Real-world applicability of differentiated thyroid cancer guidelines

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Abstract

Objective: Thyroid cancer (TC) is the most common endocrine malignancy with constantly growing incidence. Radioiodine ablation is a safe and effective method for managing TC. Recently various Guidelines (GL) have been published on whom should be ablated, when and under which circumstances. Our study compares 6 GL with a given patient cohort. Additionally, we evaluated each GL's quality via an independent tool. **Material and Methods:** We compared six Guidelines (GL) for TC ablation on a cohort of 336 patients, implementing GL retrospectively: 2009 and 2016 American Thyroid Association (ATA), European Thyroid Association's (ETA) Consensus Statement, UK's National Institute for Health and Care Excellence (NICE), German position paper from Surgery and Nuclear Medicine (German) and European Association of Nuclear Medicine and Society of Nuclear Medicine and Molecular Image (EANM/SNMMI). Quality assessment was conducted using the Appraisal of Guidelines, Research and Evaluation instrument II (AGREE II). **Results:** Results showed significant variability among GL. American Thyroid Association 2016, a clear improvement of the ATA 2009, presents a large grey area of "probable ablation candidates". European Thyroid Association and NICE agree that only a small portion of our ablated patients would benefit from it and the AGREE II tool shows a lack of applicability, but very good scores elsewhere. German and EANM/SNMMI GL agree that most of our clinical decisions to ablate were correct and their AGREE II scores are the highest in all six domains. **Conclusions:** Considering that dynamic risk classification plays a major role in determining the most appropriate treatment, it appears that the guidelines should be updated in order to support individualized patient management. However, it is the experience of the individual physician that will determine the final decision.

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Introduction

Thyroid cancer (TC) is the most common endocrine malignancy, accounting for approximately 3% of all new malignancies diagnosed annually [1], showing the fastest-growing incidence among all types of cancer for most countries worldwide, during recent decades. The proportion of smaller and early-stage cancers increases over larger and more advanced ones, mainly due to overdiagnosis via the more widespread use of diagnostic imaging and fine-needle aspiration biopsies of thyroid nodules [2-4]. As a result, intermediate and low-risk patients constitute the majority of cases to be treated, to whom different approaches of iodine-131 (^{131}I) therapy (ablation) have been implemented. The uncertainty and inconclusiveness regarding the ideal management of low-risk TC patients, especially concerning ablation use, emphasises the pressing need for "real life" applicable guidelines (GL), which will be able to ensure the best clinical practice.

Official GL should be clear, specific, evidence-based, frequently updated, structured, applicable and independent. All these characteristics capture a unique dimension of GLs' quality, which can be evaluated by tools such as the Appraisal of Guidelines, Research and Evaluation Instrument II (AGREE II) [5]. Several scientific organisations have developed official GL for TC management. Still, contradictions exist on "when and to whom should ablation be applied", as highlighted by our team in previous publications, comparing the 2009 and 2016 American Thyroid Association (ATA) [6, 7] GL with the National Comprehensive Cancer Network (NCCN) [8] and the European Association of Nuclear Medicine (EANM) [9] ones. By conducting a retrospective study involving 336 low-risk (pT1-2, M0) differentiated thyroid cancer (DTC) patients ablated at two reference hospitals, we showed that, despite initial evaluation of patients as low risk, there had been characteris-

tics -other than histopathology- denoting higher or uncertain risk. As a result, we discussed the strengths and limitations of each official GL, regarding the "real life" applicability of them [10, 11].

Since then, several new GL have been developed, such as the ones by EANM and the Society of Nuclear Medicine and Molecular Image (SNMMI) [12], the "Martinique Principles" [13], the European Thyroid Association's (ETA) Consensus Statement [14], the UK's National Institute for Health and Care Excellence (NICE) GL [15] and the "German position paper from Surgery and Nuclear Medicine" [16]. This article's scope is to retrospectively implement these new GL onto our 336 ablated patients' cohort used in our previous publications [10, 11] and evaluate each GL using the AGREE II tool [5].

Material and Methods

Our cohort included 336 low/intermediate-risk patients ablated between September 2010 and October 2013 at the Nuclear Medicine Departments of the Bank of Cyprus Oncology Centre, Strovolos Nicosia, Cyprus ("BOCOC") (n=198) and Papageorgiou Hospital, Thessaloniki, Greece ("PGH") (n=138). Cohort's clinical, pathological and lab characteristics, as well as technical details on Thyroglobulin (Tg) and Thyroglobulin Antibodies (TgAb) determinations, may be found in our original publications [6, 7]. Before ablation, patients provided written informed consent allowing the use of their data in analyses such as the present study. All patients' charts had been anonymised before being analysed. Working by consensus, two experienced nuclear medicine physicians (PE, EG) reviewed each patient's charts classifying the patient as having a definite indication, a possible indication, or no indication for ablation according to 6 different DTC management GL (ATA 2009 [6] and 2016 [7], ETA [14], NICE [15], German [16] and EANM/SNMMI [12]).

Concerning GLs' quality assessment, four evaluators (PE, EG, II, SF) independently appraised all selected guidelines by using the AGREE II tool [5], mainly focused on GL recommendations concerning whether to ablate or not our low/intermediate-risk patients. We compared the mean values of each of the six domain scores and the total scores obtained by all four evaluators.

Results

Table 1 presents the summary of the characteristics of the GLs under investigation. Except for ATA, the other four GL were published between 2022 and 2023. They were all developed by professional organisations, notable for their high-quality scientific work, except for the German position paper from Surgery and Nuclear Medicine. The German thesis was also the only new, while the rest were updates.

Table 2 and Figure 1 present the various GL recommendations for our cohort.

Table 1. *Characteristics of TC management GL included in the study ATA, American Thyroid Association; ETA, European Thyroid Association's Consensus Statement; NICE, UK's National Institute for Health and Care Excellence; GERMAN, German position paper from Surgery and Nuclear Medicine; EANM/SNMMI, European Association of Nuclear Medicine and Society of Nuclear Medicine and Molecular Imaging.*

Guidelines (Year)	Organisation	Country	Level of Development	Status
ATA 2009	American Thyroid Association	USA	Professional Organisation	Updated
ATA 2016	American Thyroid Association	USA	Professional Organisation	Updated
ETA 2022	European Thyroid Association	Europe	Professional Organisation	Updated
NICE 2022	National Institute for Health and Care Excellence	UK	Professional Organisation	Updated
GERMAN 2022	German Surgery and Nuclear Medicine	Germany	National Independent body	New
EANM/SNMMI 2023	European Association of Nuclear Medicine, Society of Nuclear Medicine and Molecular Imaging	Europe, USA	Professional Organisation	Updated

Table 2. *Classification of our cohort concerning ablation according to the 6 GL under investigation. Data presented are percentages (number) of patients in the entire cohort.*

Category/criterion	ATA 2009	ATA 2015	ETA	NICE	GERMAN	EANM/SNMMI
Definite ablation candidates ("indication")	32,7% (110)	26,8% (90)	18,8% (63)	22% (74)	70,2% (236)	71,1% (239)
Probable ablation candidates ("recommendation")	28,6% (96)	42% (141)	9,5% (32)	10,1% (34)	7,1% (24)	6,3% (21)
Possible ("selective") ablation candidates	38,7% (130)	31,3% (105)	71,7% (241)	67,9% (228)	22,6% (76)	22,6% (76)

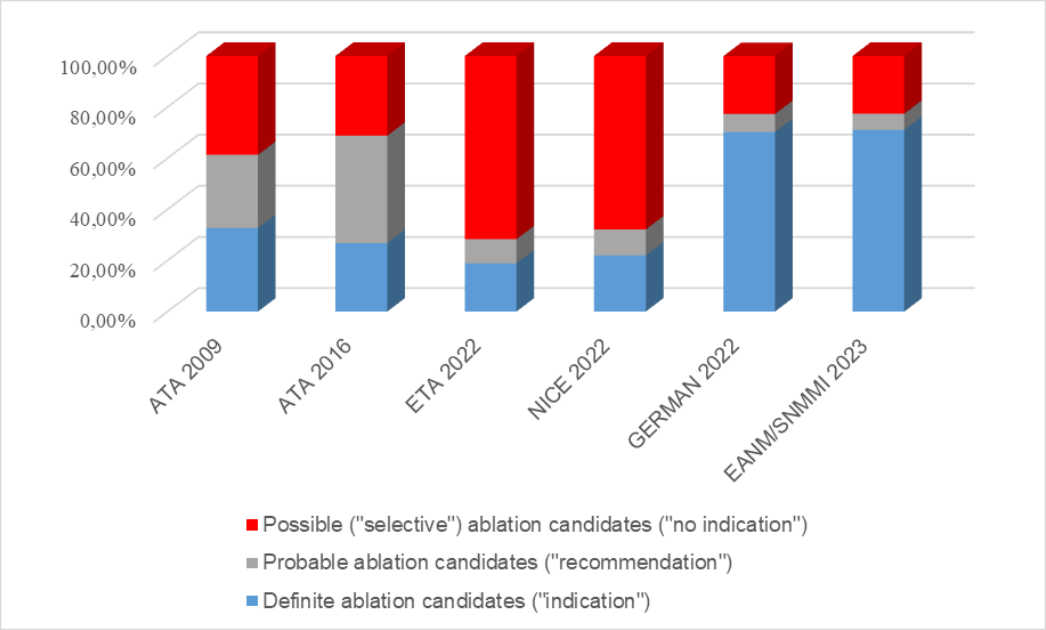

Figure 1. Classification of our cohort concerning ablation according to the 6 GL under investigation.

As seen in Table 2 and Figure 1, the "no indication" classification is quite common for our cohort. American Thyroid Association 2016 reclassified 10,7% (n=36) "no indication" and 10,1% (n=34) "definite ablation candidates" patients to "probable ablation candidates", the move for most of the cases was due to more than one clinicopathological characteristics. It is also worth mentioning that the most frequent classification based on ATA GL 2016 is "probable ablation candidates" (more than 4 out of 10 patients in our cohort).

There seems to be an agreement between ETA and NICE GL, as well as between the German and EANM/SNMMI. European Thyroid Association and NICE GL seem to run counter to our clinical decision-making, since they find "no indication" for ablation for about 7 out of 10 of our patients, and we should have definitely ablated only about 10% of our patients. On the contrary, the German and EANM/SNMMI GL would definitely ablate about 7 out of 10 of our patients. It should also be noted that the German and EANM/SNMMI GL effectively limit the range of the "grey area", since the "recommendation" subgroup is the less populous for both of them.

Tables 3 and 4 and Figures 2 and 3 show the average scores of all AGREE-II 23 items, as well as per the 6 main domains. 2009 ATA GL were evaluated with the lowest scores in all six AGREE-II domains, however, the 2016 updated version is documented to be of a much higher overall quality, with applicability presenting the biggest improvement. European Thyroid Association and NICE GL were evaluated as satisfactory, achieving a better than 50% score in all six domains. However, when compared with all other GL except for 2009 ATA GL, ETA GL applicability got the lowest score. German EANM/SNMMI GL got the highest scores in all six domains. It is worth mentioning that the EANM/SNMMI GL scored the highest applicability, which is in accordance with our previously described results, showing the importance of the recommendations' implementation in real-life clinical practice.

Table 3. *Quality of thyroid cancer guidelines for the six domains of the Appraisal of Guidelines for Research and Evaluation II (AGREE-II) Instrument (D1-D6) and the overall impression. All AGREE-II items are rated on a seven-point scale ranging from 7 (strongly agree) to 1 (strongly disagree). Numbers represent the average score given by the four evaluators of our group.*

	ATA 2009	ATA 2016	ETA	NICE	GERMAN	EANM/SNMMI	DOMAIN
1. OVERALL OBJECTIVE	4	4.25	4.5	4.75	6.25	6.25	scope and purpose
2. HEALTH QUESTIONS ARE SPECIFICALLY DESCRIBED	3.25	4	5.25	5	6	6	
3. POPULATION TO WHOM THE GUIDELINE IS MEANT TO APPLY IS SPECIFICALLY DESCRIBED	6	6.25	6.75	7	7	7	
4. INDIVIDUALS FROM ALL RELEVANT PROFESSIONAL	7	6.75	7	7	7	7	
5. VIEWS PREFERENCES	5.5	5.5	6.25	6.25	7	7	
6. TARGET USERS OF THE GUIDELINE ARE CLEARLY DEFINED	5	4	5.75	6.25	7	7	
7. SYSTEMATIC METHODS WERE USED TO SEARCH FOR EVIDENCE	4	4.75	4.5	6	7	7	rigour of involvement
8. CRITERIA OR SELECTING EVIDENCE ARE CLEARLY DESCRIBED	4.25	5	5	6	7	7	
9. STRENGTHS AND LIMITATIONS OF THE BODY OF THE EVIDENCE CLEARLY DESCRIBED	3.5	4.25	5.5	5	6	5.75	

(Continued)

10. THE METHODS FOR FORMULATING THE RECOMMENDATIONS ARE CLEARLY DESCRIBED	4.75	4.5	6.25	6.5	5.75	6	
11. HEALTH BENEFITS SIDE EFFECTS AND RISKS HAVE BEEN CONSIDERED IN FORMULATING THE RECOMMENDATIONS	4	5.25	6	5.75	7	7	
12. THERE IS AN EXPLICIT LINK BETWEEN RECOMMENDATIONS AND THE SUPPORTING EVIDENCE	3.5	3.75	5	5.25	6.25	6.25	
13. THE GUIDELINE HAS BEEN EXTERNALLY REVIEWED BY EXPERTS PRIOR TO ITS PUBLICATION	3.5	4	5	5.5	5.5	6	
14. A PROCEDURE FOR UPDATING THE GUIDELINE IS PROVIDED	6.25	6	5.5	5	2.5	5.5	
15. THE RECOMMENDATIONS ARE SPECIFIC AND UNAMBIGUOUS	3.75	4.25	5.25	5	6	6.5	clarity of presentation
16. THE DIFFERENT OPTIONS FOR MANAGEMENT OF THE CONDITION OR HEALTH ISSUE ARE CLEARLY PRESENTED	4	3.75	5.25	5.75	6.25	6.25	
17. KEY RECOMMENDATIONS ARE EASILY IDENTIFIABLE	3	3	5	5	6	6	applicability
18. THE GUIDELINE DESCRIBES FACILITATORS AND BARRIERS TO ITS APPLICATION	3	3.25	3.5	3	4.75	5.25	

(Continued)

19. THE GUIDELINE PROVIDES ADVICE AND/OR TOOLS ON HOW THE RECOMMENDATIONS CAN PUT INTO PRACTICE	3.25	4	4.75	6.25	7	7	
20. THE POTENTIAL RESOURCE IMPLICATIONS OF APPLYING THE RECOMMENDATIONS HAVE BEEN CONSIDERED	3.5	6	4	4.5	3.5	6	
21. THE GUIDELINE PRESENTS MONITORING AND/OR AUDITING CRITERIA	3	6.25	5	3.5	4.25	6.25	
22. THE VIEWS OF THE FUNDING BODY HAVE NOT INFLUENCED THE CONTENT OF THE GUIDELINE	6.25	6	6	6.75	6.5	6	editorial independence
23. COMPETING INTERESTS OF GUIDELINE DEVELOPMENT GROUP MEMBERS HAVE BEEN RECORDED AND ADDRESSED	7	7	7	7	7	7	
RATE THE OVERALL QUALITY OF THIS GUIDELINE	3.5	3.75	5.25	5.5	6.25	6.5	

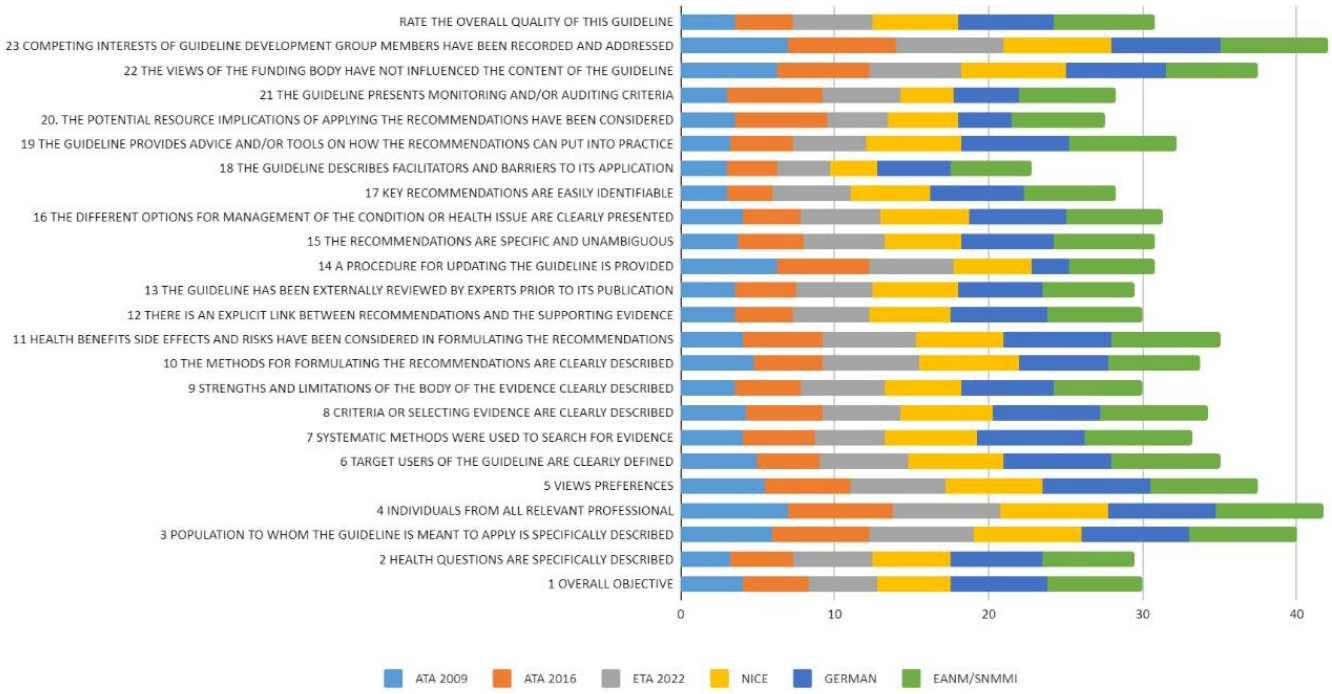

Figure 2. Thyroid cancer GL assessed quality for all six AGREE-II domains and overall impressions.

Table 4. *Domain scores (%) of the six clinical practice guidelines assessed using the AGREE-II instrument.*

Domain	ATA 2009	ATA 2016	ETA	NICE	GERMAN	EANM/SNMMI
Scope and Purpose	56,94%	63,89%	75,00%	76,39%	90,28%	90,28%
Stakeholder Involvement	80,56%	73,61%	88,89%	91,67%	100,00%	100,00%
Rigour of Development	53,65%	61,46%	72,40%	77,08%	81,25%	88,54%
Clarity of Presentation	43,06%	44,44%	69,44%	72,22%	84,72%	87,50%
Applicability	31,25%	64,58%	55,21%	55,21%	64,58%	85,42%
Editorial Independence	93,75%	91,67%	91,67%	97,92%	95,83%	91,67%

Discussion

Most risk stratification systems of DTC include age, tumor size, grade and, the presence of local, regional or distant disease [17]. This rather static prediction of the disease's trajectory, which is mainly available at initial diagnosis, is what most GL take into account, to set their recommendations. This major limitation was also already pointed out in our previous work [10, 11]. Based on the literature review, as well as on our everyday clinical practice, we sought to investigate the applicability and the overall quality of the most recent and commonly used GL for the management of DTC. Acknowledging that dynamic risk stratification is the only active process to determine the most appropriate treatment for each DTC patient individually [17], we examined whether ATA 2009 GL and their updated version, ETA 2022, NICE 2022 GL and the German opinion as well as the EANM/SNMMI consensus, fulfil their major objective, to enable best, clear, effective and safe treatment of low/intermediate-risk DTC patients.

Our findings suggest that ATA 2016 GL rely on Tg values as a basic confounder to ablation-related decision much more than the previous version. The great impact of postopera-

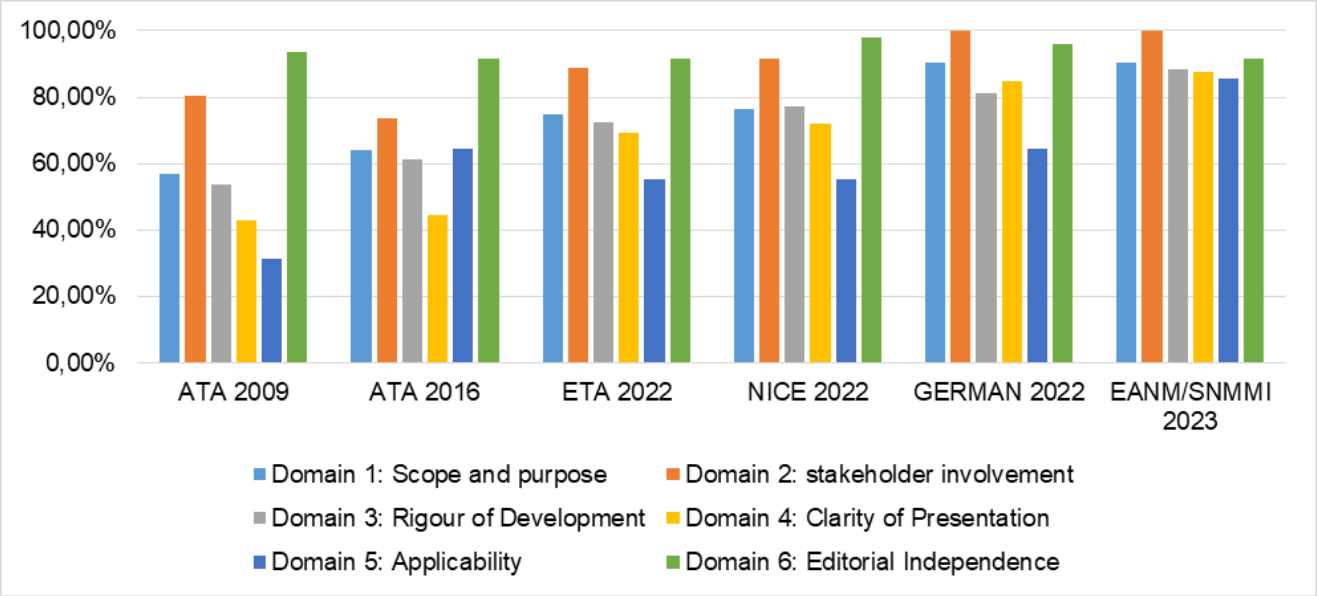

Figure 3. Domain scores (%) of the 6 AGREE-II domains.

tive stimulated Tg level has been shown to be one of the most potent, independent risk factors influencing the risk for relapse and therefore decision-making in DTC patients, by several studies [18-20]. Contrary to our decision to ablate all patients of our cohort, ATA GL suggest that there is no indication for 38,7% and 31,3% of them, according to the 2009 and 2016 GL, respectively. Moreover, ATA GL are more subjective than the rest of the reviewed GL, since the "recommendation" category appears to be one of the most populous classifications, especially for the 2016 version (42%). On the one hand, the clinician needs to use their expertise and judgement to decide whether to ablate or not each patient individually. On the other hand, the main scope of evidence-based protocols and GL is to clarify which patients should undergo which treatment and under which conditions [21]. Thus, in our opinion even the updated 2016 ATA GL have plenty of room for improvement towards this objective. As new management options become constantly available, it is essential to conduct studies that will provide evidence-based clinical practice information to GL, so that the latter can be more clear, accurate, subjective and applicable [22]. These conclusions agree with our findings when we attempted to evaluate the ATA GL with the AGREE II tool. ATA 2009 GLs' applicability was rated with a mere 31,25%, revealing its limitation in providing adequate advice and tools on how their recommendations can be put into practice. Thankfully, ATA 2016 GL are documented to be of a much higher overall quality. The four evaluators agreed that the potential resource implications of applying the recommendations have been considered much more by ATA in 2016 rather than in 2009 (Item mean score=6), which reveals the intention of the American scientific organisation to implement their recommendations in real-life clinical practice.

The gap between our ablation decisions and ETA and NICE is documented to be even greater. These GL find "no ablation indication" for more than two-thirds of our patient cohort, which indicates their conservative DTC management regarding ablation. According to ETA no T1aN0M0 stage patient should be ablated, regardless of their clinical, biochemical or imaging profile. However, we are opposed to accepting this statement, our clinical experience, along with numerous studies and clinical trials, has shown that several factors may be associated with a higher risk of relapse, even among the seemingly indolent disease of the so-called low-risk patients [23, 24]. For the same group of patients NICE GL suggest "not to offer RAI to people with a solitary microcarcinoma (T1a), unless there are adverse features (prognostically poor histological subtypes or an R1 resection margin)". Although NICE acknowledge poor histological subtypes, multifocality and the extent of tumour excision as potential factors of higher risk, they neglect confounders such as Tg and TgAb levels [25-28] and clinical or imaging evidence of structural disease [29], which demonstrably interfere with the disease's prognosis and should be taken into consideration for the final decision-making. For T1b DTC ETA seems to consider the biochemical and imaging status of each patient, while NICE insists on not ablating even patients with multifocal disease, unless there are adverse features, such as poor histological subtypes or an R1 resection, regional lymph node involvement, or evidence of other metastatic disease. The above easily explains the comparatively low percentages of "recommendation" and "indication" classifications when applying ETA and NICE GL in our cohort. Concerning their AGREE-II scores, ETA and NICE GL achieved a higher than 75% score in all domains, except for applicability, where their score was among the lowest of all GL.

It is very interesting to note, how in many respects, we are on the same page with the German thesis and the EANM/SNMMI GL that appear to be the closest to our clinical decisions concerning our cohort, since they both consider our decision to ablate as correct for more than 70% of our patients. Another point of interest is that both GL extensively

limit the "grey area" zone, since the "recommendation" subgroup is the less populous for both of them (less than 10%). German GL recommend considering ablation for all stages of low-risk patients, including those with T1aN0M0, when risk modifiers -such as multifocality, aggressive histology or BRAF mutation- coexist. According to both GL ablation is definitely indicated for T1b and T2 tumours regardless of lymph node infiltration. Consequently, our clinical decision agreement with German and EANM/SNMMI GL is also reflected by the AGREE-II tool quality evaluation results. Both GLs were rated with the highest scores in all six domains and overall quality, and are thus considered by the evaluators as the most clear, specific, evidence-based, updated, structured, applicable and independent GL.

Most DTC risk stratification systems include age, tumour size, grade and presence of local, regional or distant disease [17]. This rather static prediction of the disease's trajectory, which is mainly available at initial diagnosis, is what most GL consider in their recommendations, an issue already pointed out [10, 11]. Acknowledging that dynamic risk stratification is the only active process to determine the most appropriate treatment for each DTC patient individually [17], more accurate, clear and evidence-based GL are needed, encouraging individualised and patient-centred management, to ensure a better prognosis and quality of life in DTC patients.

Based on the literature review, as well as on our everyday clinical practice, we sought to investigate the applicability and the overall quality of the most recent and commonly used GL for the management of differentiated thyroid cancer. Acknowledging that dynamic risk stratification is the only active process to determine the most appropriate treatment for each TC patient individually [17] we examined whether ATA 2009 GL and their updated version, ETA 2022, NICE 2022 GL and the German opinion as well as the EANM/SNMMI consensus, fulfil their major objective, to enable best, clear, effective and safe treatment of low-intermediate-risk TC patients.

In conclusion, our findings reveal that current GL varied in methodological quality, which is directly associated with their recommendations regarding radioactive iodine (RAI) in low/intermediate-risk patients.

The authors declare that they have no conflicts of interest.

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