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**Are Evidence-Based Guidelines Reflected in Clinical Practice? An Analysis of Prospectively Collected Data of the Italian Thyroid Cancer Observatory**

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(Article begins on next page)

# Thyroid

**Are evidence-based guidelines reflected in clinical practice? An analysis of prospectively collected data of the Italian Thyroid Cancer Observatory (ITCO#1).**

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36 37	Keyword: Thyroid Cancer- clinical, Surgery, Iodine
38 39	Manuscript Keywords (Search Terms): differentiated thyroid cancer, evidence based guidelines, clinical practice, thyroid surgery, radioiodine remnant ablation
40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Abstract: Objectives: The goal of evidence-based practice guidelines is to optimize the management of emerging diseases, such as differentiated thyroid cancer (DTC). The aim of this study was to assess therapeutic approaches for DTC in Italy and to see how closely these practices conformed to those recommended in the 2009 American Thyroid Association (ATA) guidelines. Methods: The Italian Thyroid Cancer Observatory (ITCO) was established to prospectively collect data on thyroid cancers consecutively diagnosed in participating centers (uniformly distributed across the nation). We analyzed data on the initial treatment of all pathologically confirmed DTC cases present in the database from January 1, 2013 (database creation) to January 31, 2016. Results: 1748 patients (77.2% females; median age 48.1 years [10-85]) were enrolled in the study. Most (n=1640, 93.8%) were papillary carcinomas (including 84 poorly differentiated/aggressive variants); 6.2% (n=108) were follicular and Hürthle-cell carcinomas. Median tumor diameter was 11 mm (1-93 mm). Tumors were multifocal in 613 (35%) and presented extrathyroidal extension in 492 (28%) cases. Initial treatments included total thyroidectomy (involving one or two procedures) (n =1726, 98.8%) and lobectomy (n=22, 1.2%). A quarter of the patients that underwent total thyroidectomy had unifocal, intrathyroidal tumors,

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	<p>≤1cm (n=408; 23.6%). Neck dissection was performed in 40.4% of the patients (29.5% had central compartment dissection). Radioiodine remnant ablation (RRA) was performed in 1057 (61.2%) of the 1726 patients who underwent total thyroidectomy: 460 (41.2%) of the 983 classified by 2009 ATA guidelines as low-risk, 570 (87.1%) of the 655 intermediate-risk, and 82 (93.1%) of the 88 high-risk patients (p&lt;0.001). RRA was performed in 44% of the cases involving multifocal DTCs measuring ≤1cm.</p> <p>Conclusions: The treatment approaches for DTCs used in Italy display areas of inconsistency with those recommended by the 2009 ATA guidelines. Italian practices were characterized by underuse of thyroid lobectomy in intrathyroidal, unifocal, ≤1cm DTCs. The use of RRA was generally consistent with risk-stratified recommendations. However, its frequent use in small DTCs (≤1cm) that are multifocal persists despite the lack of evidence of benefit. These data provide a baseline for future assessments of the impact of international guidelines on DTC management in Italy.</p>
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1 **Are evidence-based guidelines reflected in clinical practice?** An analysis of prospectively  
2 collected data of the Italian Thyroid Cancer Observatory (ITCO#1).

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4 Francesco F, Zatelli MC, Rossi R, Puxeddu E, Morelli S, Torlontano M, Crocetti U, Montesano T,  
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9 These data were presented at the 39<sup>th</sup> European Thyroid Association Meeting as oral  
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103 surgery, radioiodine remnant ablation

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109 **Abstract**

110 **Objectives:** The goal of evidence-based practice guidelines is to optimize the management of  
111 emerging diseases, such as differentiated thyroid cancer (DTC). The aim of this study was to assess  
112 therapeutic approaches for DTC in Italy and to see how closely these practices conformed to those  
113 recommended in the 2009 American Thyroid Association (ATA) guidelines.

114 **Methods:** The Italian Thyroid Cancer Observatory (ITCO) was established to prospectively collect  
115 data on thyroid cancers consecutively diagnosed in participating centers (uniformly distributed  
116 across the nation). We analyzed data on the initial treatment of all pathologically confirmed DTC  
117 cases present in the database from January 1, 2013 (database creation) to January 31, 2016.

118 **Results:** 1748 patients (77.2% females; median age 48.1 years [10-85]) were enrolled in the study.  
119 Most (n=1640, 93.8%) were papillary carcinomas (including 84 poorly differentiated/aggressive  
120 variants); 6.2% (n=108) were follicular and Hürthle-cell carcinomas. Median tumor diameter was  
121 11 mm (1-93 mm). Tumors were multifocal in 613 (35%) and presented extrathyroidal extension in  
122 492 (28%) cases. Initial treatments included total thyroidectomy (involving one or two procedures)  
123 (n =1726, 98.8%) and lobectomy (n=22, 1.2%). A quarter of the patients that underwent total  
124 thyroidectomy had unifocal, intrathyroidal tumors,  $\leq 1$ cm (n=408; 23.6%). Neck dissection was  
125 performed in 40.4% of the patients (29.5% had central compartment dissection). Radioiodine  
126 remnant ablation (RRA) was performed in 1057 (61.2%) of the 1726 patients who underwent total  
127 thyroidectomy: 460 (41.2%) of the 983 classified by 2009 ATA guidelines as low-risk, 570 (87.1%)  
128 of the 655 intermediate-risk, and 82 (93.1%) of the 88 high-risk patients ( $p < 0.001$ ). RRA was  
129 performed in 44% of the cases involving multifocal DTCs measuring  $\leq 1$ cm.

130 **Conclusions:** The treatment approaches for DTCs used in Italy display areas of inconsistency with  
131 those recommended by the 2009 ATA guidelines. Italian practices were characterized by underuse  
132 of thyroid lobectomy in intrathyroidal, unifocal,  $\leq 1$ cm DTCs. The use of RRA was generally

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133 consistent with risk-stratified recommendations. However, its frequent use in small DTCs ( $\leq 1\text{cm}$ )  
134 that are multifocal persists despite the lack of evidence of benefit. These data provide a baseline for  
135 future assessments of the impact of international guidelines on DTC management in Italy.

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5 137 **Introduction**

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7 138 The incidence of differentiated thyroid cancer (DTC) is on the rise, and it now represents the  
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9 139 fourth most common cancer in women in Italy (1). Differentiated thyroid cancers generally have an  
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11 140 excellent prognosis, with a 5-year survival rate of 98.1% (2) and low rates of recurrence (3). The  
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13 141 challenge today is to develop increasingly individualized treatment strategies with due emphasis on  
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15 142 quality of life. A first step toward this goal involves classification of cases according to the risk of  
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17 143 recurrence, as proposed by international evidence-based guidelines, such as those issued regularly  
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19 144 by the American Thyroid Association (ATA) (4, 5). A recent study showed that cases of thyroid  
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21 145 cancer managed in accordance with evidence-based guidelines are associated with better outcomes  
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23 146 (6). Little information is available on current practices in the treatment of thyroid cancer in Italy and  
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25 147 the degree to which they are affected by international evidence-based guidelines.

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27 148 To address these issues, we recently conducted a retrospective analysis of prospectively  
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29 149 collected cases of DTC in the web-based thyroid cancer database set up by the Italian Thyroid  
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31 150 Cancer Observatory (ITCO) foundation, a network of physicians, scientists, and patients with  
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33 151 interests in thyroid cancer (<http://www.itcofoundation.org>). The principal aims of the foundation  
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35 152 are: 1) to facilitate and promote the development of collaborative research projects on various  
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37 153 aspects of thyroid cancer, ranging from its molecular biology and epidemiology to its treatment and  
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39 154 long-term management; 2) to create a network of thyroid tumor experts willing to share and  
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41 155 exchange knowledge and tools for patient care; and 3) to provide scientific support for healthcare  
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43 156 policy makers. The ITCO network is expanding steadily. It currently includes 36 centers involved  
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45 157 in the care of thyroid cancer patients, which are distributed throughout the Italian national territory.  
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47 158 They include tertiary referral centers operating at the national level as well as smaller hospital-based  
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49 159 units with local or regional catchment areas.

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3 160 We retrospectively analyzed ITCO data on 1748 patients with DTC who were operated on in  
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5 161 Italy between January 1, 2013 and January 31, 2016. Our aims were to characterize approaches to  
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7 162 the treatment of DTC patients used during this period, in terms of the extent of thyroid surgery and  
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9 163 the use of radioiodine remnant ablation (RRA), and to see how consistent these practices were with  
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11 164 the ATA Guidelines for the Management of Thyroid Cancer available at that time (i.e., those issued  
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14 165 in 2009) (4).

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## 167 **Methods**

168 The ITCO's web-based database was opened in 2013 at the Thyroid Cancer Center of the  
169 University of Rome La Sapienza (the network's Coordinating Center), and it was subsequently  
170 expanded to include data from centers belonging to the newly founded ITCO. It now includes  
171 prospectively collected data on over 3500 Italian patients with histologically confirmed diagnoses  
172 of differentiated, medullary, or anaplastic thyroid cancer. Cases are included in the database at the  
173 time of primary treatment in the reporting ITCO center or, if the patient was operated on elsewhere,  
174 at the time he/she began follow-up in the reporting center. (Cases are ineligible for inclusion if  
175 contact with the reporting center began more than 12 months after primary treatment.) Each case  
176 record includes information on patient demographics and biometrics, circumstances of the  
177 diagnosis, tumor pathology, surgical and radioactive iodine treatments, and the results of periodic  
178 follow-up examinations. Sensitive data are encrypted, and the database is managed in an  
179 anonymous fashion by a dedicated team of expert biostatisticians, who are also responsible for all  
180 statistical analyses of the data.

181 For the purposes of the present study, we reviewed the database and selected consecutive  
182 cases satisfying both of the following inclusion criteria: 1) histological diagnosis of DTC, including  
183 papillary, follicular, and poorly differentiated tumors, as well as their variants; 2) registration in the  
184 ITCO database between January 1, 2013 and January 31, 2016 (date of publication of the 2015

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3 185 version of the American Thyroid Association Guidelines for the Management of Thyroid Cancer)  
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5 186 (5). Cases were excluded if the database record lacked complete information on the initial treatment  
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7 187 or tumor pathology.  
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10 188 For each case, we recorded the following information: *Initial treatment*: thyroid surgery  
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12 189 procedure (total thyroidectomy, thyroid lobectomy, or lobectomy followed by completion  
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14 190 thyroidectomy); cervical lymph node dissection (none, central compartment dissection, lateral  
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16 191 compartment dissection, central and lateral compartment dissection). For patients who had  
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18 192 undergone total thyroidectomy, we also recorded the use of RRA (performed or omitted). *Risk of*  
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20 193 *recurrence*: The risk category was calculated by the study team in accordance with the 2009 ATA  
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22 194 Guidelines (4). Classification was based on the data available at the time of the initial treatment,  
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24 195 with the following exceptions: 1) In cases involving lobectomy followed by completion  
25  
26 196 thyroidectomy, we considered pathologic data on tissues collected during both surgical procedures;  
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28 197 2) in patients who underwent RRA, post-treatment whole body scintigraphy findings were excluded  
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30 198 from risk assessments. *Aggressive PTCs*: These included solid, insular, tall-cell, columnar-cell,  
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32 199 hobnail-cell, sclerosing, and poorly differentiated variants as well as PTCs with foci of invasion of  
33  
34 200 intratumoral vessels. *Follicular thyroid cancers (FTC) and Hürthle cell carcinomas*: These tumor  
35  
36 201 types were combined and analyzed separately from other DTCs. FTCs were classified as *widely*  
37  
38 202 *invasive* (presence of extensive vascular or capsular invasion or *minimally invasive* (absence of such  
39  
40 203 extensive invasion) (7).  
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#### 47 **Statistical analysis**

48  
49 206 In descriptive analysis, continuous variables were expressed as medians with interquartile  
50  
51 207 ranges (IQR) and nominal variables as numbers and percentages. Difference between categoric  
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53 208 variables were calculated with the chi-square test; differences between continuous variables were  
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209 assessed with the Mann Whitney test. All statistical analyses were performed with SAS software  
210 (SAS Institute, Inc.).

211

## 212 **Results**

213 We analyzed a total of 1748 cases of DTC enrolled in the ITCO database between January 1, 2013  
214 and January 31, 2016. The cases were reported by a total of 28 ITCO centers (Supplementary Table  
215 1). The population characteristics are summarized in **Table 1**. The median age at diagnosis was 48.1  
216 years (range 10 – 85), and the majority of patients were women. Over 90% of the tumors were  
217 PTCs—classic forms [n=1556] or aggressive variants [n=84]. The remaining 108 (6.2%) were  
218 FTCs (n=80) or Hürthle cell carcinomas (n=27).

219

## 220 *Surgical management*

221 On the basis of strong evidence, the 2009 ATA guidelines recommended total or near-total  
222 thyroidectomy for all thyroid cancers except for unifocal intrathyroidal tumors with maximum  
223 diameters of  $\leq 1$  cm. In the ITCO cohort, total or near-total thyroidectomy was performed on almost  
224 all patients (97.9%), including 408 with unifocal intrathyroidal tumors measuring  $\leq 1$  cm. Thirty-six  
225 (2.1%) patients were treated with thyroid lobectomy, but 14 of these patients later had completion  
226 thyroidectomies.

227 Lymph node dissection was performed in 706 patients (40.4% of the total cohort) and  
228 involved the central compartment alone in 516 patients, both central and lateral compartments in  
229 160, and the lateral compartment alone in 30. **Lymph node metastases were found in 383 (54%) of**  
230 **the 706 patients who underwent lymph node neck dissection and in 157 (83%) of the 190 that**  
231 **underwent lateral neck dissection.**

232 The 22 patients treated with thyroid lobectomy alone were older (median age 50.7 years).  
233 One had a Hürthle cell carcinoma measuring 28 mm; the other 21 had PTCs. Most PTCs in this

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3 234 group were classified as low-risk (19/21, 86.4%) according to the 2009 ATA guidelines. In the  
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5 235 remaining two cases (13.6%), the recurrence risk was considered intermediate owing to the  
6  
7 236 metastatic involvement of a single central-compartment lymph node in one and evidence of  
8  
9 237 vascular invasion in the other. All but four of the 22 patients in this group had unifocal tumors, and  
10  
11 238 in all but six, maximum tumor diameters measured  $\leq 1$  cm (range 1 -15 mm).  
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14 239

16 240 *Use of RRA*

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18 241 Of the 1726 total thyroid resections (including those preceded by lobectomy), well over half  
19  
20 242 (1057, 61.2%) were followed by RRA. Patients in this subgroup were significantly younger than  
21  
22 243 those who did not undergo ablation (median: 46.3 years [IQR 36.5-57.4] vs. 51.1 [41.0-60.3]; p  
23  
24 244 <0.001). RRA was done after 41.2% (405/983) of the thyroidectomies performed on patients  
25  
26 245 considered at low risk for recurrence, 87.1% (570/655) of those performed on patients at  
27  
28 246 intermediate risk, and 93.1% (82/88) of those done in the high-risk group (p<0.001). The median  
29  
30 247 dose of radioiodine administered to low-risk patients was 50 mCi (IQR 50-100), and it was  
31  
32 248 significantly lower than the median doses recorded for the intermediate- and high-risk groups (100  
33  
34 249 mCi, IQR 70 -100 and 100 mCi, IQR 100 - 100 respectively) (p<0.001). This observation is  
35  
36 250 consistent with the 2009 ATA recommendation (no. 36), which advocates (on the basis of fair  
37  
38 251 evidence) the use of the lowest activity of radioiodine capable of producing successful remnant  
39  
40 252 ablation, especially in low-risk patients. Preparation for RRA involved thyroid hormone withdrawal  
41  
42 253 in 636 (60.2%) of the 1045 cases in which this information was available. Recombinant human  
43  
44 254 TSH (rhTSH) was used in the remaining 409 (38.7%) cases—that is, 207 (51.1%) of the 405 low-  
45  
46 255 risk patients who underwent RRA, 176 (30.9%) of the 570 in the intermediate-risk group, and 26  
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48 256 (31.7%) of the 82 at high-risk for recurrence. The guidelines specified that, on the basis of strong  
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50 257 evidence, either method could be used to prepare patients for RRA.  
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3 259 **Consistency with the 2009 ATA Guidelines**

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5 260 These data were then analyzed in light of the ATA's 2009 recommendations on the use of  
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7 261 RRA in *subgroups* of patients within each risk category (4). The 1619 patients undergoing  
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9 262 thyroidectomies for PTCs (**Table 2**) and the 107 patients who had thyroidectomies for FTCs or  
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11 263 Hürthle cell carcinomas (**Table 3**) were analyzed separately. The results are presented along with  
12  
13 264 the recommendations contained in both the 2009 and 2015 ATA guidelines. The former were used  
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15 265 for the primary analysis since they were the reference point during the treatment period considered  
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17 266 in the study (2013-2016); practices in the cohort were also analyzed to see how they corresponded  
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19 267 with the 2015 recommendations, which were published after the study period.

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21  
22 268 *Patients with PTCs.* As shown in **Table 2**, in 2009 the ATA issued an unequivocal  
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24 269 recommendation *against* the use of RRA only for low-risk patients harboring intrathyroidal PTCs  
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26 270 with maximum diameters of  $\leq 1$  cm and nonaggressive histology, even when multiple lesions are  
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28 271 present. This decision was based on fair evidence showing that this intervention does not improve  
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30 272 important health outcomes or that its potential harms outweigh its expected benefits. In the ITCO  
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32 273 cohort, RRA was performed on fewer than one out of five patients with unifocal PTCs  $\leq 1$ cm  
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34 274 (16.8%) but almost half of those whose microcarcinomas were multifocal (44%).

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37 275 At the other end of the spectrum, unequivocal recommendations *for* the use of RRA (albeit  
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39 276 based on evidence with different strength ratings) were made for all high-risk PTC patients, as well  
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41 277 as for specific subgroups at intermediate- or low-risk of recurrence. In the ITCO cohort, 96.3%  
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43 278 (53/55) of the high-risk patients were treated in accordance with the strong recommendation for  
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45 279 RRA. In the intermediate-risk group, the ATA recommendation for RRA in patients with lymph  
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47 280 node metastases was based solely on expert opinion, but it nonetheless corresponded to the  
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49 281 treatment used in the vast majority (91.6%; 241/263) of cases. Use of RRA appeared to be unrelated  
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51 282 to the location and number of the metastatic lymph nodes: it was done in 87.7% of patients with  
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53 283 metastatic involvement of  $<5$  central-compartment lymph nodes, 83.3% of those with involvement  
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3 284 of  $\geq 5$  central compartment nodes, and 87.6% of those metastatic disease restricted to the lateral  
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5 285 compartments. In the low-risk category, RRA was recommended only for patients with tumors  
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7 286 larger than 4 cm. Although this decision was based on fair evidence of benefit, treatment in the  
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9 287 ITCO cohort coincided with this recommendation in only 70.6% (12/17) of cases.

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11 288 For the PTC patients in the remaining low- and intermediate-risk subgroups, the ATA  
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13 289 recommended *selective* use of RRA, based on the clinical judgment of the practitioner and  
14  
15 290 consideration of “risk-modifying” factors, such as the presence of multiple tumor foci, aggressive  
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17 291 histology, or vascular invasion. In the low-risk category, selective use of RRA was advised for  
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19 292 tumors ranging in size from  $>1$  cm to 4 cm. In the ITCO cohort, RRA was done in most cases of  
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21 293 this type, although the frequency was slightly higher in the presence of multifocal disease (65.6%  
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23 294 vs. 57.7% of patients with unifocal disease). As for the use of RRA in patients at intermediate risk,  
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25 295 the frequency ranged from 74.9% in patients with minimal extrathyroidal extension  
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27 296 (microscopically evident) to over 90% in the presence of aggressive histology.

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29 297 *Patients with FTCs or Hürthle cell carcinomas.* As shown in **Table 3**, the ATA  
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31 298 unequivocally recommended RRA for FTCs that were widely invasive and for Hürthle cell  
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33 299 carcinomas. Both decisions were based on expert opinion alone. Use of RRA in the ITCO cohort  
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35 300 was consistent with these recommendations in all cases of widely invasive FTC and in most cases  
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37 301 of Hürthle cell carcinomas (77.8%; 21/27). Selective use was recommended for minimally invasive  
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39 302 FTCs. RRA was used to treat over 80% of patients with such tumors (as well as two others with  
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41 303 FTCs whose invasiveness was not classified).

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43 304 Multivariate analysis showed that the likelihood of undergoing RRA increased significantly  
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45 305 with recurrence risk class (OR 10.2 and 17.8 for intermediate- and high-risk patients, 95% CI 7.80-  
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47 306 13.21 and 7.70-41.20 respectively) and decreased with advancing age (OR 0.93, 95% CI 0.90-0.96,  
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49 307  $p < 0.0001$ ).

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3 309 **Discussion**

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5 310 The aim of this study was to assess surgical approaches and use of RRA in Italy for  
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7 311 treatment of DTC and to see how closely these practices conformed to those advocated by the ATA  
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9 312 in 2009. The treatment period analyzed—January 2013 through January 2016—was considered  
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11 313 appropriate for assessing the effects of the 2009 ATA guidelines in Italy. By October 2009, these  
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13 314 guidelines had been translated into Italian and were available for consultation by the Italian medical  
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15 315 community. On the whole, the ATA recommendations reflected a clear preference for more  
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17 316 conservative management of selected DTCs in terms of surgery and RRA. In both cases, the real-  
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19 317 life clinical practice we documented in Italy during this period was somewhat less selective than  
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21 318 that recommended.

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25 319 This was especially true of surgical management. The DTCs were almost invariably treated  
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27 320 with total or near-total thyroidectomy, regardless of the estimated risk for recurrence. Overuse of  
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29 321 total thyroidectomy in the ITCO cohort may be due in part to the high prevalence of bilateral  
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31 322 multinodular thyroid disease in Italy (10). Unfortunately, the ITCO database records contain no  
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33 323 information about nodules in the lobe without cancer that could confirm or disprove this hypothesis.  
34  
35 324 In experienced hands, the rate of permanent complications of total thyroidectomy can be very low  
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37 325 (11). A frequent preference for thyroidectomy has also been documented in the United States.  
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39 326 Recent surveys indicate that up to 60% of physicians caring for thyroid cancer patients and involved  
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41 327 in the National Cancer Database studies still advocate total/near-total thyroidectomy for small  
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43 328 tumors, in spite of recommendations favoring lobectomy in these cases (12, 13). This preference  
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45 329 was also strongly associated with a tendency to overuse RRA in low-risk patients (12).

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49 330 There was a more evident trend towards selective use of RRA. Ablation was restricted to  
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51 331 roughly 60% of the patients who underwent thyroidectomy, including all those at high-risk for  
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53 332 recurrence. Its use in the low- and intermediate-risk cases was generally associated with the  
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55 333 presence of lymph node metastases and/or aggressive histotypes, as recommended. However, its

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3 334 frequent use for microPTCs that were multifocal (44% vs. 16.8% of unifocal microPTCs) was in  
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5 335 clear contrast with the 2009 ATA guidelines. This trend may stem in part from some reports  
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7 336 indicating that these tumors are more likely to recur than their unifocal counterparts (14, 15),  
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9 337 although other studies have failed to confirm this difference, even among microPTCs harboring  
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11 338 *BRAF* mutations (16). Differential risk notwithstanding, RRA has been shown to have virtually no  
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13 339 impact on the likelihood of microPTC recurrence (14, 15). Again, the preferences observed in the  
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15 340 ITCO cohort have also been documented in the United States. Few of the American thyroid  
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17 341 surgeons surveyed felt that RRA was appropriate for unifocal PTCs measuring < 1 cm, but up to  
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19 342 40% advocated its use when the microPTC was multifocal (12).

22 343 Many low-risk patients in the ITCO cohort were still being treated with high activities of  
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24 344 <sup>131</sup>I. However, the median <sup>131</sup>I dose used in the low-risk subgroup was lower (50 mCi) than those  
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26 345 administered in intermediate- and high-risk cases (100 mCi), which is consistent with 2009 ATA  
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28 346 recommendations and with increasing awareness of the higher rate of side effects associated with  
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30 347 high <sup>131</sup>I activities (17). The efficacy and safety of lower-activity of radioiodine (30 mCi) in low  
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32 348 risk patients were also confirmed during the study period by the results of two European  
33  
34 349 randomized clinical trials (ESTIMABL and HiLo) (8, 9).

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36 350 Recombinant human TSH, rather than thyroid hormone withdrawal, was used for RRA preparation  
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38 351 in nearly a half the low-risk patients. The use of rhTSH is consistent with the growing concern with  
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40 352 quality of life and the need to avoid whenever possible unpleasant symptoms provoked by  
41  
42 353 withdrawal of thyroid hormone therapy (18), and the efficacy of this approach has been re-  
43  
44 354 confirmed by the results of the ESTIMABL and HiLo trials (8, 9). The heterogeneity of its use in  
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46 355 real-life clinical practice may also reflect lack of uniformity in terms of local, regional, or national  
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48 356 healthcare budgets and/or the availability of tools and/or technology required for guideline  
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50 357 implementation. Such factors might partly explain the widespread use of hormone withdrawal in  
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52 358 our cohort. The cost of rhTSH is undeniably a consideration. However, cost-effectiveness data  
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3 359 published a year before the treatment period considered in our study had already demonstrated that  
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5 360 the higher cost of rhTSH could be outweighed by savings related to the shorter hospital stays it  
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7 361 allows (19). This is an important consideration in a country like Italy, where RRA is always  
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9 362 performed on an in-patient basis due to a strict policies on radioprotection and the cost of in-patient  
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11 363 procedures are covered by the public healthcare system. Healthcare budgets and the number of  
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13 364 nuclear medicine units can vary considerably between one region of Italy and another.

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16 365 Implementation of practice guidelines also requires time. Publication is inevitably followed  
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18 366 by a “latency period” during which the recommendations have to be read, considered, and discussed  
19  
20 367 by clinicians, healthcare policymakers, and patient advocacy groups, and this lag can be particularly  
21  
22 368 significant for recommendations that fall into “gray zones” where the evidence is less clear-cut.

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25 369 In addition, for international guidelines like those of the ATA, an accurate and validated  
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27 370 translation of the recommendations must also be produced to ensure their widespread diffusion  
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29 371 throughout the local community, where knowledge and understanding of English vary. Language  
30  
31 372 barriers are likely to be lower in certain settings, such as metropolitan and/or academic healthcare  
32  
33 373 facilities, and this might favor earlier access to and understanding of recommendations drafted in  
34  
35 374 English. Unfortunately, we were not able to analyze ATA guideline implementation in our cohort  
36  
37 375 by treatment facility type or location because the reporting center and the center where the patient  
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39 376 was treated were not always the same.

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43 377 The results of our study were also analyzed in light of *evolving* trends as reflected in the  
44  
45 378 2015 ATA guidelines on DTC management. In most respects, the 2015 edition confirms or  
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47 379 strengthens the positions adopted in the 2009 version. For example, the recommendation for the use  
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49 380 of thyroid lobectomy—apparently rejected by most Italian thyroid surgeons, even for treatment of  
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51 381 *microscopic* unifocal intrathyroidal tumors—was broadened in the 2015 edition to include all  
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53 382 unifocal intrathyroidal tumors up to 4 cm in size. The ATA continues to strongly recommend RRA  
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55 383 in patients at high risk for recurrence, and this position is rarely disputed. In contrast, its persistent

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3 384 rejection of RRA for intrathyroidal microcarcinomas without aggressive histology, including those  
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5 385 that are multifocal, is, as we have seen, another area in which real-life and recommended practices  
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7 386 display substantial divergence in Italy [Table 2] and elsewhere (12)-(13). It will be interesting to  
8  
9 387 see whether and how practices in the ITCO network change in light of the increasingly strong  
10  
11 388 evidence supporting this “no” in the 2015 guidelines. In cases characterized by intermediate-risk,  
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13 389 RRA use rates in Italy were high (Table 2). This trend was fully in keeping with the 2009 guidelines  
14  
15 390 on patients with lymph-node metastases in general, but less so with the 2015 recommendations on  
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17 391 this group. The latter are more articulated, and RRA is no longer considered mandatory in certain  
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19 392 subgroups (e.g., patients with fewer than five microscopic nodal metastases).  
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22  
23 393 In summary, our study reveals discrete areas in the management of DTC in which daily  
24  
25 394 clinical practice seems to diverge from the internationally endorsed guidelines issued by the ATA.  
26  
27 395 Extensive surgical treatment is still widely used for DTC in Italy, regardless of disease stage and  
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29 396 risk status. Use of radioiodine remnant ablation appeared to be more consistent with the 2009 ATA  
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31 397 risk stratification. These data provide a useful baseline for future analyses of ITCO data aimed at  
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33 398 assessing the impact of international guidelines on real-life clinical management of DTCs in Italy.  
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Table 1. Characteristics of the study cohort

<b>No. patients</b>	1748
<b>Age (years) - median (IQR)</b>	48.1 (38.1-58.8)
<b>Sex - N (%)</b>	
-Female	1348 (77.2)
-Male	399 (22.8)
<b>Thyroid cancer diagnosis - N (%)</b>	
Presurgical	1407 (69.7)
<b>Surgical approach- N (%)</b>	
Total/near-total thyroidectomy	1712 (97.9)
Lobectomy	22 (1.2)
Lobectomy + completion thyroidectomy	14 (0.9)
<b>Neck dissection - N (%)</b>	
- Not done	1042 (59.6)
- Central neck dissection alone	516 (29.5)
- Central and lateral neck dissection	160 (9.2)
- Lateral neck dissection alone	30 (1.7)
<b>Histology - N (%)</b>	
- Papillary thyroid cancer	1640 (93.8)
- Follicular thyroid cancer or Hürthle cell carcinoma	108 (6.2)
<b>Tumor size (mm) - median (IQR)</b>	11.0 (6.0-19.0)
<b>Tumor foci - N (%)</b>	
- Not specified	4 (0.2)
- Unifocal	1131 (64.8)
- Multifocal-laterality not specified	27 (1.5)
- Multifocal-unilateral	165 (9.4)
- Multifocal-bilateral	421 (24.1)
<b>Extrathyroidal extension - N (%)</b>	
- None	1256 (71.9)
- Microscopic (T3)	435 (24.9)
- Macroscopic (T4a)	53 (3.0)
- Macroscopic (T4b)	4 (0.2)
<b>Lymph node status - N (%)</b>	
Nx	508 (29.1)
N0	857 (49.0)
N1a	233 (13.3)
N1b	150 (8.6)
<b>Number of metastatic lymph nodes - median (IQR)</b>	3.0 (1.0-6.0)
<b>2009 ATA risk - N (%)</b>	
- Low	1002 (57.3)
- Intermediate	657 (37.6)
- High	89 (5.1)

Abbreviations: ATA: American thyroid association; IQR: inter quartile range

Table 2. Use of RRA in patients with PTC treated with total or near total thyroidectomy

ATA risk category TNM		Description	RRA used in ITCO cohort n (%)	RRA recommended by ATA guidelines (strength of evidence*)		Estimated risk of recurrence
				2009	2015	
ATA low risk N= 921 (56.9%)			358 (38.9)	Selective use	Selective use (WR, LQ)	
T1a, N0/x N= 399	Tumor size: ≤1 cm Unifocal	67 (16.8)	No (E)	No (SR, MQ)	≈1-2%	
T1am, N0/x N=161	Tumor size: ≤1 cm Multifocal	71 (44)	No (E)	No (WR, LQ)	≈4-6%	
T1b-T2, N0/x N=222	Tumor size: >1-4 cm Unifocal	128 (57.7)	Selective use (I)	No	≈5%	
T1b-T3, N0/x N=122	Tumor size: >1 cm Multifocal	80 (65.6)	Selective use *	Selective use	≈5%	
T3 size N=17	Tumor size: >4 cm	12 (70.6)	Yes (B)	Selective use		
ATA intermediate risk N=643 (39.7%)			559 (86.9)	Selective use	Selective use (WR, LQ)	
T3 mETE N=167	Microscopic ETE	125 (74.9)	Selective use (I)	Selective use (consider age)	≈3-8%	
T1-3, N1 N=263	Metastatic lymph nodes No aggressive histology	241 (91.6)	Yes (C)	-		
T1-3, N1a N=163	< 5 metastatic lymph nodes in the central compartment	143 (87.7)	-	Selective use (consider size)	≈5%	
T1-T3, N1a N=24	≥5 metastatic lymph nodes in the central compartment	20 (83.3)	-	Insufficient data	≈20%	
T1-T3, N1b N=97	metastatic lymph nodes in the lateral compartment	85 (87.6)	-	Selective use	≈20%	
T1-T3, N0/x/1 N=213	Aggressive histology (including N1)	193 (90.6)	Selective use ** (B)	Selective use	≈30%	
ATA high risk N=55 (3.4%)			53 (96.3)	Yes (A, B)	Yes (SR, MQ)	

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Abbreviations: ATA: American Thyroid Association; RRA: radioiodine remnant ablation; PTC: papillary thyroid cancer; ETE: extrathyroidal extension.

\*Strength of evidence: A: strong evidence for; B: fair evidence for; C: expert opinion favors; E: fair evidence against; I: neither for nor against; WR: weak recommendation; LQ low-quality evidence; MQ: moderate-quality evidence; SR: strong recommendation.

\*\*Modifying factors: aggressive histology, multifocality and vascular invasion.

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**Table 3. Use of RRA in patients with FTC or Hürthle cell carcinoma treated with total or near-total thyroidectomy**

ATA risk TNM	RRA used in ITCO cohort n (%)	RRA recommended by ATA guidelines (strength of evidence)		Estimated risk of recurrence
		2009	2015	
<b>FTC/HCC N=107</b>	87 (81.3)			
<b>Minimally invasive N= 59</b>	48 (81.4)	Selective use	Selective use	≈2-3%
<b>Widely invasive N= 16</b>	16 (100)	Yes (C)	Yes	≈30-55%
<b>Hürthle cell carcinoma N=27</b>	21 (77.8)	Yes (C)	-	
<b>FTC NOS N=5</b>	2 (40)	-	-	

Abbreviations: ATA: American thyroid association; RRA: radioiodine remnant ablation; C: expert opinion favors; FTC: follicular thyroid cancer; NOS: not otherwise specified

Supplementary Table 1. List of the ITCO centers involved in the study

Region	N. of centers
<b>North of Italy</b>	<b>14</b>
<b>Bologna:</b>	1
- Ospedale di Bentivoglio, Department of Endocrinology, Unità Operativa Semplice	
<b>Brescia:</b>	1
- Università degli Studi di Brescia, Spedali Civili, Nuclear Medicine Unit	
<b>Ferrara:</b>	1
- Azienda Ospedaliero Universitaria S. Anna, Endocrine Unit	
<b>Livorno:</b>	1
- Azienda Sanitaria Locale Nord Ovest Toscana, Unità Operativa di Endocrinologia	
<b>Milano:</b>	2
- IRCCS Istituto Auxologico Italiano, Division of Endocrine and Metabolic Diseases	
- Università degli Studi di Milano, Department of Pathophysiology and Transplantation	
<b>Novara:</b>	1
- Università del Piemonte Orientale, Endocrinology, Department of Translational Medicine	
<b>Padova:</b>	1
- University-Hospital of Padua, Endocrinology Unit, Department of Medicine-DIMED	
<b>Parma:</b>	1
- University of Parma, Department of Medicine and Surgery	
<b>Torino:</b>	4
- University of Turin, Department of Medical Sciences,	
- University of Turin, Department of Oncology, Division of Endocrinology and Metabolism, Humanitas-Gradenigo Hospital	
- Mauriziano Umberto I Hospital, Division of Endocrinology, Diabetology and Metabolism	
- University of Turin, Division of Endocrinology, Diabetology and Metabolism, Department of Medical Sciences, Molinette Hospital, A.O.U. Città della Salute e della Scienza di Torino	
<b>Verona:</b>	1
- University of Verona, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine	
<b>Center of Italy</b>	<b>8</b>
<b>Latina:</b>	1
- University of Rome Sapienza, Polo Pontino, Dipartimento di Scienze e Biotechnologie Medico-Chirurgiche	
<b>Perugia:</b>	1
- University of Perugia, Department of Medicine	
<b>Pisa:</b>	2
- University of Pisa, Geriatrics Unit, Department of Clinical & Experimental Medicine	
- University of Pisa, Department of Clinical and Experimental Medicine	
<b>Roma:</b>	4
- University of Rome Sapienza, Department of Internal Medicine and Medical Specialties, Policlinico Umberto I	
- University of Rome Sapienza, Department of Nuclear Medicine, Policlinico Umberto I	
- University of Rome Sapienza, Ospedale S. Andrea	
- Fondazione Policlinico Gemelli, Catholic University, Division of Endocrinology and Metabolic Diseases and Division of Endocrine Surgery	

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3	<b>South of Italy</b>	<b>6</b>
4	<b>Catania:</b>	<b>1</b>
5	- University of Catania, Dipartimento di Medicina Clinica e Sperimentale	
6	<b>Matera:</b>	<b>1</b>
7	- Ospedale di Tinchi-Pisticci, Unità di Endocrinologia	
8	<b>Napoli:</b>	<b>1</b>
9	- University of Naples Federico II, Department of Clinical Medicine and Surgery	
10	<b>Palermo:</b>	<b>1</b>
11	- Cervello Hospital, Division of Endocrinology	
12	<b>Salerno:</b>	<b>1</b>
13	- Division of Endocrinology	
14	<b>San Giovanni Rotondo – Foggia:</b>	<b>1</b>
15	- Ospedale Casa Sollievo della Sofferenza-IRCCS, Department of Medical Science	
16	<b>Total</b>	<b>28</b>
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