Is less always more in a national well-differentiated thyroid cancer population?

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With great interest, we have read the manuscript of Sawant and Nixon et al. in the European Journal of Surgical Oncology [1] and the subsequent comments of Shaha and Tuttle [2]. Both highlight the need for understanding the biology for well-differentiated thyroid cancer and the philosophy of "less is more" in this population. Whether or not to perform a total thyroidectomy followed by radioactive iodine for low-risk well-differentiated thyroid cancer is a daily subject of debate in the Netherlands, but also worldwide.

In this letter to the editor we want to discuss the following; although the guideline of the American Thyroid Association (ATA) is very clear about the option of de-escalating treatment with a hemithyroidectomy, we would like to caution for extrapolating this practice worldwide. Each nation has its own pathway in which the patients are referred to the hospital and diagnosed with papillary thyroid cancer (PTC) or follicular thyroid cancer, also known as well-differentiated thyroid cancer (DTC). This nation specific form of selection greatly affects the biological behaviour of DTC the local treating physicians are confronted with. Therefore, we envision that prior to implementing ATA guidelines one must assess the comparability of the patient population.

It is known that the incidence of thyroid cancer is rising due to increased use of imaging modalities such as ultrasonography, MRI and PET/CT scan, which mainly leads to the identification of small well-differentiated papillary thyroid carcinomas and thyroid incidentalomas without improving survival rate of the disease [3,4]. DTC has an excellent 10-year overall survival rate of 96% [5] and the stable overall survival rate suggests widespread overtreatment following current treatment strategy [4]. Therefore, changing treatment strategies for low-risk DTC patients is of great importance. This is reflected by the 2015 ATA guidelines stating that hemithyroidectomy is sufficient for patients with low-risk DTC [6] based on large national USA registration database studies [7]. However, the main question is: "Is the patient selected with low-risk DTC in the USA similar to the low-risk DTC patient in the Netherlands or any other country?".

Here we explain our doubt regarding the comparability of the USA and Dutch patient selection. The ATA guideline (recommendation 6) states: *"Diagnostic ultrasound should be performed in all patients with a suspected radiographic abnormality suggesting a thyroid nodule incidentally detected on another imaging study."* [6] The decision to perform FNA is thereafter based on the sonographic characteristics and size of the nodule. In contrast, our 2015 Dutch guideline states to fully refrain from further diagnostic work-up of the thyroid incidentalomas (TI). TI's are defined as an unexpected, asymptomatic thyroid nodule discovered during the investigation of an unrelated condition by means of any imaging modality, such as ultrasound, CT-scan or MRI. (For clarity, FDG-avid TI discovered by means of PET/CT scanning are subsequently analysed by ultrasound and FNA) [8]. These differences in guideline result in a completely different population by selection, whereas in the Netherlands probably small TI's mainly comprising of DTC are not diagnosed.

The USA following the ATA 2015 guideline results that in the practice more patients are diagnosed with cancer after which treatment is de-escalated, whereas the Dutch guidelines make sure these patients are not selected and subsequently not diagnosed at all. Survival rates of patients with thyroid cancer in the Netherlands are excellent and comparable to international literature [9]. This supports our belief that early diagnosis and treatment of low-risk DTC patients does not lead to better outcomes in terms of oncological benefit. This was illustrated a decade ago in an almost shocking way when the South Koreans started a screening program which resulted in an explosion of small PTC rates in the general population without a change in mortality pathognomonic for overdiagnosis [3].

The answer to the question "Is the population of patients selected with low-risk DTC in the USA similar to the low-risk DTC patient in the Netherlands?" seems therefore be answered with "No". We compared the population of Sawant et al. used to support their conclusion to only perform completion thyroidectomy for patients who will benefit from surgery with our Dutch DTC population, refer to Table 1. We collected data from the Netherlands Cancer Registry from 2010 to 2015. Median age at diagnosis was higher in the Netherlands compared to Sawant et al. which will affect mortality. Additionally, we identified an important difference in TNM stage in the data In the Netherlands, a higher percentage of pT1 tumour, N+ and PTCs was observed.

A sub-analysis of our DTC population between 2005 and 2015, also showed a different population low risk PTCs compared to Adam et al. [7], which is based on the National Cancer Database in the United states of America. As expected Fig. 1 shows a higher percentage of PTCs ranging from 2 to 4 cm found during histopathological examination in the Dutch population, which is a considered a prognostic factor. However, we do observe a lower percentage of nodal and distant metastasis in our population. All mentioned differences in our DTC and PTC subpopulation are still leading to an excellent survival rate [9] and do not indicate any undertreatment in the Netherlands as a consequence of a significantly different diagnostic work-up and therefore selection of patients.

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Table 1
Comparison of DTC populations. In column A data of Sawant et al. [1] and in column B the Dutch DTC population based on data of the Netherlands Cancer Registry.

Disease	A: Sawant et al.		B: Dutch DTC population	
	Number of cases	Percentage (%)	Number of cases	Percentage (%)
pT stage				
T0/Tx	na	na	45	1.5
T1	44	27	1273	43.5
T2	73	45	691	23.6
T3	40	25	728	24.9
T4	4	3	66	2.3
T missing	na	na	121	4.1
pN Stage				
N0/Nx	151	94	2120	72.5
N+	10	6	683	23.4
N missing	na	na	121	4.1
pM Stage				
M0/Mx	na	na	2865	98
M1	na	na	55	1.9
M missing	na	na	4	0.1
Histology				
FTC	73	45	452	15.5
PMC	87	54	2472	84.5
FTC/PMC	1	0.6	na	na

na: not available.

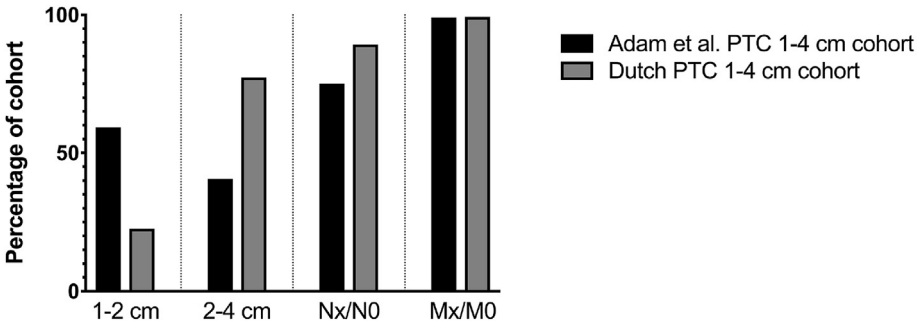

Fig. 1. Comparison of PTCs ranging from 1 to 4 cm cohorts of Adam et al. (black bars) and the Netherlands (grey bars). This figure shows the differences in tumour size 1–2 cm (59.3% vs 22.6%) and tumour size 2–4 cm (40.7% vs 77.4%) between cohorts. Differences in percentages of absent nodal metastasis (75.1% vs 89.3%) and absent distant metastasis (99.1% vs 99.3%) are displayed.

We postulate that the Dutch population harbours less incidentally discovered indolent tumours and consequently question the safety of implementing a de-escalated treatment following the 2015 ATA guideline in the Netherlands without the thorough analysis of our own data.

Therefore, to assess the safety and impact of de-escalation of treatment in the already selected Dutch population with low risk PTCs ranging from 1 to 4 cm a national randomized controlled trial is currently designed comparing total thyroidectomy followed by radio-active iodine treatment with hemithyroidectomy followed by active surveillance.

In this comment, we explained our concerns about implementing a de-escalated treatment without thorough data analysis and we showed the differences in the Dutch DTC population as a consequence of differences in diagnostic work-up. We still believe in “less is more” and look forward to conduction the national trial. It is our ambition to combine both reduced diagnostics with reduced treatments while maintaining safe oncological care and higher quality of life.

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Declaration of competing interest

None.

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