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ORIGINAL ARTICLE

Outcomes of surgery and radioiodine treatment for neck recurrence in papillary thyroid cancer

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Summary

Purpose: *Persistent/recurrent disease in the neck is frequent in patients with papillary thyroid cancer (PTC). The goal of this study was to evaluate the efficacy of the reoperation and radioiodine (RAI) treatment for persistent/recurrent disease after the initial treatment.*

Methods: *A total of 30 patients (13 M/17 F) with PTC were enrolled in this study. All had been submitted to total thyroidectomy for PTC and subsequently to reoperation for local persistent/recurrent disease. All had received RAI, before and/or after reoperation. The mean age at initial thyroidectomy and cancer diagnosis was 41.4±15.2 years. Initial T status was T1 in 22 cases (73.3%), T2 in 4 cases (13.3%) and T3 in 4 cases (13.3%). Initial N status was N0 in 2 cases (6.6%), N1 in 15 cases (50%) and Nx in 13 cases (43.3%).*

Results: *Reoperation reduced the mean stimulated thyroglobulin (stimTg) serum concentration from 76.1±165.5 ng/mL to 20.1±28.8 ng/mL, p=0.002. The RAI treatment provided to 19 patients after reoperation reduced further the stimTg values from 28.6±32.4 ng/mL after reoperation, to 11.3±20.4 ng/mL, p=0.003. According to the dynamic risk stratification after the reoperation 7 patients (23.3%) had excellent response, 4 (13.3%) had biochemically incomplete response, 9 (30.0%) had indeterminate response and 10 (33.3%) had still structural incomplete response.*

Conclusion: *Surgery for local persistent/recurrent disease in papillary thyroid carcinoma reduces tumor burden, improves the biochemical and structural disease. Administration of therapeutic RAI after lymph node resections appears to further improve biochemical disease.*

Key words: *Papillary thyroid cancer, RAIU treatment, recurrence of thyroid cancer*

Introduction

Over the last years an increased prevalence in the differentiated thyroid cancer is observed worldwide [1] as well in Greece [2] and the increase is mostly observed in papillary than in follicular thyroid cancer [3].

The 10-year and 20-year survival remains high and reaches >90% for papillary thyroid cancer, whereas the 10-year survival for follicular thyroid cancer reaches 80%. Local persistent/recurrent disease affects survival [4] hence, it is important to

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diagnose and treat as soon as possible local recurrence, in an effort to render patients free of disease.

In the present study we evaluated the efficacy of the reoperation and RAI treatment for persistent/recurrent disease after the initial treatment of DTC.

Methods

This study was conducted in the Department of Endocrinology of a tertiary cancer center, Metaxa Cancer Hospital in Piraeus, Greece. The study was approved by the scientific committee of the hospital.

A total of 30 patients (13 male; 43.3% and 17 female; 56.7%) were enrolled in this study. Inclusion criteria were: initial treatment with a total thyroidectomy with or without neck dissection and reoperation with a curative intent for recurrent/persistent differentiated thyroid cancer; evaluation of cure by serum stimTg measurement and neck imaging; and follow-up of at least 3 months.

All the patients underwent a total thyroidectomy as primary treatment. Initial operations were performed from 1998 until 2017. A total of 17 patients (56.6%) had therapeutic (12 patients) or prophylactic (5 patients) lymph node dissection during the initial operation.

After primary treatment patients were followed every 3 to 12 months with physical examination, serum Tg measurement under LT4 therapy (suppressed Tg) or after TSH stimulation (stimTg). Only stimTg values were used in this study, since these are considered more sensitive for the detection of persistent/recurrent disease. All patients were antithyroglobulin antibodies negative at the time of reoperation and remained so during follow up.

TSH was elevated either with hormone withdrawal or recombinant human TSH administration. Imaging screening included neck ultrasonography in all patients and when necessary, RAI-Whole Body Scan, CT or MRI.

Local disease was considered as persistent if diagnosed within 1 year after the initial operation and recurrent if diagnosed thereafter.

The type of surgical procedure at reoperation was *en bloc* compartment-oriented neck dissection or focused dissection in case of recurrence in a previously dissected compartment.

Disease status

Disease status was determined after the primary treatment, after reoperation, and at the last assessment. Disease status was defined according to American Thyroid Association (ATA) Guidelines 2015 [5] for dynamic risk stratification, as follows:

1. Excellent response defined by serum stimTg≤1 ng/mL, with normal neck imaging.
2. Biochemical incomplete response, defined by serum stimTg≥10 ng/mL with normal neck imaging.
3. Structural incomplete response, defined by abnormal neck imaging findings, either confirmed by FNB, or lymph node features highly suspicious for infiltration by the tumor (round shape, calcifications, peripheral vascularity).
4. Indeterminate response, defined by serum stimTg between 1-10 ng/mL and/or the presence of nonspecific imaging abnormalities.

Twenty one (70%) patients had received RAI treatment for ablation of thyroid remnant before reoperation and 19 (63.3%) received RAI after reoperation.

Measurement of Tg levels

The Tg was measured with IRMA. The kit was hTg[^{125}I] IRMA Kit, Isotop Institute of Isotopes Ltd, 1535 Budapest Pf: 851.

Statistics

Wilcoxon rank test and binary logistic regression were used for statistical analyses. Data were analysed using SPSS analytical software 25 (SPSS Inc.-IBM Corp., New York, NY, USA). Differences in p values of less than 0.05 were considered significant.

Results

Initial characteristics

The clinical characteristics of the 30 patients are presented in Table 1. All patients underwent total thyroidectomy, followed by 1 reoperation in the neck in 24 patients, by 2 reoperations in 4 patients and by 3 reoperations in 2 patients.

Table 1. Initial patient and disease characteristics

Initial characteristics	*n=30 patients (%)* *n (%)*
Male / Female	13 (43.3) / 17 (56.7)
Mean age of thyroidectomy and at cancer diagnosis ±SD (years)	41.4±15.2 (range 16-72, median 39)
Mean diameter ±SD of larger tumor (cm)	2.1±2.0 (range 0.2-9.0, median 1.5)
Tumor foci	
Unifocal	14 (46.7)
Multifocal	16 (53.3)
pT at initial diagnosis	
T1a	9 (30.0)
T1b	13 (43.3)
T2	4 (13.3)
T3	4 (13.3)
pN at initial diagnosis	
N0	2 (6.6)
N1	15 (50)
Nx	13 (43.3)
Median number of resected N at initial operation	26 (range 1-60)
Median number of metastatic N at initial operation	4 (range 1-8)
pM at initial diagnosis	
M0	30 (100)

Right or left lateral neck procedures were performed in 19 patients (63.3%), bilateral in 6 patients (20.0%), central and left or right lateral procedure in 3 patients (10%), and central and bilateral in 2 patients (6.6%).

The mean patient age±SD of initial thyroidectomy and cancer diagnosis was 41.4±15.2 years (range 16 to 72 years, median 39 years). Seven patients (23.3%) had aggressive subtype of papillary carcinoma, mostly of the tall variant (6 patients, and 1 with the diffuse sclerosing variant). At the initial operation there was invasion or rupture of the thyroid capsule by the tumor in 9 patients (30.0%), minimal extrathyroidal extension of the cancer in 9 (30.0%), and microscopic positive margins in 4 patients (13.3%).

According to the TNM classification system: Initial T status was T1 in 22 cases (73.3%) (9 [30.0%] with T1a and 13 [43.3%] with T1b), T2 in 4 cases (13.3%) and T3 in 4 cases (13.3%). Initial N status was N0 in 2 cases (6.6%), N1 in 15 cases (50%) and Nx in 13 cases (43.3%). M status was M0 for all the patients.

The mean time between the diagnosis of the cancer (initial operation) and the detection of local persistent/recurrent disease was 1.8±2.6 years (median 1.0 year, range 0.3-12 years). In 18 patients (60.0%) the local disease was considered persistent and in 12 (40.0%) recurrent (Table 1).

The mean time between the reoperation for the local disease and the last follow up was 3.8±3.4 years (median 2.0, range 0.3-14).

The whole time of follow up since the initial operation was 5.6±3.6 years (median 4.0, range 1.0-14).

In 17 patients (56.6%) the recurrence was diagnosed after a fine needle aspiration biopsy of the suspicious lymph nodes and in the rest of the patients by typical ultrasound features of infiltrated lymph nodes, such as round shape, calcifications, cystic degeneration and peripheral vascularity.

The median number of resected lymph nodes at reoperation was 26 (range 1-60) and the median number of metastatic lymph nodes was 4 (range 1-13). The lymph node ratio at reoperation was 0.36±0.33 (median 0.24, range 0.04-1.00).

In 9 patients (30.0%) there was local recurrence from the tumor, in addition to metastasis to regional lymph nodes.

Biochemical findings

The reoperation reduced significantly the stimTg values. The mean stimTg value at the time of diagnosis of the persistent/recurrent disease was 76.1±165.5 ng/mL, versus 20.1±28.8 ng/mL after the reoperation (p=0.002).

A total of 24 patients (80%) showed a reduction of stimTg after the reoperation between 13 and 99%, (mean 68.7%±27.3, median 66.0%, range 13-99%). Two patients (6.6%) showed no change of Tg levels and 4 patients (13.3%) showed an increase of Tg levels between 30-253%. A thorough screening of these latter 4 patients with multiple imaging methods did not reveal any distant metastasis, other than persistence of local disease in 2 patients, of whom 1 died due to uncontrollable local disease progression, and no evidence of structural disease in the other 2 patients.

Classifying the patients after reoperation according to the dynamic risk stratification, as proposed by the ATA[5], 7 patients (23.3%) had excellent response, 4 (13.3%) had biochemically incomplete response, 9 (30.0%) had indeterminate response and 10 (33.3%) had still structural incomplete response.

A total of 19 patients (63.3%) received RAI treatment after the reoperation. Among them, 9 (47.3%) showed uptake only in the neck in the post therapy whole body scanning, while 10 (52.6%) patients showed no uptake at all. All patients but 3 showed an additional percentage decrease of stimTg levels of 68.7%±26.6% (median 76.6%, range 20.0%-99.7%), whereas the mean stimTg value was reduced significantly from 28.6±32.4 ng/mL after reoperation and before the RAI treatment to 11.3±20.4 ng/mL, after the RAI treatment (p=0.003). Examining separately the 14 patients who had already ablated the thyroid remnant before the reoperation, and received a second dose of RAI after the reoperation, there was still, a significant decrease in the stimTg levels after the second RAI treatment, from 27.8±30.7 ng/ml to 12.6±22.5 ng/ml (p=0.023).

Disease status at the last follow up

At the last follow up, after 3.8±3.4 years (median time 2.0 years, ranging between 0.3 and 14 years) from reoperation, 6 more patients turned to excellent response from indeterminate or biochemically incomplete response, all of whom had received RAI after reoperation, while 1 patient, who had also received radioiodine, turned from excellent response to indeterminate response.

Of the 10 patients who were classified as structural incomplete response after reoperation, and of whom 9 received RAI, at last follow up 9 were still structural incomplete response and 1 had turned to biochemical incomplete response.

In the whole, at last follow up, 12 patients (40%) showed excellent response, 2 (6.7%) had biochemically incomplete response, 7 (23.3%) had indeterminate response, and 9 (30.0%) had still structural incomplete response (Figure 1).

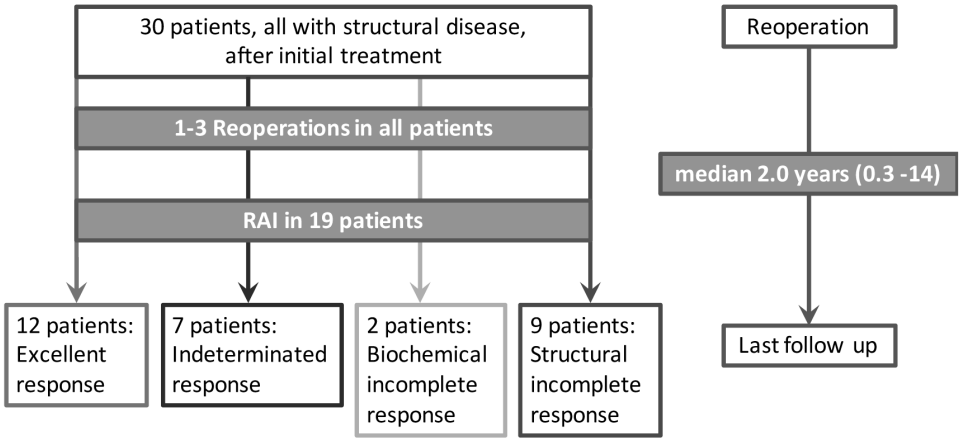

Figure 1. Dynamic risk stratification of the patients after reoperation and RAI treatment.

We used binary logistic regression to test for factors that had possibly impacted on stimTg levels <1 ng/ml or ≥1 ng/ml at last follow up, introducing as covariates the age at diagnosis of PTC (at initial operation), the gender, the dissection or not of infiltrated lymph nodes during the initial operation, and the ratio of infiltrated to dissected lymph nodes during the reoperation. The only significant factor was the dissection of infiltrated lymph nodes during the initial operation which decreased probability for stimTg levels <1 ng/ml by 3 times at the last follow up (B=-3.1, p=0.033).

Discussion

Reports from many countries around the world confirm an increasing incidence of differentiated thyroid cancer in the last three decades, mostly of the papillary type. The trend concerns all age groups [6], both genders [7] and all tumor sizes [4], not only the micropapillary cancer. Till now it was considered that mortality remains stable despite this tremendously increased incidence. A recent study though, from a large database, ascertained a worrisome, slight but significant, increase in incidence-based mortality, mostly of patients with advanced-stage PTC [4].

Local persistent/recurrent disease, especially in the regional lymph nodes, is not rare in PTC and most study results converge in that it negatively affects survival [4,8-11]. The initial treatment of choice is surgery aiming at dissecting structural disease. A varying degree of outcomes is reported in several studies, due to heterogeneous patient population, various numbers of surgical procedures, different Tg cut offs and imaging methods used [12-16]. Most of these studies refer the results of reoperation as "biochemical response" using cut offs, for stimulated or not Tg, from <2 ng/ml to <0.5 ng/ml, or the percentage of decrease in Tg levels. They report post operation outcome for "structural disease" using various imaging methods. According to these criteria biochemical response is achieved in 21-66%, and the absence of recurrent structural disease after one or more reoperations is reported from 51 to 100% [12-16].

We evaluated the outcome of 30 patients who have undergone one to three neck reoperations for locally recurrent/persistent PTC. All patients had initially been treated with total thyroidectomy and 70% of the patients had subsequent remnant ablation before reoperation. A second dose of RAI was administered in 46.6% of the patients after reoperation.

We used the ATA dynamic stratification of risk, so results of both treatments could be evaluated in a more objective and generally conceived manner. We also used only stimTg for the evaluation of outcome, in order to increase the sensitivity of patients' classification after reoperation and RAI treatment.

Only a minority of our patients (23.3%) was rendered from structural incomplete response to excellent response with reoperation. A recent report [17] that also used ATA dynamic risk stratification reported a "complete" response in 63% of patients. It must be noted, however, that in the above report, as criterion for classification was used either stimulated or suppressed Tg, and is well known that suppressed Tg <1ng/ml may be compatible with regional or even distant metastasis [18]. In fact, after reoperation, 20% of our patients had suppressed Tg <1ng/ml but stimTg ≥1ng/ml and so, they were classified as indeterminate response. Nevertheless, reoperation in our patients succeeded in decreasing the percentage of structural disease, the one with the worst prognosis, by 66.6%.

We found that RAI treatment decreased significantly stimTg levels, though it failed to further reduce considerably the percentage of patients with

structural incomplete response. Only one patient with structural incomplete response was rendered to biochemical incomplete response after RAI treatment. The patients that seemingly had benefit from RAI were mostly those with biochemical incomplete response and indeterminate response after reoperation. However, most of the patients that received RAI after reoperation, even if thyroid remnant had previously been ablated, showed an additional significant decrease of stimTg levels. The fact that only 43.7% of the patients showed uptake of RAI on the neck does not exclude the therapeutic action of RAI in micrometastatic foci, not detected by post therapy scanning [19]. Infiltrated lymph nodes may be as small as≤5 mm [20] and therefore, not detected by imaging. In any case, biochemical incomplete response indicates virtually structural disease not visualized by currently available means, but apparently in some cases, still responsive to RAI. From this point of view, RAI treatment does have a complementary role to surgery in the management of patients with persistent/recurrent disease.

The majority of recurrences in PTC are diagnosed within the first 5 years after initial therapy [21]. Most of the studies examining the results of reoperation for local disease report a short median time for the detection of persistent/recurrent disease, between 8 months and 3 years [12-16] , as is the case in our study also. Most of our patients who were subjected to lymph node dissection during the initial operation had a therapeutic, not a prophylactic dissection. This raises a concern regarding the extent of the initial operation that we recommend and reintroduces the controversy of prophylactic versus therapeutic neck dissection of lymph nodes [22,23]. In many patients with PTC, cervical lymph node metastasis will have a long, indolent course [24], without affecting substantially their quality of life. Though, if the goal is to get rid of the disease as many as possible patients, we should opt in favor of a detailed preoperative mapping of cervical lymph nodes [25], prophylactic dissection of lymph nodes in the central compartment [26] and therapeutic dissection of the lateral compartments [27] at the initial operation.

Additionally, the malignant potential of the tumor appears to be at least equally important predictor for persistent/recurrent disease, and even so, for the results of its management. We found that infiltrated lymph nodes, present already at the initial operation (an indirect, though still indicator of tumors aggressiveness), affected negatively the probability for stimTg levels <1 ng/ml, after reoperation and RAI treatment. Conceivably, more aggressive tumors tend to become clinically significant earlier than more indolent tumors [28]. ATA, in an effort to include clues of tumor aggressiveness in the risk stratification, has introduced the number and size of metastatic lymph nodes dissected during the initial operation, as indicators for risk stratification, based solely on statistical data [29]. However, a statistical evidence, as significant as it might be, it can't always be linearly equated to biological significance. For example, what would be the biological difference between 4, 5 or 6 metastatic lymph nodes? Or, between lymph nodes of 3 or 2 cm in size? In fact, most of our patients had stage tumor T1, yet they had local persistent/recurrent disease, indicating that the current indices of tumor aggressiveness predict patients' outcome inadequately, and genetic markers, such as mutations of the BRAF gene, can explain only part of the malignant behavior of a PTC [29,30].

In conclusion, the type of the initial operation and the aggressiveness of the tumor appear to determine the most the results of treatment for local persistent/recurrent disease.

The limitations of our study are its retrospective nature which is inevitable, and the small number of patients. Its advantage is the use of the recent, generally accepted classification for the ongoing risk stratification of patients with differentiated thyroid cancer, for which data in the literature are scarce.

Conclusion

Reoperation for loco-regional recurrence in patients with PTC rarely rids the patient completely from the disease. Still, it decreases significantly the percentage of patients with the worst prognosis, those with structural disease. RAI treatment may have a further beneficial impact on disease burden. The extent of the initial operation and the biological potential of the tumor appear important factors for the final outcome, after reoperation and RAI treatment for local disease.

Conflict of interests

The authors declare no conflict of interests.

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