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Differentiated thyroid cancer in two European referral centres: impact of different diagnostic and therapeutic strategies

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Abstract

Objective: To evaluate differences in the presentation, diagnostic/therapeutic approaches, and outcome of differentiated thyroid cancer (DTC) in an Italian and a Dutch referral centre.

Methods: We retrospectively included 919 patients (586 Italian, 333 Dutch), and compared the two cohorts as a whole and according to ATA risk classes. Dynamic risk stratification (DRS) and Kaplan–Meier curves were used to compare progression-free survival (PFS) and disease-specific survival (DSS).

Results: Several differences ($P < 0.001$) were found in clinicopathological features and in diagnostic/therapeutic modalities. The Dutch cohort had a higher age at diagnosis, a higher number of patients presenting with metastatic disease, and patients with stage III/IV. Most Italian patients showed a low/intermediate ATA risk, while high-risk patients represented half of the Dutch cohort. The Dutch cohort received a more intensive first treatment and more additional treatments during follow-up (i.e. surgery, radiotherapy, and systemic treatments). DRS analysis showed comparable excellent and biochemical incomplete responses, while the Dutch cohort had a lower rate of indeterminate and a higher rate of structural incomplete responses ($P < 0.001$). The Dutch cohort had a significantly worse 5-year PFS, and TC-related mortality was 10 and 1% for the Dutch and Italian cohorts, respectively, in line with the higher rate of advanced disease at presentation, with DSS still excellent for both.

Conclusion: Data reported in the present comparison between two European countries highlight a different prevalence, presentation, and outcome of DTC, likely due to variabilities in healthcare systems, iodine nutritional status, and diagnostic and treatment approaches.

Keyword: thyroid cancer; overdiagnosis; outcome; radioiodine; thyroglobulin

Introduction

The current epidemiological scenario of differentiated thyroid cancer (DTC), with the consistently rising incidence observed in the past 3 decades, strongly indicates the occurrence of overdiagnosis in many countries (1). South Korea provides a striking example of this phenomenon, since cancer screening programmes incorporating neck ultrasound (US) led to a fivefold increase in DTC incidence, making it the most diagnosed cancer among South Korean women (2, 3). Similar trends are evident worldwide, largely because of the increased use of thyroid US and heightened medical surveillance. This often leads to the detection of small papillary thyroid cancer (PTC) cases that would not have affected patients' life expectancy if not diagnosed (4). Therefore, various scientific societies now advocate more conservative diagnostic and treatment strategies (5, 6).

Major differences in TC incidence are still to be noted between countries: in particular, in Italy the DTC incidence is 36.7 cases per 100,000 women per year, while in the Netherlands it is 5.6 cases per 100,000 women per year (with PTC being the main contributor to these differences) (7).

This disproportion could be explained by several factors. In Italy, for example, neck US is widely used, with at least 6.9% of women and 4.6% of men undergoing annual examinations, partly due to the high prevalence of multinodular goitre (MNG) (8) in the context of a long-standing nationwide iodine deficiency, which has only recently been addressed (9). In contrast, the Netherlands, with more adequate iodine coverage than Italy, presents a much lower prevalence of MNG (10). Moreover, in the Netherlands, routine US is not performed in asymptomatic patients with nodular thyroid diseases.

Furthermore, since 2015, Dutch guidelines have sought to minimise the occurrence of clinically occult DTC diagnosis by establishing stricter criteria for thyroid nodule investigations, recommending them solely for symptomatic nodules (11). Moreover, according to the same guidelines, incidental thyroid lesions detected by US, computed tomography, and magnetic resonance imaging should not be routinely investigated, given their low risk of malignancy. In addition, it was suggested that the decision to perform fine-needle aspiration cytology (FNAC) should not be based on nodule US characteristics but rather on its dimensions (>1 cm) and clinical manifestations (11).

Conversely, Italy mostly adheres to the European Thyroid Association (ETA) guidelines, which emphasise the necessity for at least one evaluation of each (incidental) nodule. In addition, the US characteristics of the nodule should determine whether to proceed with FNAC (6). These contrasting diagnostic strategies, in addition to other potential contributing elements, may partly explain the significant discrepancies in TC incidence

between these two countries. Moreover, they could result in different disease stages at presentation, different treatment strategies, and potentially different outcomes. Understanding how different diagnostic approaches influence the treatment burden and outcome of patients in the real-life setting can help tailor widespread management recommendations.

This study aims to compare disease presentation and outcomes between large DTC cohorts from two countries that differ strongly in terms of TC incidence and diagnostic strategies.

Methods

Study design and population

The study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration. The Italian cohort includes patients enrolled in a clinical protocol ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT05752604), while Dutch patients consented to the use of their anonymised clinical data for research purposes, with the study approved by the Medical Ethics Review Committee East Netherlands (file number 2024-17318). Both centres are tertiary referral centres, recognised as Centres of Expertise for Thyroid Carcinoma in their country.

Data were retrospectively collected and analysed from medical records at both centres. A total of 919 DTC patients (586 from Istituto Auxologico Italiano (IAI) and 333 from Radboud University Medical Centre (RUMC)) diagnosed between January 2016 and January 2024, with a follow-up (FU) of at least 6 months since primary treatment, were included. Patients with incomplete FU data were excluded.

Clinical and pathological evaluation

The Bethesda System for Reporting Thyroid Cytology (12) was used to classify FNAC specimens. Operated patients with a Bethesda 5 or 6 were considered as receiving 'therapeutic surgery', while those with a Bethesda 3 or 4 were considered as receiving 'diagnostic surgery'. The detection of a DTC in a thyroid removed for other clinical reasons (e.g. MNG or Graves' disease) was referred to as 'incidental TC', and patients diagnosed via a biopsy/operation on a metastatic site of an initially unknown TC were referred to as 'metastasis biopsy'.

All patients underwent total thyroidectomy (TT) or hemithyroidectomy (HT), besides a small proportion who were considered inoperable at diagnosis because of the extent of the tumour. Lymphadenectomy was classified following neck compartment involvement, thus being central (level VI), lateral (levels I–V), or central + lateral. Tumour staging followed the 8th edition of the AJCC staging system (13).

Pathology reports were consulted for each patient to assess tumour size (cm), number of metastatic nodes, presence of extrathyroidal extension (ETE), multifocality, vascular invasion, and ATA risk stratification (5).

For a proportion of patients, primary treatment also included radioactive iodine (RAI) administration, either after thyroid hormone withdrawal or after rhTSH stimulation. RAI was administered for ablative (1.1 GBq), adjuvant (3.7 GBq), or therapeutic (5.5–7.4 GBq) purposes. Secondary treatment during FU consisted of one or more of the following: surgery for local and/or distant metastases, palliative/curative radiotherapy (RT), and tyrosine kinase inhibitors (TKIs) treatment. Patient risk of recurrence was assessed at the last FU visit according to dynamic risk stratification (DRS), and patients were classified as follows: excellent response (ER), indeterminate response (IR), biochemically incomplete response (BIR), and structurally incomplete response (SIR). DRS analysis was done according to the initial extent of primary treatment. ER was defined as follows: non-stimulated thyroglobulin (Tg) level <0.2 ng/mL with undetectable anti-Tg antibodies (AbTg) and negative imaging in case of total thyroidectomy ± RAI, or stable non-stimulated Tg level with undetectable anti-Tg and negative imaging in case of lobectomy. IR was defined as follows: non-stimulated Tg level 0.2–1 ng/mL and/or stable/declining AbTg levels in case of total thyroidectomy + RAI, or non-stimulated Tg level 0.2–5 ng/mL and/or stable/declining AbTg levels in case of total thyroidectomy without RAI, or stable/declining AbTg levels in case of lobectomy; non-specific imaging findings also accounted for IR. BIR was defined as follows: non-stimulated Tg level >1 ng/mL and/or increasing AbTg levels in case of total thyroidectomy + RAI, or non-stimulated Tg level >5 ng/mL and/or increasing AbTg levels in case of total thyroidectomy without RAI, or increasing Tg or AbTg levels in case of lobectomy; all the above in the absence of positive imaging. SIR was defined by the presence of structural or functional evidence of disease, independent of the extent of initial treatment.

Distant metastasis progression was assessed according to the RECIST Criteria v 1.1 (14), and DSS analysis included only TC-related deaths.

Statistical analysis

Results are expressed as the mean for normally distributed continuous variables or as absolute frequencies and percentages for categorical variables. Comparison of continuous variables among the different groups was performed using one-way ANOVA and Bonferroni correction for post hoc analysis. Categorical variables were compared by the χ^2 test or Fisher exact test, as appropriate. DSS and progression-free survival (PFS) analyses were performed using the

Kaplan–Meier method, and both populations were compared using the log-rank test. $P < 0.05$ was considered statistically significant. All analyses were carried out using SPSS Statistics for Windows (version 29.0).

Results

The differences in clinicopathological features, diagnostic and treatment modalities of the two cohorts are reported in Table 1. The IAI cohort included a significantly lower proportion of male patients (27.1 vs 37.4%, $P = 0.001$), and had a younger age at diagnosis (48 ± 15.8 vs 53 ± 17.5 years, $P < 0.001$). The RUMC cohort showed a higher rate of follicular (FTC), oncocytic (OTC), and poorly differentiated TC (PDTC), and a relatively lower proportion of PTC ($P < 0.001$). IAI cases were significantly more frequently small T1a/b tumours (69 vs 34%), while RUMC patients showed a higher rate of T2, T3a/b, T4a/b (T2–4, 66 vs 31%) and of lateral neck metastases (N1b, 33 vs 9%) (for both, $P < 0.001$). The Dutch cohort had a higher proportion of patients diagnosed with distant metastases since diagnosis (18 vs 4%) and patients with stage III or IV disease (stage III–IV, 18 vs 3%) (for both, $P < 0.001$). The two cohorts showed a similar proportion of ETE (26 vs 29%, $P = 0.31$), multifocality (36 vs 31%, $P = 0.15$) and vascular invasion (24 vs 18%, $P = 0.23$). According to ATA risk stratification, most IAI patients showed a low/intermediate risk (90 vs 53%) while high-risk patients represented up to half of the RUMC cohort (47 vs 10%) ($P < 0.001$). As far as the diagnostic modalities are concerned, the two cohorts had similar proportions of therapeutic (57 vs 57%) and diagnostic surgeries (28 vs 24%). Differently, IAI had more ‘incidental DTC’ cases (18 vs 9%), while RUMC had more diagnoses based on the metastatic presentation of an initially unknown TC (6 vs 0.6%) ($P < 0.001$). Concerning treatment modalities, the rates of TT and HT were similar in the two groups (TT: 87 vs 83%; HT: 13 vs 17%, $P = 0.6$), while the RUMC cohort showed a higher rate of inoperable disease (3.9 vs 0.3%, $P < 0.001$). Moreover, Dutch patients were more frequently treated with lateral neck dissection (33 vs 10%) and RAI therapy (79 vs 41%) (for both, $P < 0.001$). Among the patients receiving RAI, the Dutch cohort was administered a higher cumulative dose (7.5 GBq vs 4.66 GBq, $P < 0.001$). Interestingly, the median number of cycles per patient was similar between the two groups (1.18 vs 1.27, $P = 0.12$), but Dutch patients were more frequently treated with 7.4 GBq as a therapeutic dose (61 vs 9%, $P < 0.001$). Additional treatments during FU were more frequently used in the RUMC cohort than in the IAI cohort: surgery for loco-regional disease control (16 vs 4%), radiotherapy in a palliative and/or curative setting (14 vs 0.8%), and TKI therapy (12 vs 3%) ($P < 0.001$).

Table 1 Comparison of tumour presentation and treatment modalities between the Italian cohort (Istituto Auxologico Italiano-IAI) and the Dutch cohort (Radboud University Medical Centre-RUMC).

Variables	IAI (n = 586)	RUMC (n = 333)	P-value
At presentation			
Sex, males	157 (27.1%)	113 (37.4%)	0.001
Age (years)	48.3 ± 15.8	53.0 ± 17.5	<0.001
Inoperable disease	2 (.3%)	13 (3.9%)	<0.001
Histology			<0.001
PTC	524 (89%)	248 (76%)	
FTC	35 (6%)	33 (10%)	
OTC	15 (3%)	29 (10%)	
PDTC	10 (2%)	10 (4%)	
T			<0.001
T1a/b	393 (69%)	109 (34%)	
T2	108 (19%)	97 (31%)	
T3a/b	61 (11%)	86 (27%)	
T4a/b	7 (1%)	25 (8%)	
NA	15	3	
N			<0.001
N0-x	413 (72%)	173 (56%)	
N1a	111 (19%)	39 (17%)	
N1b	50 (9%)	105 (33%)	
NA	10	3	
M			<0.001
M1	21 (4%)	59 (18%)	
T (cm)	1.7 (0.1–11)	3.2 (0.1–14)	<0.001
NA	24	10	
N (n)	5.5 (1–33)	8.6 (1–40)	<0.001
NA	5	7	
Stage			<0.001
I–II	546 (97%)	266 (82%)	
III–IV	19 (3%)	57 (18%)	
NA	21	10	
ETE	163 (29%)	82 (26%)	0.31
NA	21	10	
Multifocality	183 (31%)	115 (36%)	0.15
NA	21	2	
Vascular invasion	93 (18%)	79 (24%)	0.23
NA	145	2	
ATA risk stratification			<0.001
Low	346 (60%)	94 (28%)	
Intermediate	172 (30%)	82 (25%)	
High	58 (10%)	156 (47%)	
NA	10	1	
At diagnosis			
Modalities			<0.001
Therapeutic surgery	324 (57%)	173 (57%)	
Diagnostic surgery	133 (24%)	85 (28%)	
M + presentation	3 (<1%)	15 (5%)	
Incidental	105 (18%)	27 (9%)	
NA	21	33	
Treatment			
Thyroidectomy			0.6
TT	509 (87%)	275 (83%)	
HT	75 (13%)	45 (17%)	
LN adenectomy			<0.001
CC	133 (23%)	52 (16%)	

(Continued)

Table 1 Continued.

Variables	IAI (n = 586)	RUMC (n = 333)	P-value
LC ± CC	60 (10%)	110 (33%)	
No	387 (67%)	157 (51%)	
NA	4	1	
RAI yes	246 (41%)	263 (79%)	<0.001
1st dose			<0.001
Ablative	17 (7%)	22 (8%)	
Adjuvant	196 (84%)	80 (31%)	
Therapeutic	21 (9%)	160 (61%)	
NA	12	1	
Total RAI dose			<0.001
Median (GBq)	4.66	7.5	
NA	12	2	
RAI cycles			0.12
Median (n)	1.18	1.27	
NA	9	0	
Secondary treatment			<0.001
Second surgery	26 (4%)	52 (16%)	
RT	5 (.8%)	38 (14%)	<0.001
TKIs	17 (3%)	40 (12%)	<0.001

NA, not available (data), not included in the statistical analysis; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; OTC, oncocytic thyroid cancer; PDTC, poorly differentiated thyroid cancer; TNM and staging according to AJCC-TNM staging system 8th edition; T (cm), dimension of the tumour (in centimetres) according to the primary operation pathology report; N (n): number of metastatic nodes according to the primary operation pathology report; ETE, extrathyroidal extension; M+, metastatic; TT, total thyroidectomy; HT, hemi-thyroidectomy; LN adenectomy, lymphadenectomy; CC, central compartment; LC, lateral compartment; RAI, radioiodine therapy; GBq, gigabecquerel; RT, radiotherapy; TKIs, tyrosine kinase inhibitors; ATA risk stratification according to the 2015 American Thyroid Association Guidelines for DTC.

ATA risk stratification subanalysis

Stratification by ATA risk revealed differences in treatment strategies for patients with the same estimated risk of recurrence. Results are reported in Table 2.

ATA low-risk patients

The IAI cohort showed higher rates of TT (84 vs 56%, $P < 0.001$), while neck dissection modalities and metastatic nodal involvement did not differ between the cohorts ($P = 0.41$ and $P = 0.58$). Dutch patients received more RAI (44 vs 22%, $P < 0.001$) and achieved a higher ER rate (82 vs 67%, $P = 0.01$). No differences were found in secondary treatment modalities, and no progression or death events were observed in either cohort (Fig. 1A and B).

ATA intermediate-risk patients

In this subgroup, Dutch patients showed more N1b cases (32 vs 18%, $P = 0.02$) and received more TT (99 vs 92%, $P = 0.03$), RAI therapy (99 vs 68%, $P < 0.001$), subsequent surgeries (15 vs 6%, $P = 0.02$), and RT (4 vs 0%, $P = 0.01$). RUMC patients exhibited

Table 2 Comparison of treatment and outcome variables between the Italian cohort (Istituto Auxologico Italiano-IAI) and the Dutch cohort (Radboud University Medical Centre-RUMC), according to ATA risk stratification category.

Variables	IAI	RUMC	P-value
ATA low-risk			
Surgery			<0.001
TT	291 (84%)	53 (56%)	
HT	55 (16%)	41 (44%)	
LN adenectomy			0.41
CC	59 (17%)	12 (12%)	
LC ± CC	9 (3%)	4 (5%)	
No	278 (80%)	78 (83%)	
N			0.58
N0-x	301 (88%)	86 (92%)	
N1a	35 (10%)	7 (8%)	
N1b	7 (2%)	0 (0%)	
NA	3	1	
RAI			<0.001
Yes	77 (22%)	41 (44%)	
Secondary treatment			0.44
Surgery	8 (2%)	1 (1%)	
RT	0 (0%)	0 (0%)	1
TKIs	0 (0%)	0 (0%)	1
DRS			0.01
ER	232 (67%)	75 (82%)	
IR	90 (21%)	13 (14%)	
BIR	9 (2%)	4 (4%)	
SIR	13 (4%)	0 (0%)	
NA	2	2	
ATA intermediate-risk			
Surgery			0.03
TT	158 (92%)	81 (99%)	
HT	14 (8%)	1 (1%)	
LN adenectomy			0.27
CC	64 (37%)	23 (28%)	
LC ± CC	35 (21%)	25 (24%)	
No	72 (42%)	34 (42%)	
NA	1	0	
N			0.02
N0-x	72 (43%)	35 (42%)	
N1a	66 (39%)	21 (26%)	
N1b	30 (18%)	26 (32%)	
NA	4	0	
RAI			<0.001
Yes	117 (68%)	81 (99%)	
Secondary treatment			0.02
Surgery	10 (6%)	12 (15%)	
RT	0 (0%)	3 (4%)	0.01
TKIs	1 (6%)	1 (1%)	0.59
DRS			0.005
ER	91 (53%)	52 (63%)	
IR	32 (19%)	22 (27%)	
BIR	16 (9%)	5 (6%)	
SIR	33 (19%)	3 (4%)	
ATA high-risk			
Surgery			0.09
TT	52 (90%)	140 (90%)	
HT	4 (7%)	3 (2%)	
Not operated	2 (3%)	13 (8%)	

(Continued)

Table 2 Continued.

Variables	IAI	RUMC	P-value
LN adenectomy			0.02
CC	10 (18%)	17 (12%)	
LC ± CC	15 (27%)	81 (57%)	
No	31 (55%)	45 (31%)	
Not operated	2	13	
N			<0.001
N0-x	33 (60%)	52 (37%)	
N1a	9 (16%)	11 (8%)	
N1b	13 (24%)	79 (55%)	
Not operated	2	13	
NA	1	1	
RAI			0.008
Yes	49 (88%)	140 (98%)	
Not operated	2	13	
Secondary treatment			0.09
Surgery	8 (14%)	38 (24%)	
RT	5 (9%)	42 (27%)	0.004
TKIs	16 (28%)	39 (25%)	0.7
DRS			0.25
ER	12 (21%)	50 (32%)	
IR	5 (8%)	12 (8%)	
BIR	3 (5%)	15 (10%)	
SIR	36 (66%)	78 (50%)	
NA	0	1	

NA, not available (data), not included in statistical analysis; LN adenectomy, lymphadenectomy; CC, central compartment; LC, lateral compartment; N, nodes according to TNM staging (8th edition); RAI, radioiodine therapy; RT, radiotherapy; TKIs, tyrosine kinase inhibitors; DRS, dynamic risk stratification; ER, excellent response; IR, indeterminate response; BIR, biochemically incomplete response; SIR, structurally incomplete response.

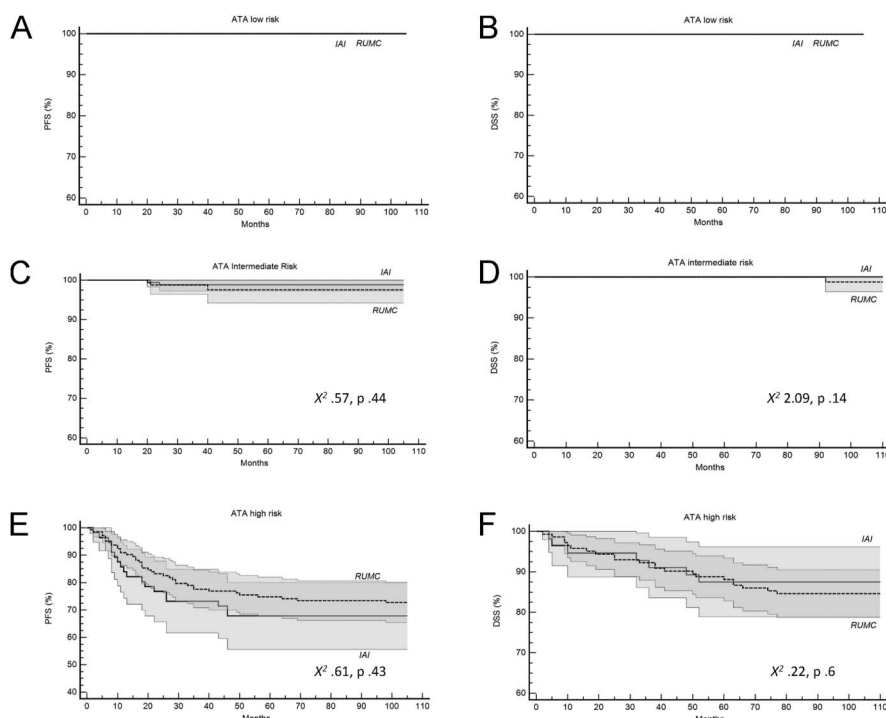
fewer SIR (4 vs 19%) and BIR (6 vs 9%) cases and achieved higher ER rates (63 vs 53%, $P < 0.001$). No significant differences were found in progression ($P = 0.44$, $\chi^2 = 0.57$) and in survival outcomes ($P = 0.14$, $\chi^2 = 2.09$) (Fig. 1C and D).

ATA high-risk patients

The Dutch cohort more frequently received a lateral neck dissection because of more N1b cases (55 vs 24%, $P < 0.001$), while no differences were found for distant metastases at diagnosis (36 vs 38%, $P = 0.82$). More RAI therapies (98 vs 88%, $P = 0.008$) and RT (27 vs 9%, $P = 0.004$) were given in the RUMC cohort, while TKIs were used in comparable proportions. No significant disease status differences according to DRS at last follow-up were present between the two cohorts: ER RUMC 32% vs IAI 21%, SIR RUMC 50% vs IAI 66% ($P = 0.25$). No significant differences were found in progression ($P = 0.43$, $\chi^2 = 0.61$) and in survival outcomes ($P = 0.6$, $\chi^2 = 0.22$) (Fig. 1E and F).

Outcome

Considering the whole cohort, regardless of ATA risk stratification, DRS analysis at last FU showed

**Figure 1**

(A) Kaplan-Meier analysis for PFS in ATA low-risk patients; (B) Kaplan-Meier analysis for disease-specific survival in ATA low-risk patients; (C) Kaplan-Meier analysis for PFS in ATA intermediate-risk patients; (D) Kaplan-Meier analysis for disease-specific survival in ATA intermediate-risk patients; (E) Kaplan-Meier analysis for PFS in ATA high-risk patients; (F) Kaplan-Meier analysis for disease-specific survival in ATA high-risk patients. IAI (Istituto Auxologico Italiano, Italian series, continuous line), RUMC (Radboud University Medical Centre, Dutch series, dotted line).

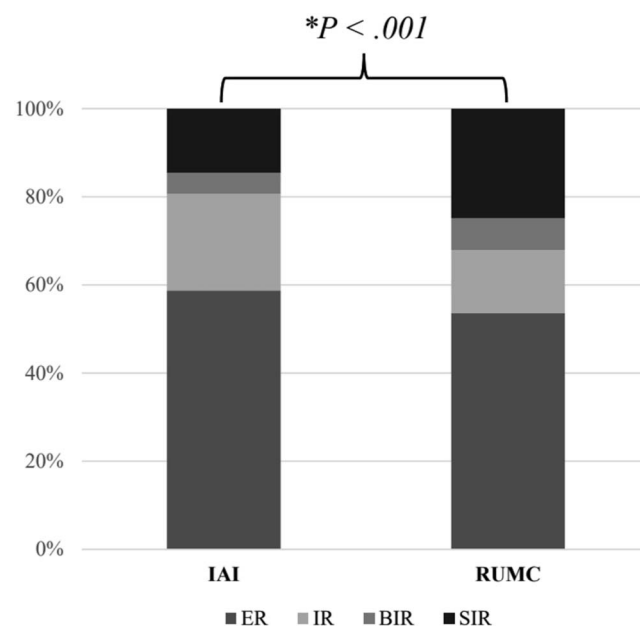
comparable ER (RUMC 54%, IAI 58%) and BIR (RUMC 7%, IAI 5%) rates. However, IAI showed a higher rate of IR (22 vs 14%), while RUMC showed a higher rate of SIR (25 vs 15%), thus resulting in a different response distribution between the two cohorts ($P < 0.001$, Fig. 2).

The RUMC cohort showed higher rates of distant metastatic progression (15.3 vs 3.7%, $P < 0.001$) with a relatively worse 5-year PFS (85 vs 96%, $P < 0.001$, $\chi^2 = 39.2$) (Fig. 3A). TC-related mortality was 10% for the Dutch cohort and 1% for the Italian cohort, with a high 5-year DSS in both groups (IAI 99% vs RUMC 93%, $P < 0.001$, $\chi^2 = 44.3$) (Fig. 3B).

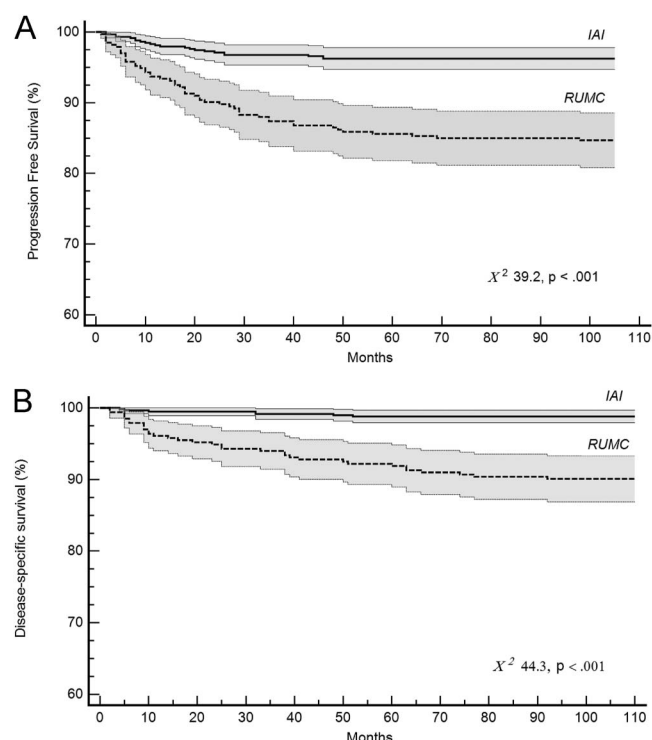
Discussion

This study investigates two large cohorts of patients with DTC diagnosed after 2016 in two tertiary referral centres, from two European countries (Italy and the Netherlands) strongly differing in terms of TC incidence. On one hand, the lower incidence of DTC in the Netherlands is likely due to the limited use of US for screening purposes and to an accurate selection of cases that are likely to be or become clinically meaningful and thus require treatment. On the other hand, in Italy, the wide use of thyroid US, only partially justified by the high incidence of nodular goitre, is predicted to generate an overdiagnosis of a high number of small and indolent DTC, which may increase the burden for patients and for the healthcare system. Thus, the analysis of the differences in both the clinical presentation and the outcome between an Italian and a Dutch DTC cohort has great interest also in a socioeconomic setting.

Interestingly, major differences in the clinical features at presentation between the two cohorts were found, with the Dutch cohort showing a larger proportion of patients with more advanced disease at diagnosis, in terms of both

**Figure 2**

Comparison between DRS outcomes at last FU visit according to 2015 ATA guidelines for thyroid cancer (5). IAI (Istituto Auxologico Italiano, Italian series), RUMC (Radboud University Medical Centre, Dutch series); ER: excellent response; IR: indeterminate response; BIR: biochemically incomplete response; SIR: structurally incomplete response.

**Figure 3**

(A) Kaplan-Meier analysis for PFS; (B) Kaplan-Meier analysis for disease-specific survival. IAI (Istituto Auxologico Italiano, Italian series, continuous line), RUMC (Radboud University Medical Centre, Dutch series, dotted line).

TNM staging and risk of recurrence according to the ATA criteria (5). The data obtained in the Italian cohort are consistent with those reported in two studies based on the Italian Thyroid Cancer Observatory (ITCO) concerning both the rate of stage III and/or IV (3 and 5%, respectively) and that of ATA high-risk cases (10 and 8%, respectively) (15, 16). On the other hand, in the RUMC Dutch series, the rate of stage III and/or IV was even higher than that reported in the Netherlands Cancer Registry (18 vs 10%) (<https://nkr-cijfers.iknl.nl>), whereas the percentage of ATA high-risk cases was similar to that reported in another series from a Dutch academic hospital (45 and 37%) (17). The latter data suggest that in the Netherlands, there is a selection towards more advanced cases being referred to academic hospitals. Therefore, the Dutch cohort is likely representative of the patient population treated in tertiary referral centres in the Netherlands but may not accurately reflect the general DTC patient population in that country. Nevertheless, because the proportion of patients with stages III-IV in the Netherlands Cancer Registry surpasses the proportion found in the Italian cohort, it is most likely that also at a nationwide level, a larger proportion of patients diagnosed with DTC in the Netherlands have more advanced disease at presentation than those diagnosed in Italy.

Interestingly, similar data have also been reported in a recent study comparing the DTC presentation in two cohorts from a Dutch and a German university hospital (18). The authors found that lymph node metastases were significantly more frequently present in PTC tumours ≤ 1 cm and distant metastases in tumours ≤ 2 cm in patients with restrictive use of US for thyroid screening (the Netherlands) when compared to those from a country with ubiquitous availability of thyroid US screening (Germany).

In the present study, we accurately evaluated possible differences in the treatment modalities and found that the Dutch cohort received RAI therapy more frequently (and at a higher cumulative activity), second surgeries during FU, and RT for palliative or curative purposes. These results were likely influenced not only by the tumour presentation at diagnosis but also by different protocols followed in the two centres. For RAI treatment indications, RUMC mostly relied on the 2016 ATA guidelines (5), thus administering RAI treatment in all high-risk and in a high proportion of intermediate-risk patients. In contrast, in the IAI cohort, RAI treatment is guided by tumour markers (thyroglobulin and/or thyroglobulin antibodies) and post-operative US findings (19). Likewise, the higher prevalence in the RUMC cohort of second surgeries and RT is based on a different approach to disease persistence/recurrence, which is not addressed by current guidelines, as it is not supported by strong evidence and is based on a case-by-case deliberation with the multidisciplinary team and in a shared-decision process together with the patient. In particular, the above-mentioned multidisciplinary team is composed of an endocrinologist, oncologist, thyroid surgeon, nuclear medicine doctor and, if needed, radiotherapist. Differently, most Italian cases were treated according to the endocrinologist's indication, with the most challenging ones referred for multidisciplinary evaluation. Moreover, in the Italian cohort, active surveillance is frequently chosen for stable small metastatic nodal disease (20), while in the RUMC cohort, radicality and a curative approach tend to be more frequently sought. For both cohorts, TKIs treatment was chosen only for progressive metastatic RAI-refractory disease (21): the higher use of TKIs in the Dutch cohort reflects the higher number of progressive metastatic cases with a more advanced clinical presentation at diagnosis.

The Dutch cohort had a significantly worse 5-year PFS, and TC-related mortality was 10% for the Dutch cohort and 1% for the Italian cohort, likely related to the higher proportion of patients with advanced disease at presentation in the Dutch cohort. These data are consistent with those found in the Dutch and German cohorts mentioned above, with a TC-related mortality of 6.5 and 0.9%, respectively (18). It is worth noting that the worse PFS and DSS found for the Dutch cohort are also consistent with the higher degree of case selection in the

Netherlands, where more advanced patients are referred to tertiary care hospitals, and more indolent cases are also treated in peripheral hospitals. Importantly, it should be underlined that the survival outcomes are still excellent for both cohorts, highlighting that DTC remains efficiently manageable also in more advanced forms.

An interesting and original finding of the present paper is the evaluation of the two cohorts according to the ATA risk classification. This subanalysis highlighted interesting differences mostly related to the treatment strategies between the two centres in patients with an estimated similar risk of recurrence. Particularly, in the ATA low-risk cases, TT was significantly more frequent than HT in the Italian centre, reflecting the higher prevalence of incidental cases found during surgeries planned for benign nodular diseases. On the other hand, RAI residue ablation was significantly more frequent in the Dutch cohort, and this resulted in a higher prevalence of ERs in this cohort. No impact on PFS and DSS was observed in this low-risk category, confirming that a less aggressive approach can be safely adopted as suggested in the ATA guidelines (5). RAI, external radiotherapy and second surgery were also significantly more frequently used in the Dutch cohort for the ATA intermediate-risk category, and a higher frequency of ERs was recorded, without differences in the progression or survival outcome. Finally, in the ATA high-risk category, the lateral neck compartment was significantly more frequently dissected in the Dutch cohort, as well as RAI treatment and external radiotherapy, while TKI treatment was started in 20–25% of cases in both groups. Inoperable cases represented 3% of the Italian high-risk patients and 8% of the Dutch high-risk patients. PFS and DSS did not significantly differ between the two cohorts of high-risk patients.

Study limitations

This study has certain limitations that must be acknowledged. First, the academic setting of the research may limit the generalisability of the findings to the broader national population. Nevertheless, the series are large enough to ensure a reliable statistical analysis for referral centres. Second, we did not include in our comparative analyses the tumour genetic pattern, and the possibility that one cohort would be enriched by more aggressive mutations cannot be discarded. On the other hand, genetic data were available in a minority of cases, and the whole genetic characterisation of these two large series goes beyond the scope of the study. Furthermore, the different cultural approaches to the prevention, diagnosis and treatment of diseases between these two countries have not been considered. Finally, a cost-effectiveness analysis should have been carried out to evaluate the impact of both overdiagnosis and diagnosis in a more advanced stage on national health systems, but this evaluation is

challenging because of the two profoundly different health systems involved (public in Italy and insurance-based in the Netherlands).

Conclusion

Data reported in the present comparison between two European countries highlight the impact of diagnostic practices on the different prevalence of TC and the role of US in the overdiagnosis. On the other hand, the earlier diagnosis inevitably leads to a better presentation and a significantly higher PFS and DSS, though the rate of cured patients remains high, likely due to the more aggressive therapeutic strategies applied in the Dutch cohort and to the low aggressiveness of the majority of TCs. Finally, our data demonstrate that caution should be exercised when analysing TC prevalence and outcome in different European countries, since relevant differences exist, likely due to variabilities in either healthcare systems, iodine nutritional status, or diagnostic and treatment approaches.

Declaration of interest

LF received consultancy fees from Eisai, Ipsen, Lilly and Bayer. The other authors have no conflicts of interest to declare.

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Author contribution statement

DC, LF and RTN-M designed the current study. DC, CC, SDeL, HJB created and/or managed the original databases to collect the clinical data. DC conducted the statistical analyses. DC, LF and RTN-M wrote the initial manuscript. All authors reviewed and revised the manuscript to improve its intellectual and technical content.

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