Radioiodine ablation after thyroidectomy could be safely abandoned or postponed in selected stage I papillary thyroid carcinoma patients of low-risk group: an observational prospective study

Abstract. Background. The European Thyroid Association consensus for the management of differentiated thyroid cancer (2006) suggested to avoid radioactive iodine (RAI) after thyroidectomy in patients with unifocal microcarcinoma (≤ 1 cm) with no extension beyond the thyroid capsule and without lymph node metastases. As the new data was collected and the risk stratification was revised, in 2022 the same recommendation was expanded to the patients with microcarcinoma and central neck lymph node involvement. The American Thyroid Association guidelines (2015) advocated no RAI ablation after hemi- or total thyroidectomy for thyroid cancer less than 1 cm with 5 and less micrometastases up to 2 mm in central neck lymph nodes as this strategy has no negative impact on the disease prognosis. In low-risk patients, no sufficient evidence of the obligatory postsurgical radioiodine ablation has been yet demonstrated. The aim of our study was to reveal whether RAI after thyroidectomy can be abandoned or postponed until the disease progression is confirmed in low-risk patients.

Materials and methods. Two groups of patients (30 per group, 60 in total) with papillary microcarcinoma Т1N1a (5 and less level VI micrometastases up to 2 mm) were observed during a 5-year follow-up. In the first group, patients received 100 mCi (3.75 GBq) I\textsubscript{131} shortly after total thyroidectomy while in the second group, postponed RAI was applied when progression signs were observed (elevated serum thyroglobulin level and US/CT suspected findings) after thyroid surgery. Results. After 5 years, no significant difference between groups was observed regarding post-RAI local recurrences (one in the first group and two in the second group) and/or distant metastases (t-test, p = 0.58). All cases of neck recurrences were treated with subsequent surgical excision, with no new data of progression within the specified follow-up. Conclusions. RAI adjuvant therapy for papillary thyroid carcinoma Т1N1a may not be necessary for patients with small number of level VI micrometastases. Local and distant metastases revealed during the careful follow-up by thyroglobulin level elevation and when using visualization techniques can be effectively treated with postponed RAI therapy and/or surgery.

Keywords: papillary thyroid carcinoma; low risk; thyroidectomy; postponed radioiodine ablation

Introduction

The European Thyroid Association (ETA) consensus for the management of differentiated thyroid cancer (2006) suggested to avoid radioactive iodine (RAI) after thyroidectomy in patients with unifocal microcarcinoma (≤ 1 cm) with no extension beyond the thyroid capsule and without lymph node metastases [1]. As the new data was collected and the risk stratification was revised, in 2022 the same recommendation was expanded to the patients with microcarcinoma and central neck lymph node involvement. The American Thyroid Association (ATA) guidelines in 2015 advocated no RAI ablation after hemi- or total thyroidectomy for thyroid cancer less than 1 cm with 5 and less micrometastases up to 2 mm in central neck lymph nodes as this strategy has no negative impact on the disease prognosis [2, 3].

Papillary thyroid carcinoma (PTC) is one of the most prognostically beneficial thyroid malignancies [4, 5]. It is known that low-risk stage I PTC carries minimal risks of either
local recurrence (2–3%) or cancer-related death (less than 1%). However, concurrent negative prognostic factors might have a significant influence on oncological outcomes [6].

Curative surgery remains standard of care, but adjuvant treatment approaches, such as RAI ablation, are controversial. In advanced or high-risk cases of PTC, RAI may improve the progression-free survival [7]. However, it is yet controversial if an adjuvant RAI can improve oncological outcomes for low-risk tumors [8]. Besides questionable survival benefits, RAI can cause short- or long-term adverse events, such as gonadal dysfunction and secondary malignancy development, though the evidence level of these effects is low [9]. It seems to us an important issue to define proper patient subgroups with low-risk PTC who could have no potential treatment benefit from RAI and for whom this method may not be applied or may be postponed.

According to the 2022 ETA guidelines, RAI treatment is not indicated in differentiated thyroid cancer < 1 cm (uni- or multifocal) [2]. ATA defines the low-risk category of patients wider and here the following tumor pathology features are regarded: intrathyroidal PTC without vascular invasion, with or without small volume lymph node metastases (clinical N0 or ≤ 5 pathologic N1a, all < 0.2 cm in largest dimension); intrathyroidal encapsulated follicular variant of PTC or intrathyroidal well-differentiated follicular carcinoma with capsular or minor vascular invasion (<4 vessels involved); intrathyroidal papillary microcarcinomas that are either BRAF WT or BRAF mutated [10]. Thus, the benefit of postoperative 131I therapy remains a matter of intensive scientific debate and no definitive consensus has been reached on this point.

The aim of our study was to reveal whether RAI after thyroidectomy can be abandoned or postponed until the disease progression is confirmed in low-risk patients.

Materials and methods

A prospective observational study on the safety of delayed post-thyroidectomy RAI was conducted. An informed consent form was signed by the patients.

From January 2018 to January 2023, 60 patients (18 males, 42 females; mean age 46.2 ± 10.2 years, range 20–78 years) were enrolled. All of them had PTC stage classified as T1N1a (5 and less central neck micrometastases up to 2 mm). The follow-up period was 5 years. In the first group (n = 30), all patients received 100 mCi (3.75 GBq) I 131I shortly after total thyroidectomy (up to 4–5 weeks). Seven patients in the second group (n = 30) were treated with RAI in case of disease progression signs such as gradual thyroglobulin (TG) level elevation of more than 1 mg/ml and US/CT/scintigraphy evidence of a new lesion after thyroid surgery. Continuous variables were reported as means ± SD, categorical variables were reported as frequencies or percentages.

The data were compared using the Fisher exact test and the Wilcoxon rank test. P < 0.05 was considered as a significant difference. The chi-square test was applied to compare the categorical, non-numerical parameters (gender, recurrence). The continuous numerical data (age, TG values) with normally distributed continuous parameters were compared with the paired t-test.

Results

With regard to the baseline characteristics of patients and tumor pathology features, no statistically significant difference was observed in the groups, as shown by the p-value (Table 1). None of the patients enrolled has developed any relevant surgical complications that could impinge the further treatment strategy. All patients in the RAI group received the above-mentioned adjuvant treatment within 4–5 weeks after thyroidectomy under hypothyroidism induced by thyroxine withdrawal.

The patients in the group I were substituted with levothyroxine in a dosage calculated according to a formula 1.7–1.8 × weight (kg) starting from the first postoperative day. RAI was administered to 7 patients of the group II when laboratory and radiological disease progression signs were diagnosed (gradually increased serum unstimulated TG during 6–12 months and rising above 1 ng/ml; appearance of new suspected neck lymph nodes with positive TG washout after fine-needle aspiration).

The treatment outcomes at the 5-year follow-up are presented in Table 2. No case of local recurrence in the thyroid bed (growth of residual or recurrent malignant tissue after surgery) was detected. As for the regional lymph node recurrence endpoint, no difference was found between the groups (2/30 patients in group I and 3/30 patients in group II had neck lymph node involvement within one year after surgery; p = 0.521). In all cases, the affected lymph nodes were subsequently successfully excised.

Neck lymph node recurrences correlated with growing serum TG level in all patients. In 3 cases of TG increase to 1.1–1.7 mg/ml among patients of group II, no abnormal RAI uptake has been detected after adjuvant I 131I therapy. Among other 4 cases, neck lymph nodes metastases were detected in 3 participants and one patient had solitary pulmonary metastasis without neck lymph node involvement.

By comparing the distance metastases rate, no statistical difference was found between groups as well. In one patient (29-year-old man) in surgery-only group, a solitary lung metastasis was revealed in scintigraphy at 15 months follow-up.

### Table 1. Baseline characteristics of patients and tumor pathology features

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Primary postsurgery RAI group</th>
<th>RAI-postponed group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size, mm</td>
<td>9.4 ± 3.5</td>
<td>8.1 ± 4.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Number of lymph node metastases</td>
<td>3.2 ± 1.2</td>
<td>3.8 ± 1.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>46.7 ± 11.4 (20–78)</td>
<td>43.2 ± 9.7 (22–71)</td>
<td>0.2</td>
</tr>
<tr>
<td>Female-to-male ratio</td>
<td>22 : 8</td>
<td>20 : 10</td>
<td>0.58</td>
</tr>
<tr>
<td>Pretreatment TG-Ab, iU/ml</td>
<td>13.6 ± 8.2</td>
<td>17.3 ± 9.2</td>
<td>0.105</td>
</tr>
<tr>
<td>Pretreatment TG, ng/ml</td>
<td>29.8 ± 12.2</td>
<td>22.6 ± 9.5</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Note: p < 0.05 shows the absence of any statistical difference when the two groups’ parameters are compared.
Table 2. The treatment outcomes at the 5-year follow-up

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary postsurgery RAI group</th>
<th>RAI-postponed group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG 1 month after surgery, ng/ml</td>
<td>0.62 ± 0.12</td>
<td>0.71 ± 0.53</td>
<td>0.37</td>
</tr>
<tr>
<td>TG 6 months after surgery, ng/ml</td>
<td>0.79 ± 0.24</td>
<td>0.84 ± 0.11</td>
<td>0.113</td>
</tr>
<tr>
<td>TG 5 years after surgery, ng/ml</td>
<td>0.64 ± 0.29</td>
<td>0.75 ± 0.23</td>
<td>0.109</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>0/30</td>
<td>0/30</td>
<td>-</td>
</tr>
<tr>
<td>Regional metastases</td>
<td>2/30</td>
<td>3/30</td>
<td>0.65</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>0/30</td>
<td>1/30 (lung)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

(TG started to rise gradually from 0.32 to 3.4 mg/ml from month 6 to month 15). Therapeutic dose of 131I (3.75 GBq) was administered 4 weeks after thyroxine withdrawal. Excellent response to RAI treatment has been achieved: at the control scintigraphy and CT after 11 months, no RAI uptake and structural abnormality were detected. Serum unstimulated TG dropped down to 0.1 mg/ml six months after RAI adjuvant therapy. No significant negative impact on the quality of life or survival was detected in the patient diagnosed with metastatic disease.

Discussion

Despite the possible benefits of postoperative RAI, this treatment modality is associated with body radiation exposure; therefore, its administration should be justified in terms of oncological outcomes (overall survival or disease-free survival and quality of life). Accurate risk stratification for patients with differentiated thyroid cancer is pivotal while choosing the best treatment strategy [11].

RAI is widely administered as an adjuvant therapy for PTC recurrence [12, 13]. There is no conclusive data whether or not first RAI administration for PTC recurrence is less effective compared to those who already received adjuvant RAI treatment for primary tumor [14]. If second adjuvant RAI would be required after previous failure of adjuvant treatment, overall dosage escalation would be required. That might increase the risk of short- and long-term adverse events.

That is why routine adjuvant RAI might be considered as overtreatment regarding its miserable impact on long-term outcomes. On the other hand, overall dosage of adjuvant RAI shows no increased risk for radiation therapy adverse events or secondary malignancy development in elderly people. However, among people younger than 45 years, RAI administration was associated with 23% increased risk of solid cancer and 92% increased risk of leukemia relative to those who did not receive such a therapy [15].

J. Ahn et al. [16] has demonstrated that timing of the first RAI had no clinical impact in patients with low-risk PTC. The authors concluded that the clinical decision for RAI might be determined > 3 months after total thyroidectomy considering other prognostic factors.

Our study data show that the first RAI can be considered upon the diagnosis of disease progression. This approach might be safe for low-risk differentiated thyroid cancer patients in terms of oncological results. In one case in the group, where no scheduled RAI was administered after surgery, a distant metastasis in lung was detected after 24 months; however, it had no impact on patient’s quality of life or further disease progression. Given that our study was observational, it has certain limitations and further randomized studies could provide more evidence on the discussed topic. Moreover, the new evolving data demonstrate that susceptibility and related benefits of adjuvant RAI after thyroidectomy in thyroid cancer may be linked to certain genetic tumor profile (BRAF, RAS and TERT mutation status). Considering this fact, the histological features may no longer play the sole role in decision making regarding the mentioned treatment option [17, 18].

Conclusions

While RAI benefits in low-risk patients with differentiated thyroid cancer have not been indisputably demonstrated and potential long-term adverse effects cannot be excluded, it seems reasonable to avoid standard RAI administration after thyroidectomy and restrict its application to chosen cases, where the evidence of disease progression is defined.

References


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