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EDITORIAL

Radioiodine treatment after surgery for differentiated thyroid cancer: a reasonable option

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Introduction

Until recently, the usual treatment for differentiated thyroid cancers (DTC) with a size >1.0 cm undisputedly consisted of total or near-total thyroidectomy followed by radioiodine administration. Observational data support lower recurrence rates after radioiodine treatment (RAI) following surgery [1–3]. In recent years, and especially so since the publication of the 2015 American Thyroid Association (ATA) differentiated thyroid cancer guidelines (DTC) [4], the systematic use of RAI has declined, or at least has been called into question. The decision on whether to give RAI, and if so what ^{131}I activity to administer, increasingly relies upon risk stratification systems (RSS) such as the ATA risk of recurrence system or the DTC-specific survival oriented UICC/AJCC TNM staging system. Each system takes into account the extent of disease at surgery and additional characteristics such as age, histology, and possibly other patient- or treatment-related factors. The ultimate goal of such systems is to predict risk of recurrence (ATA) or of death from DTC (UICC/AJCC) in order to modulate the intensity of primary treatment and subsequent long-term follow-up strategy. Their use theoretically provides a scientific rationale to prescribe or abstain from RAI following surgery, with the aim of avoiding "overtreatment". In the recent DTC guideline update from ATA [4], less than total thyroidectomy is recommended for intrathyroidal tumors < 4.0 cm, which de facto cancels the possibility of using post-operative therapeutic radio-iodine administration. Even in some more advanced situations, avoidance of post-operative therapeutic radioiodine administration is advised for patients considered at low-to-intermediate risk of recurrence according to the current risk stratification model. However, a safe application of this "de-escalation" approach is still hampered by several significant simplifications and approximations, contradictions and most importantly the lack of solid evidence to support the choices made based on stratification systems predicated on limited surgical pathology information. Additionally, the objectives for RAI administration (e.g. remnant ablation, adjuvant 131-I therapy, or 131-I therapy for metastatic disease) are often merged in the recommendations, with implications for the 131-I activity selected and the intended outcome of RAI treatment. Finally, some recommendations are based on studies with too short follow-up periods (<10–15 years) to assess reliably disease-free survival estimates for most patients [5].

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Are there limitations in the current stratification systems used for guiding RAI therapeutic decision-making for DTC patients?

Several limitations in the current stratification systems impede the effective use of RAI in the patients that may benefit from this treatment. Thyroid cancer is usually a well-differentiated,

slowly growing disease with a very low disease-specific mortality rate for local-regional disease after complete initial therapy (5-year survival 99.9% for localized disease, and 97.8% for regional metastatic disease); however, distant metastatic disease is associated with significantly worse prognosis (5-year survival 55.3%) (http://seer.cancer.gov/statfacts/html/thyro.html). Therefore, staging and stratification systems predicated on "hard oncological criteria" (e.g. overall survival) are not particularly applicable to the majority of DTC patients and are little informative to guide decisions about RAI. Therefore, secondary outcome variables such as rates of persistent disease, rates of recurrent disease, medico-economic issues, and quality of life outcomes, should be taken into consideration as well.

One of the most concerning issues in the 2015 ATA Guidelines [4] is the modification of the 2009 ATA risk stratification [6] to include tumors with extra-thyroidal extension (T3) or associated with lymph nodal (LN) metastases (pN1with ≤ 5 LN involved; all < 0.2 cm) in the low-risk category for which RAI ablation is not recommended, based on low recurrence rates reported in published studies that included RAI ablation after total thyroidectomy. The study cited in support of the contention that similar low recurrence rates occur in patients treated with lobectomy alone, and without post-operative RAI, had sub-optimal surveillance (no assessment for distant metastatic disease, nonstimulated Tg), and a short follow-up (median 5.1 years) [7]. In addition, a risk stratification predicated solely on surgical pathology information is inherently limited not only by the extent of surgical dissection and the accuracy of histopathology examination, but also by the complete absence of any information regarding the presence of distant metastases. Without a post-therapy ^{131}I scan, or at least a high-quality diagnostic radio-iodine scan to assess regional and distant metastatic disease in the neck compartments unexplored at surgery and in the remainder of the body, staging, and risk stratification systems are abridged of essential information. The principle of precise initial staging is often disregarded in current guidelines, despite the propensity of DTC for local invasion and metastatic spread. Because of its indolent nature and excellent overall survival in local-regional disease, DTC appears to be managed rather as a chronic condition with serial follow-up than with curative intent. Decisions to omit ^{131}I therapy are made on incomplete staging and risk stratification, despite well-established evidence for improved recurrence-free survival, disease-specific survival, and overall survival for patients who received ^{131}I therapy postoperatively [2, 8, 9]. The strategy of surveillance without ablation based on the assumption of an indolent disease course cannot be accepted in the context of current evidence demonstrating adverse clinical outcomes when ^{131}I therapy is delayed, both for regional [2] and for distant metastatic disease [10]. Until more prolonged follow-up becomes available to compare the benefits from various strategies, RAI administration remains a reasonable option, especially in the numerous situations where the literature is controversial [2, 11].

Is the current risk stratification for disease recurrence internally concordant for decision-making strategies?

The current risk stratification has several internal incoherencies, which limit its applicability for post-operative RAI decision making. The ATA risk stratification is used to inform on the indication for RAI after thyroidectomy in primary management of DTC as follows: RAI is not recommended in low risk patients, while it should be considered in ATA intermediate risk ones, and is routinely recommended in high risk DTC patients [4]. However, the risk classification, which is used for making the decision to perform or withhold RAI partially depends on the ^{131}I image pattern itself, since "no RAI positive metastatic foci outside the thyroid bed" is a selected criterion for the low risk category in this system. In contrast, abnormal RAI uptake in the neck corresponds to intermediate risk. Distant metastatic foci seen using either ^{131}I or ^{18}FDG will correspond to high risk disease. It seems somewhat contradictory to determine the indication for RAI ablation depending on the results of the post-therapy ^{131}I image. To solve this conundrum it would be possible to perform diagnostic pre-ablation ^{123}I or ^{131}I imaging (henceforth abbreviated as Dx WBS), as done by some teams. [3, 12–15] The main purpose of pre-ablation imaging is to identify regional and distant metastatic disease which would require higher administered 131-I activities as opposed to low-dose remnant ablation strategy, or identification of bulky regional metastatic disease in unexplored neck compartments, which will direct toward reoperation before ^{131}I therapy [12]. In addition to surgical pathology and stimulated thyroglobulin (Tg) levels, the information obtained from DxWBS regarding the presence of iodine-avid regional and/or distant metastases can be used for ^{131}I treatment planning [12, 13, 16]. In a study of the University of Michigan Medical Centre, Dx scans - identified regional metastases in 35% of patients, and distant metastases in 8% of patients referred for post-operative ^{131}I therapy [13] and this information in conjunction with the results of stimulated Tg levels led to a change in management for 31% of patients, as compared to proposed management predicated on histopathology findings alone [12]. Visualization of metastatic deposits on DxWBS confirms their capacity to concentrate ^{131}I (iodine-avid disease) and, therefore, their potential to respond to therapeutic ^{131}I activity. Location and size of metastatic lesions can be determined on SPECT/CT imaging, thus guiding management: ^{131}I therapy is most effective for smaller metastatic deposits [17, 18], whereas for large metastases, surgical debulking before ^{131}I therapy can be considered. While low ^{131}I activities (1.1 GBq; 30 mCi) successfully ablate

normal thyroid tissue remnant located in the thyroidectomy bed [19, 20], effective treatment for iodine-avid regional and distant metastatic disease has traditionally required higher ^{131}I activities, as demonstrated by lesion dosimetry calculation studies [21–24]. It is important to discuss the study of Castagna et al. [25], which assessed the effectiveness of 1.11 GBq (30 mCi) vs. 3.7 GBq (100 mCi) of I-131 for the treatment of 225 DTC patients classified as intermediate risk for recurrence. The rates of disease remission (76.5 vs. 72.1%), persistent (biochemical or metastatic) disease (18.8 vs. 23.6%), recurrent disease (2.4 vs. 2.1%), and of death (2.4 vs. 2.1%) were not statistically different in patients treated with 1.11 GBq (30 mCi) versus 3.7 GBq (100 mCi), the authors concluding that "high 131-I activities have no major advantage over low activities." Subsequently, other authors have referenced this article in support of promulgating that "less I-131 is more" for adjuvant treatment [26]. Although not statistically different in the two groups, the rates of persistent and recurrent disease and even death are concerning. This paper has then been used to advance the idea that 30 mCi is as equally effective as 100 mCi; however, it could also be argued that it shows that 100 mCi is equally ineffective as 30 mCi. The potential bias for prescribing higher RAI activity to patients with more aggressive histopathological features cannot be entirely excluded in this retrospective study. Moreover, the iodine-avidity of the metastatic disease was not assessed prior to RAI administration. Therefore, we consider that risk stratification systems need to include imaging information that will clarify the status of regional and/or distant metastatic disease (as present/or absent) and determine the functional nature of metastases (as iodine-avid or non-iodine avid).

Does surgical pathology provide reliable information for management decisions?

Post-operative management, including RAI administration or lack thereof, is predicated on a risk stratification system based on surgical pathology information [4]. However, the surgical pathology information is inherently limited by the extent of surgical dissection, and in many patients information on nodal status is either unavailable since no lymph nodes were excised (Nx), or very limited since the number of lymph nodes submitted for pathologic examination is too low to rule out the presence of occult residual disease after surgery. For example, the probability of falsely identifying a patient as node negative was estimated to be 53% for patients with a single lymph node (LN) examined; however, this probability decreased to less than 10% when more than six LNs were pathologically examined. To rule out occult nodal metastatic disease with 90% confidence, six LNs would need to be submitted for pathologic examination for patients with T1b tumors, nine LNs for patients with T2 tumors, and 18 LNs for patients with T3 disease [27]. Most concerning is that lymphadenectomy is often limited or not performed in 50–70% cases, especially when the patients are a priori considered to belong to the low- or intermediate-risk groups [25].

The central compartment is considered the first tumor drainage territory in most DTC. The role of prophylactic central compartment lymph node dissection has been debated in the literature over the past few decades. Although its routine use increases the accuracy in tumor staging, there is no clear evidence that this procedure leads to a reduction in recurrence or mortality [28]. In order to limit surgical morbidity, many surgeons perform unilateral paratracheal prophylactic lymphadenectomy (including the cervical and upper mediastinal lymph nodes). This approach is acceptable but several points need to be addressed: 1 - There is preferential drainage of cancers located at the upper poles of the thyroid into the ipsilateral lateral compartment (level III) or at the level of the superior thyroid pedicle; 2- There is preferential drainage of cancers located in the inferior-internal part of the thyroid or in the isthmus into the pretracheal compartment and the delphian lymph node. 3 – Anatomic considerations influence the extent of nodal dissection: the left inferior laryngeal nerve travels along the tracheoesophageal groove and is at low risk of injury during left paratracheal LN dissection; however, the right recurrent laryngeal nerve crosses the inferior thyroid artery and is at a much higher risk of injury during right LN dissection. Therefore, right paratracheal LN dissection may be associated with higher rates of nerve injury, or in less experienced hands may lead to incomplete dissection in order to avoid complications. For all these reasons, the information provided by the "prophylactic central lymphadenectomy" might be suboptimal and information regarding the extent of the dissection might also be missing from the operative report. The information can be further limited by the pathological analysis of extirpated nodes, which can vary in completeness and quality between centers.

Therefore, management decisions dictated on risk stratification predicated solely on surgical pathology are inherently limited, leading to incomplete staging and potentially excluding RAI administration for patients that may have benefitted from it had the extend of disease been accurately determined.

Are postsurgical low thyroglobulin levels a reliable marker to rule out RAI administration?

Post-operative Tg levels cannot be used as a cornerstone criterion to recommend for or against RAI administration. New recommendations include using postsurgical Tg measurement (either TSH stimulated or nonstimulated, obtained a few weeks after total thyroidectomy and before RAI remnant ablation) as a tool to aid in initial risk stratification and adjuvant RAI therapy decision-making [4]. However, a post-treatment

RAI whole body scan (post-Rx WBS) demonstrating residual thyroid tissue with a corresponding undetectable serum Tg was reported in up to 20% of DTC patients [29]. Moreover, up to 6% of such patients had confirmed loco-regional or distant metastases in addition to thyroid tissue remnants [30]. Most importantly, RAI administration likely contributed to good patient outcome observed in previous studies on the role of preablative Tg, while similar results in non-ablated patients remain unproved.

Different technical problems still affect Tg measurement and need to be carefully considered when using Tg as a marker for the presence of thyroid tissue. First, interference from TgAb compromises the use of serum Tg as a tumor marker in up to 25% of DTC patients by reducing Tg measurement results in immunometric methods [31]. Second, interferences by heterophilic antibodies, as well as the so-called "high-dose hook effect," or decreased immunological reactivity or changes of the structural conformation of the Tg molecule may in rare instances lead to report inappropriately low serum Tg values in sera with high Tg concentrations [32]. The importance of these interferences has been documented by analyzing sera from 47 DTC patients presenting undetectable serum Tg, but residual ^{131}I uptake on a PT-WBS [33]. This study also pointed to the variability between different Tg immunoassays [33].

As explicitly admitted in ATA 2015 guidelines, no precise Tg value cutoffs are available to define what is an excellent response after surgery justifying RAI omission. Indeed, post-operative serum Tg value is strongly dependent on the type of determination (stimulated or nonstimulated), type of stimulation (rh-TSH vs. endogenous hypothyroid stimulation), the actual level of TSH stimulation and the volume of remnant thyroid tissue. Therefore, the level of postoperative Tg cannot alone guide the decision for or against RAI administration [29, 30, 34]. It appears that the postoperative serum Tg value will be more helpful in identifying patients that will benefit from RAI ablation rather than in identifying patients that do not require ablation [4].

All in all, a low or undetectable Tg cannot be considered a completely reliable marker to safely exclude DTC patients from RAI ablation. Therefore, a benchmark between ^{131}I imaging and Tg measurement remains of pivotal value by authenticating the use of serum Tg during further follow-up of DTC patients [35].

Does postoperative RAI administration improve risk-stratified care management?

The use of RAI following total thyroidectomy has several distinct advantages: 1- the ^{131}I post-therapy scan (post-Rx WBS) completes post-operative staging, and the information obtained may modify the treatment plan and long-term surveillance, 2- it provides early reassurance of disease-free status, 3- it facilitates long-term follow-up by reducing concentrations of sensitive Tg below the threshold of detectability, 4- it avoids useless and repetitive costly medical procedures (i.e., rhTSH stimulation, neck US, and FNA biopsies for equivocal US findings).

Imaging-based staging at ablation reveals the true extent of residual disease. Notably, in about 5% of patients, the ^{131}I whole-body scan has uncovered occult distant spread, mainly pulmonary or skeletal metastases [18, 36–39]. This small percentage of cases has its importance as distant metastases are the main purveyors of death from DTC and early detection on the ^{131}I scan is a favorable situation that offers chances for cure [18, 36–39]. Moreover, the ^{131}I scan has substantially improved in recent years; ^{131}I SPECT-CT acquisition, which is performed after whole-body scan on the neck area or on suspicious body foci, allows to substantially improve specificity [40, 41]. ^{131}I SPECT-CT has an excellent reproducibility and high detection sensitivity in neck compartments II, low VI and V. Thus, DTC management may be modified by post-Rx WBS ^{131}I imaging in roughly 15% to 25% of the patients [42]. Without ablation, a substantial percentage (5–40%) of these metastatic nodes will persist. [43] Even small or occult malignant lymph nodes are likely to grow slowly with time, causing secondary costs, anxiety for the patients and sometimes worsening of the overall prognosis. Indeed, recent data indicate that microscopic lymph node involvement represents a distinct prognostic entity which is associated with an intermediate outcome between the N0/Nx and the N1 macroscopic patients [44]. Post-operative DxWBS and/or post-Rx WBS evaluation permits early detection and treatment of iodine-avid regional and distant metastases completing staging and risk stratification, provide a baseline for assessing therapeutic response and contribute to long-term follow-up decisions (such as the intensity and duration of L-T4 suppression, frequency of Tg determinations and neck US surveillance).

Does postoperative RAI administration facilitate long-term follow-up and improve dynamic risk stratification systems?

Information obtained with postoperative RAI administration provides the baseline for assessing the response to initial treatment enabling dynamic risk stratification (DRS), which determines the long-term follow-up strategy. Very early, Mellière et al., has advanced the concept that final staging of patients who received total thyroidectomy cannot be obtained until results from the ^{131}I ablation scan is obtained and results from Tg measurement at 6 months post-ablation are available [11]. They called this dynamic stratification "Extension-Thyroglobulin". They identified as the "high-risk group" patients who either have widely invasive tumors (e.g. tumors that invade the larynx, trachea, esophagus, recurrent laryngeal

nerve or vessels) or distant metastases (discovered initially or on the post-Rx WBS after initial ^{131}I ablation) or who have a stimulated Tg level at 6 months of more than 10 μg/L (after T4 withdrawal; Tg testing in association with a diagnostic ^{131}I whole-body scan and neck ultrasound examination) [11]. The 25-year actuarial rate of cancer-related death for this high risk group was 46.9%. Comparatively, the 25-year rate of cancer-related death and cancer recurrence with this approach in patients with satisfactory testing were 1.4% and 3.8%, respectively, in patients with intrathyroidal tumor (>1 cm) without nodal metastases, and 0% and 5.3% in patients with lymph node metastases [11]. Because of its clinical relevance, the concept of dynamic risk stratification achieved impetus and was first formalized as such by Tuttle et al. in 2010 [45]. DRS after total thyroidectomy and ^{131}I ablation includes Tg measurement (after stimulation or under levothyroxine, L-T4, therapy, especially with the new sensitive assays) and imaging studies including neck US, and when indicated ^{131}I scanning, ^{18}FDG PET/CT, or other imaging studies. DRS classifies response to therapy into three categories: excellent, acceptable, or incomplete response [45]. These categories are strongly predictive of the course of further follow-up, especially in the subgroup of "excellent responders" who have a very high rate of permanent remission (i.e. absence of disease) during follow-up. The DRS better identifies the risk of PRD (persistent or relapsed disease) as compared to the ATA/ETA staging systems [46] and appears to be a powerful classifier which can be used to promptly reassure a majority of patients who will not require further specialized tests. However, we must keep in mind that a follow-up of at least 10 years is needed to assess the true rate of persistent or relapsed disease (PRD) occurrence. This holds especially true for low risk patients which have been ablated using the comparatively novel strategy of administering low ^{131}I activities. However, this long follow-up period is far from being met in several high ranking, much touted recent papers [47].

The accuracy of the DRS staging now relies strongly on new Tg assays with routine sensitivity < 0.1 ngLml. After remnant ^{131}I ablation, several publications report basal Tg concentration values of over 0.3 ng/mL indicate a significant risk of relapse [48]. Unfortunately, there are no convincing data showing any Tg threshold suggesting PRD in case ^{131}I ablation is not performed. It is likely that none may be proven with sufficient sensitivity and specificity, especially considering that the ability to produce Tg varies widely between tumors and remnants. In addition, sensitive Tg is often detectable after surgery and may be influenced by variations in TSH levels. Even then, only time will prove whether a patient is really disease-free. In contrast, 6 to 9 months after ^{131}I ablation, more than 90% of the patients have undetectable sensitive Tg levels, making the subsequent follow-up extremely simple and reliable. Therefore, we conclude that patient-individualized post-operative RAI administration based on integration of histopathology, postoperative Tg level and functional imaging information is a reasonable option that simplifies clinical management and long-term follow-up surveillance strategy.

Does adjuvant or therapeutic RAI administration improve clinical outcomes?

RAI administration is an effective treatment for iodine-avid metastatic disease. The adjuvant therapeutic effect of RAI is highly interesting, especially for destroying small, at most a few millimeters in diameter sized tumor foci, in thyroid remnants or lymph nodes, or eradicating occult distant micrometastases. Many publications report a high frequency of uncovered persistent disease in the neck, mediastinal nodes, or distant spread at ablation. This is rather expected in intermediate and high risk patients, but may occur even in the so called "low-risk" group [13]. In the literature, 5% to 25% of patients show unsuspected foci of pathologic uptake using ^{131}I scanning and changes in therapy planning are reported in a significant percentage of cases.

Most published evidence demonstrates a reduced recurrence rate after RAI [2, 8, 9], despite the presence of some conflicting data (mainly from observational studies). Furthermore, the tumoricidal effect of ^{131}I has been reported to be effective (94% eliminated lymph node metastases) especially on lymph nodes smaller than 0.9 mL identified on ^{131}I SPECT-CT [17]. Such interesting studies are less frequently reported possibly because they rely upon the newer ^{131}I SPECT-CT technology and routine pathology confirmation would be difficult to obtain. Nonetheless, the adjuvant effect of ^{131}I is highly probable, resulting in elimination of small residual nodal metastases or in identification of larger structural disease that could potentially justify re-operation. A big concern arises here for many practitioners when looking at RAI decision-making tables of the 2015 ATA Guidelines [4], since recommendations mainly recommend against RAI administration, for instance in pT1b, pT2, and even some pT3 N0/Nx ATA risk groups. Even in higher risk patients often no explicit recommendation for ^{131}I therapy is given (but simply the term "consider" ^{131}I therapy). These recommendations are made in spite of the presence of conflicting observational data. In absence of any ^{131}I administration or only using low activities, the adjuvant and *a fortiori* therapeutic goals of RAI will be lost in patients with unsuspected persistent metastatic disease foci after surgery [2, 8, 9, 11]. Since the literature cannot advise for or against these statements, further long-term follow-up studies are needed before recommendations to change effective clinical practice are accepted as standard of care. As long as the results of such studies are still pending, it would be prudent to refrain from strong positions against ^{131}I where

thus far the course of disease with ^{131}I therapy has been so good [1–3].

As for the prescribed RAI activity, this should be carefully selected. To simply raise as principle "the lower the better" [26], makes little sense. In radiation oncology the proposition that a lesser radiation therapy dose is better would be unacceptable, and the same applies for chemotherapy treatment.

If the goal is *only* to perform thyroid remnant ablation (i.e. elimination of normal thyroid tissue remnant) in order to facilitate initial post-therapy scanning and dynamic restaging, especially where the assessment of Tg levels are concerned, then low ^{131}I activities provide a practical advantage (limited or no hospital stay with cost reduction) and minimize the risk of side effects, while still achieving high ablation rates. At least 12 prospective studies have shown that an activity of 1110 MBq/30 mCi met certain arbitrary endpoints roughly as effectively as the historically often-used 3700 MBq/100 mCi, provided the size of the post-surgically remaining tissue "remnant" is not too large [49]. A few papers have even reported similar ablation rates using ~20 mCi [34, 50], while in contrast, some report a significantly lower ablation rate at 30 mCi than when using 100 mCi. Most importantly, for patients ≥ 45 years, the rate of disease recurrence and DTC-specific mortality was found in some studies to be significantly higher in patients treated with lower RAI activity (≤2000 MBq or 54 mCi), as compared to higher ablative RAI activities [5].

Considering the endpoints of importance, such as rates of persistent and/or recurrent disease, disease-specific death, simplified surveillance and lower costs, the post-operative RAI administration remains a reasonable option. As we fully discussed earlier, the reasons why ^{131}I has been administered for decades goes far beyond the simple aim of "ablation" and, therefore, the activity to be administered should be carefully selected on the basis of the particular clinical situation.

Conclusion

The temptation to control every situation is strong both in medicine and in society. Guidelines should integrate these normal variations and remain rather open. Apart from that, many endpoints of ^{131}I still remain controversial or unknown. Therefore, recommendations for RAI should integrate not only hard oncological criteria, but also tailored therapy management and surveillance, patient's wellbeing, and quality of life, at a lower cost for society. Finally, we strongly believe that for the reasons explained above, RAI remains a valuable adjuvant post-operative treatment for most DTC patients. Although it is always good to question and reevaluate current practice, care should be taken not to discard previous management guidelines on postoperative ^{131}I therapy before proper evidence is produced that management without RAI is as safe and as effective in the selected patient categories as administration of this proven effective therapeutic modality.

The limited space of an editorial allows us to discuss several salient points that only scratch the surface of a flawed approach in the recent ATA Guidelines regarding the contribution of radioiodine imaging and treatment to thyroid cancer management. Taking into consideration the slow progression of thyroid cancer, the adverse clinical consequences of these recommendations may not become apparent until years have passed and we find patients with recurrences that could prove difficult to treat, and could have been avoided.

Compliance with ethical standards

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