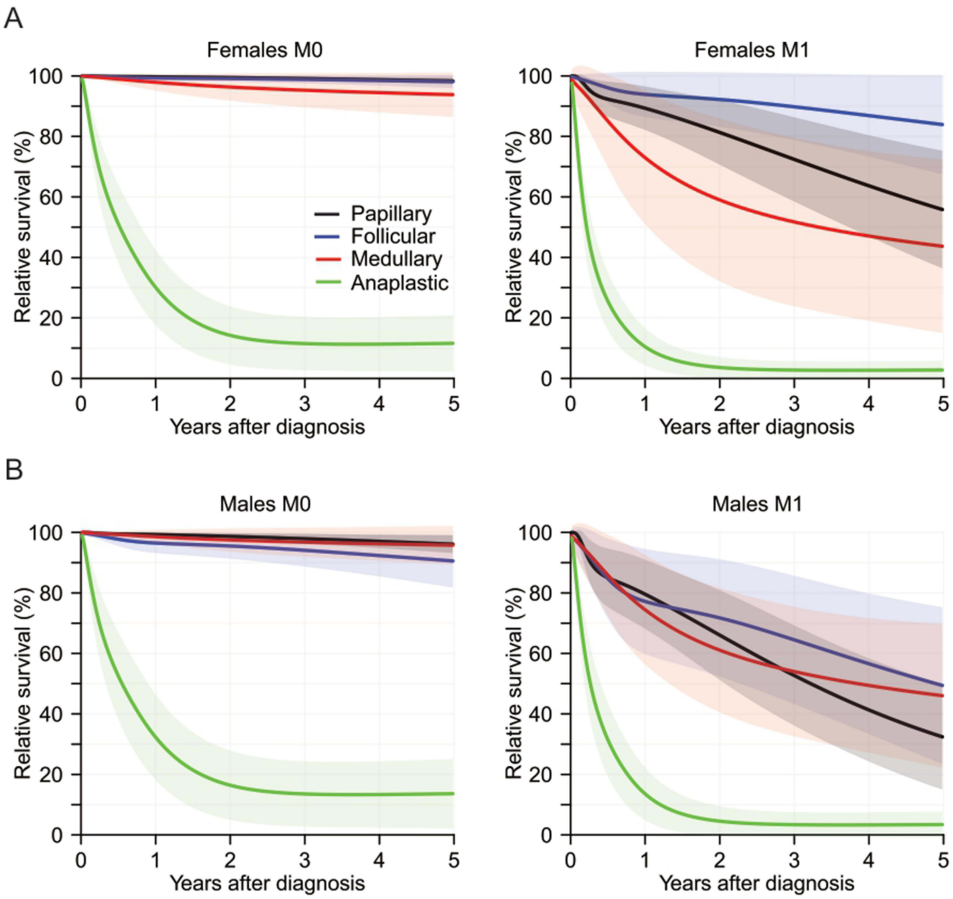

Figure 1 Relative survival in histological types of thyroid cancer without (M0) and with (M1) metastases at diagnosis in Sweden from 2009 to 2018 with 95% CIs. (**A**) is for female and (**B**) for male TC. The estimates were obtained using flexible parametric model, which included age, sex and diagnosis year as predictors (for details see Methods). Oncocytic carcinoma was not included because of sparsity of cases.

was somewhat higher for follicular than papillary cancer, overall survival in these cancers did not differ (Table 2), opposite to some literature.[10] In the rare metastatic stage, follicular cancer survival appeared to be better than that for papillary cancer, but case numbers were few.

The present results shed novel data on the probability of metastasis (Figure 2). For papillary cancer patients at age 65 years the probability of metastases was 2% women and 6% for men, which was lower than the 10% probability for follicular cancer. In both of these cancers, the probability of metastases increased further with advancing age. In papillary cancer at age around 50 years the male probability of metastases was significantly higher than that in females. At age 65 years, the probability of metastases was 9% for female and 18% for male medullary cancer and it was close to 50% for anaplastic cancer. Another novel feature about papillary and follicular was that relative 1-and 5-year survival in these cancers did not change between stages T1 to T3, in contrast to many other cancers; only T4 stage showed suppressed survival.

The molecular landscape of anaplastic cancer shares the same somatic mutations with differentiated TC, but at higher frequencies, including TP53 and TERT promoter mutations each in some 50% of patients and additionally common alterations in genes in the mitogen-activated protein kinase (MAPK) pathway, including the RAS gene family.[24,42–45] Mutations in these genes are 2–3 times more common in anaplastic cancer compared with papillary and follicular cancer, while aggressive variants of the latter cancers have intermediate levels of mutations.[42] In fact, it is known that a large proportion (up to 50%) of anaplastic cancer patients have a history of an earlier diagnosed differentiated TC or present a coexisting differentiated tumor or other thyroid disease, such as chronic goiter.[7,44] Anaplastic cancer is generally refractory to treatment, including radio-iodine therapy.[10]

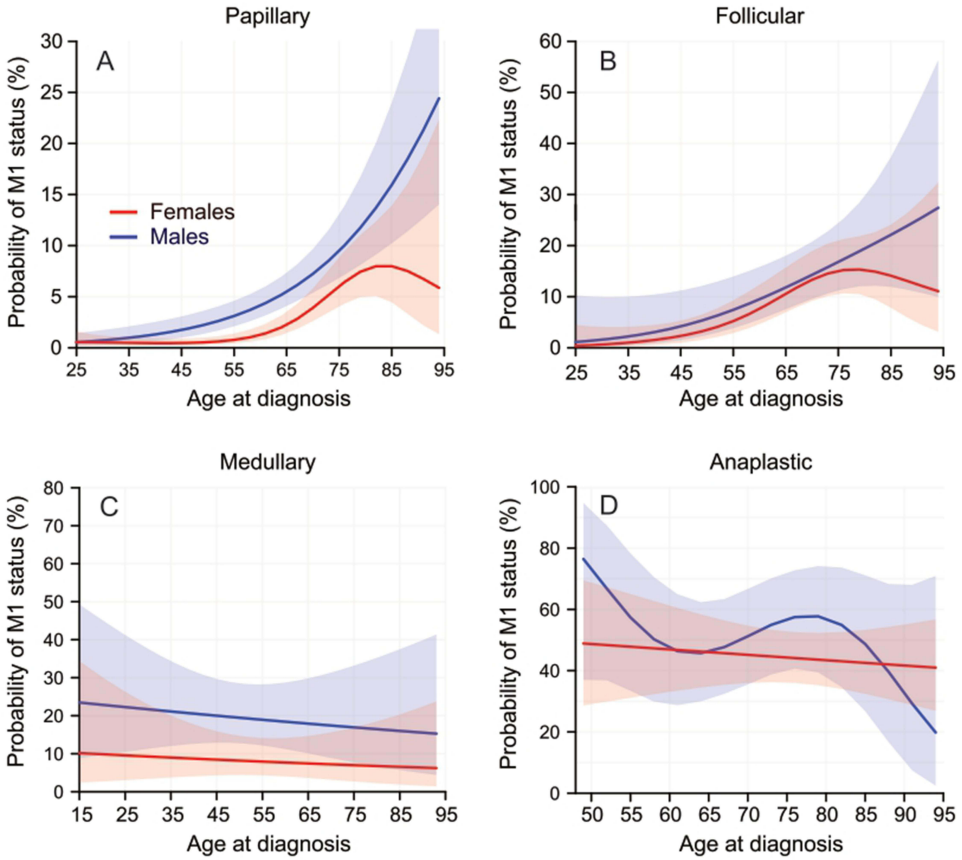

Figure 2 Logistic regression analysis of the probability of metastasis at diagnosis (M1) for (**A**) papillary, (**B**) follicular, (**C**) medullary and (**D**) anaplastic thyroid cancer by age in Sweden between years 1999 and 2018. Note that the plot for anaplastic cancer started at age 50 years as very few cases were diagnosed at younger ages. The model included main effect of sex and non-linear effect of age. Probabilities are shown with 95% CIs. There was significant age trend in papillary cancer (both sexes $p<0.001$) and follicular cancer (females: $p<0.001$, males: $p=0.024$). The proportion of metastatic patients tended to be lower in females with papillary (main effect of female sex ($\beta=-0.89$): $p<0.01$) and medullary cancers (main effect of female sex ($\beta=-1.00$): $p=0.0177$).

What characteristic of anaplastic cancer may account for its aggressiveness? According to the present results, anaplastic cancers are most commonly presented at stage T4 (tumor had invaded a nearby vital organ), while T4 was a rare class in differentiated TC. We found that at diagnosis anaplastic cancer patients presented more distant metastasis M1 (compared to M0 stage), which proportions for papillary cancer were 1.6% for women and 3.9% for men. Additionally, we found a paradoxical age relationship in anaplastic cancer, which was diagnosed at a much higher age than papillary cancer (difference of more than 30 years in women and 15 years in men). Curiously, metastatic M1 anaplastic cancer patients were younger than those without metastasis M0 (2 years women, 5 years men), in large contrast to papillary cancer patients for whom metastatic patients were 15–16 years older than those without metastasis. As metastatic spread is thought to originate from the primary tumor with a lag time, the earlier age for M1 in anaplastic cancer is inconsistent with the traditional precursor–product relationship.[46] This may indicate the presence of multiple types of anaplastic cancers (such as related to prior TC, untreated goiter or thyroid autoimmune disease); this would be consistent with the trend of decreasing probability of M1 by age (Figure 2). Whether the multiple types of anaplastic cancer were related to de novo anaplastic or to those with a history of another TC could not be properly answered. Unfortunately, our data on prior or concomitant differentiated cancers in anaplastic cancer patients were limited, most likely because the cancer registry may have not had consistent policies on how to deal with multiple cancers in the same organ.[30] For medullary cancer, the decreasing age-related probability of M1 tumors (Figure 2) is likely to be related to the much earlier onset of hereditary/familial medullary cancer (30 years) compared to sporadic cancer (50 years).[47]

As far as stage presentation at the time of diagnosis, TC differs from many other solid cancers in that T3 (tumor >4 cm limited to thyroid) (in addition to T4, discussed above) was a rare class and did not interfere with survival in

differentiated TC, most likely related to easier detection of neck tumors by palpation. However, the proportion of T3 of all T stages in papillary cancer was higher in men (21.7%) compared to women (14.9%). Another feature that differed from many other solid cancers was the lack of association of lymph node metastases (N1) with survival in all TC. The literature on this point is inconsistent with no or minor association.[7,48–50] However, drainage of cervical lymph nodes after TC diagnosis may have important implications for survival.[50] We found a female advantage in most relative survival metrics in the present study; 5-year survival for all TC in women was 93.4% compared to male survival of 83.9% in 2009–18. Also, the proportions of untoward clinical stages (T3, T4, N1 and M1) were higher in men than women. In our recent study, based on the NORDCAN database, the related figures for 5-year survival in years 2011–15 were 92.1% for women and 86.7% for men with non-overlapping 95% CIs.[12] In that study, female advantage was also significant for Finland, but it was non-significant for Denmark or Norway. In US SEER database, overall survival has been significantly higher for TC in women compared to men.[48]

The strengths of the study are the access to nationwide, high-quality data with stage information, and the present application of conditional survival to define the critical survival periods. The weaknesses are the rareness of many histological types of TC resulting in large CIs in survival estimates. A weakness may be the lacking of the most recent data (last available year in our study was 2018). However, considering that new TC classification and TNM coding were introduced in Sweden on 1.1. 2019 we may have avoided problems of comparability which may be inevitable with the numerous classification changes in the new WHO system.[5] These need to be considered in analyzing future trends in incidence and survival in TC. Anyway, international comparisons in TC survival may be problematic because of diagnostic differences, but mortality rates between 48 countries differed no more than a factors of 3, and Swedish rates were in the middle.[2]

In conclusion, the TNM data for TC showed a highly dichotomous representation for this cancer, the large majority with features of the least fatal cancers of low TNM stages, while anaplastic cancer presented with the most aggressive TNM stages.[51] As pointed out above, the used TNM system, particularly its T and N classes, carried less prognostic information as it does for many other solid cancers. The present data do not explain the mechanism, which may be some inherent property of differentiated thyroid cancer cells of low dissemination or seeding potential. The aims in the new tumor and TNM classification systems for TC are to provide more precise tools for prognostication and individualized treatment.[5] As a concrete clinical improvement, a Danish study reported that an introduction of a national fast track cancer program increased anaplastic cancer survival nearly two-fold.[52] This is an important step forward but survival needs to improve more. Anaplastic cancer is a challenge to the oncological research community; the rareness of this cancer is an obstacle, but in vitro models are available.

Data Sharing Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Ethical Considerations

The study was approved by the Regional Ethical Review Board in Lund University, February 6, 2013 (Reference 2012/795 and subsequent amendments). The Regional Ethical Review Board in Lund University waved the need to include informed consent. The study was conducted in accordance with Declaration of Helsinki.

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Disclosure

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