Review Article

Total thyroidectomy *vs.* lobectomy in differentiated thyroid cancer: is there a reasonable size cut-off for decision? A narrative review

Daniele Barbaro[1], Giancarlo Basili[2], Gabriele Materazzi[3]

[1]U.O. Endocrinology, Viale Alfieri 36 57100, Livorno, Uslnordovest Toscana, Italy; [2]U.O. General Surgery and Endocrine Surgery, Viale Alfieri 36 57100, Livorno, Uslnordovest Toscana, Italy; [3]Endocrine Surgery, Cisanello Hospital, Via di Cisanello University of Pisa, Pisa, Italy

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Correspondence to: Daniele Barbaro. U.O. Endocrinology, Viale Alfieri 36 57100, Livorno, Uslnordovest Toscana, Italy.
Email: danielebarbaro@katamail.com.

Objective: To analyze all the most recent guidelines/consensus as well as papers regarding the relationship between size of tumor, type of surgery, and prognosis, and to try to produce a critical synthesis for real practice.

Background: Differentiated thyroid cancer (DTC) is characterized by a wide range of biological behavior. The type of intervention can range from lobectomy (LT) to total thyroidectomy (TT), with tumor size being a point of discussion in choosing the treatment.

Methods: We carried out a search on PubMed, EMBASE, and Cochrane Library, looking at all the guidelines and consensus regarding DTC, as well as examining original articles, inserting as our research keys "total thyroidectomy *vs.* lobectomy in differentiated thyroid cancer" and "hemithyroidectomy in thyroid cancer". The guidelines and consensus published over the last 5 years were 6 in total: ATA Guidelines, Italian Consensus of Six Italian Societies, United Kingdom National Multidisciplinary Guidelines, ESMO Clinical Practice Guidelines, a Practical Guidance of a Multidisciplinary Panel of Experts, and The Revised Clinical Practise Guidelines on the Management of Thyroid Tumours by the Japanese Association of Endocrine Surgeons. There were 13 papers cited in the guidelines, and we found another 5 original articles, all of which were retrospective studies.

Conclusions: The type of initial surgical intervention must of course consider tumor size, but must also take into account all the risk factors, which is paramount in deciding the type of treatment. LT can have some advantages, and can represent an option that can be offered to patients. However, even in the absence of any special risk factors, a review of the literature suggests to us that patients should be informed that LT for tumors of a size between 2 and 4 cm can be associated with an increased risk of LR as well as with a possible reduced OS.

Keywords: Total thyroidectomy (TT); thyroid lobectomy; differentiated thyroid cancer (DTC)

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Introduction

Differentiated thyroid cancer (DTC), that is, papillary cancer (PC) and follicular cancer (FC), is characterized by a wide range of biological behavior, making it difficult to devise a strategy that avoids under- or overtreatment. The relationship between tumor size, type of surgery, and prognosis is still a matter of debate, and represents the topic of this review. Traditionally, the first risk stratification is carried out at the moment of surgical intervention, and, in absence of lymph node involvement, the type of intervention can range from lobectomy (LT) to total

thyroidectomy (TT). During the past decades there has been a wide range of viewpoints regarding these different kinds of approach. But in recent years the more conservative opinions, in favor of LT for less advanced cancer and based on a different risk stratification algorithm, have predominated. Before surgical intervention, the size of the tumor is one of the easiest factors which can be evaluated for the choice of treatment, and represents, as already stated, a major point of discussion. We analyzed all the most recent guidelines/consensus statement (1-6), as well as papers regarding the relationship between tumor size, type of surgery, and prognosis, examining both original papers (7-24) and expert opinions (25-35). Our objective is that of producing a reasonable critical synthesis for real practice. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/gs-21-242).

Methods

We conducted a search on the main literature databases, namely PubMed, EMBASE, and Cochrane Library, looking at all the guidelines and consensus regarding DTC, and also examining all original articles, inserting as our research keys "total thyroidectomy *vs.* lobectomy in differentiated thyroid cancer" and "hemithyroidectomy in thyroid cancer". We first analyzed the guidelines, then all those studies cited in the guidelines, and, finally, we examined all the remaining studies which we found using the above-mentioned criterion of research.

Regarding the original articles we examined, we excluded only the smallest retrospective studies. It is hardly an easy matter to establish a theoretical sample size below which a study may not have much statistical relevance, but, being that the largest studies were on the order of thousands of patients, and considering that the difference in outcome was likely very slight, we decided to exclude the smallest studies, in which no statistical difference could be discerned. Based on this presupposition we could exclude studies with 300 or fewer cases. Moreover, we excluded from our analysis studies not having a control group, unless they were quoted in the guidelines. Because the purpose of the study was to compare cancers of different size, we also excluded studies in which it was not possible to perform a comparison between pT1a and pT1b. We also carried out an examination of all "expert opinion".

Regarding the guidelines, consensus, and "expert opinion", we considered only those from the last 5 years, while we examined all studies contained in the original articles that we found. We also examined some original papers regarding pathological features if they could be of help to our review, independent of their number of cases (36,37).

Discussion

The guidelines and consensus published over the last 5 years were 6 in number, specifically: (I) ATA Guidelines, (II) Italian Consensus of Six Italian Societies, (III) United Kingdom National Multidisciplinary Guidelines, (IV) ESMO Clinical Practice Guidelines, (V) a Practical Guidance of a Multidisciplinary Panel of Experts, and (VI) The Revised Clinical Practise Guidelines on the Management of Thyroid Tumours by the Japanese Association of Endocrine Surgeons [6]. Thirteen papers were cited in the guidelines, and we found another 5 original articles, all retrospective studies. Overall, we found 18 original studies. Of these, three studies regarded SEER data, three studies regarded NCDB data, and the rest were studies from a database reporting data from different institutions. *Table 1* reports all the papers analyzed, and specifies if and in which guidelines/consensus they were quoted. As for "expert opinion", we found 11 papers. We found two more articles considered interesting to our purpose, inasmuch as they correlated, from a pathological perspective, tumor size with local and distant spreading.

Starting from the analysis of the guidelines, taken in chronological order, we can perceive the "Copernican revolution" of the ATA guidelines that, in recommendation 35, push toward a more conservative approach regarding surgical intervention. In fact, the ATA guidelines set out, for a tumor size no greater than 4 cm, and in absence of lymph-node involvement or extracapsular extension, the possibility of planning a LT (1). Previously, mainly micro carcinoma had been treated with LT alone, while, in more advanced cases, the standard surgical intervention was TT, together with, in some institutions, routine central lymph-node compartment dissection. With the ATA 2016 guidelines we witness a clear reversal, and this approach was adopted by the Italian Consensus in 2016 as well as by the United Kingdom National Multidisciplinary Guidelines. However, in these last guidelines some further features, such as age of <45 years and absence of angioinvasion, were added for recommending LT (2). The next guidelines to be published were those of ESMO, which also endorsed LT for tumors no larger than 4 cm, considering as further criteria for exclusion any radiation exposure in childhood

Table 1 Papers cited in the various guidelines

	Cited in					
	ATA	IC	UKNMG	ESMO	MPE	RCPGES
1988 Grant	Yes	No	No	No	No	No
1993 Mazzaferri	No	No	No	No	No	No
1998 Hay	Yes	No	No	No	No	No
2002 Hay	Yes	No	No	No	No	No
2005 Haigh	Yes	No	No	No	No	Yes
2007 Bilimora	Yes	Yes	No	Yes	No	No
2010 Barney	Yes	No	No	No	No	No
2010 Ito	No	No	No	No	No	Yes
2010 Mendelsohn	Yes	No	No	No	No	Yes
2012 Nixon	Yes	No	No	No	No	No
2013 Lee	No	No	No	No	No	No
2014 Adam	Yes	Yes	No	Yes	No	Yes
2014 Ebina	No	No	No	No	No	Yes
2014 Matsuzu	Yes	Yes	No	No	No	No
2018 Rajjoub	No	No	No	No	Yes	No
2019 Liu	No	No	No	No	No	No

ATA, ATA guidelines; IC, Italian Consensus; UKNMG, United Kingdom National Multidisciplinary Guidelines; ESMO, European Society of Medical Oncology Guidelines; MPE, Multidisciplinary Panel of Experts; RCPGES, Revised Clinical Practise Guidelines on the Management of Thyroid Tumours by the Japanese Association of Endocrine Surgeons.

or adolescence, any family history for thyroid cancer, any aggressive features in cytology, or any suspicion of multifocality (3). So, in point of fact, we here see a confirmation of 4 cm as the limit for performing LT. But, on the other hand, we also witness an effort to narrow the field of application for LT, and to individuate those cancers with a size of 4 cm, which could be especially suitable for such a more conservative approach. To give indirect support to this more conservative surgical intervention, the new 8th edition of the TNM Classification of Malignant Tumours has revised downward the classification of DTC. However, the Practical Guide of a Multidisciplinary Panel of Experts, which is the latest consensus, gave special consideration to the most recent original article (16). For this reason, we see in this work a return to a position which is a little more aggressive in terms of tumor size when deciding on LT (5). On the other hand, and finally, the Revised Clinical Practise Guidelines on the Management of Thyroid Tumours by the Japanese Association of Endocrine Surgeons (RCPGES), returns to the opinion expressed by the ATA guidelines, suggesting LT for PC and not widely invasive FTC up to 4 cm in size. However, for pT1b PC, central compartment dissection is recommended. The discrepancy seen in these differing views may be due to several factors, such as a special emphasis being given to certain papers in respect to others in each specific guideline, or to real disagreement which exists within the literature. Moreover, in the analysis of the prognosis of DTC, papers may consider different parameters, like local recurrence (LR), cancer specific mortality (CSM), or overall survival (OS).

We have critically reread the papers quoted in the various guidelines/consensus in order to try to understand why we see such discrepancies, and we also studied every paper we could find regarding the topic, as stated in Materials and Methods above. Starting from the papers quoted in the ATA guidelines, which cites the greatest number of works, we see that, in fact, the data supporting the opinion of performing LT for cancers up to 4 cm are not so robust. The paper of

Adam *et al*. (7) is a retrospective study regarding 61,775 cases in the NCDB, from 1998–2006. All cases were papillary cancers (PC), and its aim was to investigate OS, with no data on LR being reported. TT was performed in 54,926 cases, while the remainder were treated by LT. Those treated by TT were in more advanced stages, so this paper may have contained a selection bias. Regarding cancers having a size between 1.0–2.0 *vs*. 2.0–4.0 cm, the raw data showed a better OS for TT, although, if the data is adjusted through consideration of clinical and pathological factors, no real difference is to be noted. However, this adjusted data also showed that radioiodine treatment was associated with a better prognosis in terms of OS, which would appear to be a contradiction, and again feeds into the notion of a bias in selection.

In the paper of Mendelsohn *et al*. (8) on SEER data from 1988–2001, and which regarded 22,724 patients, the Authors find that tumor size is statistically associated with a worse disease specific survival (DSS) and OS. Concerning the type of surgical intervention, they state that even after performing subgroup analysis for tumors between 1 and 4 cm, no difference was found between TT and LT. However, although in their paper many histological and clinical variables are studied and reported upon, no table or figure is included which clearly shows the raw data to support this statement, and it is therefore difficult to understand their conclusions. Moreover, and quite surprisingly, in this paper, too, the 131I treatment improved OS but not DSS, which was seen to be even worse. So here, too, we may be justified in assuming some selection bias.

In the paper of Haigh *et al*. (9) regarding previous SEER data (1985–1995) on 5,432 cases, no difference was found between TT and LT in patients with a PC of <4 cm, but, again, 131I was associated with lower mortality, and this, as already stated in regard to the papers discussed above, is a nonsensical result which is hard to explain.

Another paper cited in the ATA is that of Barney *et al*. (10) regarding SEER data (1983–2002) on 23,605 subjects, although in this paper TT resulted in improved OS *vs*. LT for PC <4 cm. The author himself, at the end of the work, stated that the treatment should be individualized by taking into account any potential surgical complications.

Two other retrospective papers quoted in the ATA guidelines [by Hay *et al*. (11,12)] suggest that LT can be associated with CSM. The first paper regards 2,444 consecutively enrolled patients treated at the Mayo clinic. In this study, LR and CSM were generally worse in the period 1940–1949 compared to the decades more immediately preceding 1990, when LT represented 73% of surgical interventions for PC. Considering the period 1950–1999, the treatment with radioiodine did not improve LR or CSM in patients with a MACIS score (38) of <6.00. It is difficult to extrapolate from this study the importance of tumor size in the final decision regarding surgery, because, as is known, in the MACIS score, age is the major determinant. In the other paper, a different outcome resulted from a study on 1,685 patients. In this work, no difference between LT and TT was discerned regarding CSM, although patients treated by LT had a significantly higher risk of LR. In this paper, the decision concerning the initial surgical intervention was made based on the AMES score (38), which, again, takes age as a primary consideration. On the other hand, another paper [Grant *et al*. (13)], using the AGES (38) score as a basis for stratification risk on a population of 20,600 patients followed at the Mayo Clinic from 1946 to 1975, showed, even for a lower AGES score risk (equal to or less than 3.99), a lower rate of LR for patients treated by TT or near total TT compared to those treated by LT. The author also reported conflicting evidence concerning OS. In fact, none of these last studies specifically tell us anything regarding size specifically as a single factor.

The paper of Nixon *et al*. (14), regarding a retrospective series of 889 patients at Memorial Sloan Kettering Cancer Center, is the only one in which we discern no difference in OS or disease specific survival (DSS) between patients treated by LT or by TT for cancers of different sizes up to 4 cm. However, in this work we glean that, in general, LT was advised only for low-risk patients, and that patients with extracapsular extension were excluded. Moreover, as stated by the authors, there was some bias. Firstly, patients treated by LT tended to be younger (median of <45 years), and also there were more patients with follicular cancer in the LT group.

In the paper of Matsuzu *et al*. (15) on 1,088 patients with PC, the Authors observed a better DSS and a lower LR in patients with a tumor size of <4.0 compared to a PC size of >4.0 cm. However, this study didn't analyze differences regarding size—subgroups, and no comparison was made with patients who underwent TT. The paper also lacked a clear control group.

On the other hand, the paper of Bilimoria (16) on NCDB data (1985–1998) from 52,173 patients with PC showed that LR was lower and OS was better for a tumor size of >1 cm treated by TT compared to LT. Unfortunately, however, this paper doesn't report data on, comorbidity, multifocality, extrathyroidal extension, or completeness of surgical

resection. But we can perhaps suppose that these features were randomly equally distributed.

So, at this point, an analysis of all these papers cited in the ATA guidelines cannot tell us if tumors of <4 cm have the same outcome as with lobectomy. We can only say that, probably, for a very select subgroup of these tumors, LT might possibly be enough. But it is not exactly clear from the literature which risk factors should be considered, and, above all, which of these should be considered in a pre-surgical evaluation of tumors sized <4 cm for the final surgical decision.

All papers cited up to this point are quoted in all the guidelines and consensus, with the exception of the recently published Practical Guide of a Multidisciplinary Panel, where, as stated, the suggestion was to perform a TT for cancers of >2.0 cm. In fact, in this paper the Authors preferred to cite the last paper published regarding this topic [Rajjoub *et al*. (17)]. The data in this work were from the NCDB, and regarded 33,816 patients (from 2004 to 2008), which were followed for at least five years. All patients had TT or LT, and the criterion of inclusion was PC or FC with a size ranging from 1 to 3.9 cm. Analysis was performed for the subgroup 1–1.9 cm and for the subgroup 2–3.9 cm. In those patients affected by PC in this last subgroup, OS was worse if treated by LT.

The Revised Clinical Practise Guidelines on the Management of Thyroid Tumours by the Japanese Association of Endocrine Surgeons allows us to analyze two more Japanese papers which take into account Disease Free Survival (DFS). In the first paper, by Ito (18), on 2638 patients with pT1N0M0, 1037 underwent LT, and elective central compartment dissection was performed in 96% of the whole group. Patients who received more limited thyroidectomy experienced recurrence in the lobe remnant in 1% of cases, and DFS was worse for these patients. The second paper, by Ebina (19), on a group of 1,187 patients, showed the same DFS at 10 years for patients treated by TT or by LT. However, T >3 cm was one of the risk factors for distant recurrence. So, this paper is, in fact, not useful for comparing pT1a and pT1b cases.

Continuing with other works in the literature not specifically quoted in the guidelines, we find the paper of Lee *et al*. (20), which shows no difference in LR or OS between TT and LT in a group of 2014 patients followed for at least 5 years. However, all these patients had micro-PC (<1.0 cm), and both those treated by LT and by TT also had central compartment dissection.

The paper of Liu *et al*. (21), from a single institution database, and regarding 1,087 intermediate-risk cancers according to ATA guidelines, showed no difference in DSS between the groups treated by LT or by TT, but a higher LR was evidenced in patients treated by LT. The two groups were not perfectly matched because the TT group contained a significantly higher number of N1 cases, and the N1 cases in the LT group had a worse DSS, though not reaching statistical significance. No difference in DSS was reported concerning size, nor was size or pN status specified. Also not specified was if the sample size was considered adequate.

The paper of Choi (22), from a single institution database, was a study on 5,396 patients (4,266 PC and 130 FC) who presented cancers ranging from 1- to 4-cm, and with a follow-up of >5 years. Of these patients, 81% underwent TT, while 18.5% were treated by LT. TT was the preferred treatment for patients with clinical bilateral disease and/or extrathyroidal spreading. There was no difference in DSS between the two groups, although recurrence, after univariate and multivariate analysis, was seen to be higher in the group which underwent LT, notably in the 2- to 4-cm group.

Another study, by a Korean team (23), enrolled 2,345 patients with PC. Of these patients, 16.3% underwent LT, while the remainder were treated by TT. Using propensity score matching, patients who underwent LT or TT were matched by age, sex, tumor size, multifocality, and cervical lymph node metastasis in a 1:1 ratio. All patients had ipsilateral central compartment dissection or, where there was a suspicion of pathological lymph-nodes in the contralateral central compartment, bilateral compartment dissection. The primary outcome was DFS, defined as absence of structural disease. No difference in DFS was discerned between the LT and TT groups in either the pT1a group or in the pT1b group. However, recurrence was seen in the contralateral lobe in 45.8% of patients who had received LT. Moreover, and quite surprisingly, lateral-cervical recurrence was higher in the TT groups.

Finally, we should remember the ground-breaking study by Mazzaferri (24), regarding 13,355 subjects, and with a median follow-up of 15 years (extending to as many as 47 years). In this paper the authors showed that, in the long-term, tumors > or =1.5 cm that are not initially metastatic to distant sites had a better prognosis (OS and LR) if treated by TT followed by ^{131}I and thyroid hormone therapy. All the papers just discussed are reported in *Table 2*.

Two other original papers regarding the pathology of DTC can be of some help to our work. The first is a

Table 2 Papers cited in the review in chronological order

	Number of cases	Database	Type of cancer	Specific analysis for size	OS	LT *vs.* TT CSM/DSS	LR
1988 Grant	20,600	Single Institution	PC	No	–	–	In favour of TT Odds ratio >1.0
1993 Mazzaferri	1,088	Single Institution	PC	Yes	For >1.5 cm in favour of TT odds ratio >1.0	–	In favour of TT Odds ratio >1.0
1998 Hay	2,444	Single Institution	PC	No	–	No difference	–
2002 Hay	1,685	Single Institution	PC	No	–	No difference	In favour of TT odds ratio >1.0
2005 Haigh	5,432	SEER	PC	Yes	Subgroups 1–4 cm no difference	–	–
2007 Bilimora	57,173	NCDD	PC	Yes	Size >1 cm in favour of TT odds ratio >1.0	–	In favour of TT odds ratio >1.0
2010 Barney	23,605	SEER	PC	Yes	Subgroups 1–4 cm in favour of TT odds ratio >1.0	–	–
2010 Ito	2,638	Single Institution	PC	Yes	–	–	In favour of TT odds ratio >1.0
2010 Mendelsohn	22,724	SEER	PC	Yes	Subgroups 1–4 cm no difference	–	–
2012 Nixon	899	Single Institution	WDTC	Yes	1–2 *vs*. 2–4 cm no difference	–	–
2013 Lee	2,014	Single Institution	PC	Yes	<1.0 cm no difference	–	<1.0 cm no difference
2014 Adam	61,775	NCDB	PC	Yes	1–2 *vs*. 2–4 cm no difference	–	–
2014 Ebina	1,187	Single Institution	PC	Yes	Not evaluable	Not evaluable	Not evaluable
2014 Matsuzu	1,088	Single Institution	PC	Yes	Not evaluable	Not evaluable	Not evaluable
2018 Choi	2,345	Single Institution	PC	Yes	–	–	No difference
2018 Rajjoub	33,816	NCDB	PC-FC	Yes	1–2 *vs*. 2–4 cm in favour of TT odds ratio >1.0 for PC	–	–
2019 Liu	1,087	Single Institution	PC	No	–	No difference	In favour of TT odds ratio >1.0
2019 Song	5,396	Single Institution	PC-FC	Yes	–	No difference	In favour of TT odds ratio >1.0

PC, papillary cancer; WDTC, well differentiated thyroid cancer; OS, overall survival; CSM, cancer specific mortality; DSS, disease specific survival; LR, local recurrence; SEER, Surveillance, Epidemiology, and End Results Program; NCDB, National Cancer Database.

monocentric study on 500 consecutively enrolled patients, in which a TT was performed in 92.2% of cases (36). Distant metastasis was associated to a size of >2 cm for both PC and FC. In another work (37), on 128 consecutively enrolled PC, all treated by TT, both extensive extracapsular extension and lymph-node metastasis were mostly associated to a tumor size of >2 cm.

As stated, we also analyzed "Expert opinion"; unfortunately, however, we realized that these papers were helpful only in part. In fact, the authors (20-30) express opinions in favor of one or the other surgical approach owing to the fact that, beyond just tumor size, the complex balance of risk factors has also to be considered. Moreover, the expressed opinion depends upon whether OS or DSS or LR is considered, and it also sometimes depends on whether or not the author has given strong consideration to the possible complications coming from TT.

However, the purpose of this review was to try to highlight a theoretical and reasonable size cut-off for planning TT. Although a limitation of our review is that all the quoted studies are retrospective, the analysis of the literature which we conducted may, in our opinion, allow some final practical considerations regarding tumor size as a criterion for the type of surgical treatment to be performed.

Conclusion

From a purely pathological perspective, the potential of DTC spread appears more probable with a tumor size of >2 cm. Theoretically, this is not necessarily proof that these cancers will have a worse prognosis after proper surgical intervention, or that LT is not a suitable treatment. However, tumor spread is, of course, usually more difficult to treat and to cure.

Apart from this consideration, given that the decision regarding the type of treatment to be employed for DTC is linked to clinical outcome, we have to focus on a few clinical endpoints, considering these endpoints also in relation to some of the advantages of LT in terms of post-surgical quality of life and lessened chances of surgical complications. An initial consideration is that an effort must be made not only to prolong OS and CSM or DSS, but also to avoid LR, which can both have a psychological impact on the patient and also damage the noble structures in the neck. Regarding LR, we think that, to date, the literature appears to favor LT for microcarcinoma, is against LT for cancers of a size between 2 and 4 cm, and considers there to be a "grey zone" for a size between 1 and 2 cm. Furthermore, if we consider only OS, again we feel that the data are still inconclusive regarding the possibility of employing LT in cancers of a size between 2 and 4 cm. Papers which do not show a difference in OS in cancers of <4 cm treated by either LT or TT contain major bias, in our opinion. Rather, the literature suggests that the standard "principled" intervention for cancers of >2 cm should be TT, especially in the hands of a skilled surgeon. This does not exclude, however, that further, special, considerations can be made following the histological report, as histology can allow us to define the suitability and adequacy of a given type of surgical intervention. We therefore believe that LT could be considered suitable for cancers between 2 and 4 cm, after a LT has been performed for a nodule and the subsequent histology has shown a PC not very aggressive, or in the case of a minimally invasive FC, and especially in absence of further clinical or anamnestic risks.

The decision regarding the type of initial surgical intervention to be employed must take into account all risk factors and is essential for treatment, with tumor size being, of course, only one aspect to be considered. LT can offer some obvious advantages, especially in absence of any special risk factors. However, our review of the literature suggests to us that patients should be informed that LT for tumors of a size between 2 and 4 cm can be associated with a greater risk of LR, and with a possible reduced OS.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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