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Research paper

Low-risk papillary thyroid carcinoma patients who underwent near-total thyroidectomy without prophylactic central compartment lymph node dissection and were ablated with low-dose 50mCi RAI had excellent 10-year prognosis

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ABSTRACT

BACKGROUND: The current trend in the management of low risk differentiated thyroid carcinoma is to follow less aggressive strategies. OBJECTIVE: To assess the long-term morbidity and mortality outcomes of low-risk papillary thyroid carcinoma (PTC) patients undergoing minimal intervention. DESIGN: We retrospectively analyzed 137 patients with low-risk PTC (stage I: n=77; stage II: n=60). Of these patients, 107 (Group 1) had macro-PTC and underwent near-total thyroidectomy and received postoperatively 50mCi RAI. The remaining 30 patients (Group 2) had micro-PTC (<1cm) and were treated only by means of near-total thyroidectomy. RESULTS: The median follow-up for Group 1 patients was 10 years (range: 3-30). At 1-year evaluation, 8 patients of Group 1 had indeterminate or incomplete biochemical response, of whom 4 had also incomplete structural response to initial therapy. Only 1 of 4 patients with structural incomplete response underwent cervical lymph node dissection and then received an additional dose of 100mCi RAI. The remaining 7 patients received only an additional dose of 100mCi RAI. These patients have been continuously followed till the present time with no recurrences or deaths (median follow-up: 17.5 years; 3-30 years). At 15 years, 2 patients of Group 1 experienced biochemical recurrence and they received 100mCi RAI. Three patients of Group 2 experienced recurrence, with 2 receiving 50mCi RAI and 1 undergoing cervical lymph node dissection with 50mCi RAI. CONCLUSIONS: Patients with low-risk macro-PTC treated by means of near-total thyroidectomy without PCCLND and receiving postoperatively a low dose of 50mCi RAI have excellent long-term prognosis.

Key words: Low risk, Prognosis, Papillary thyroid carcinoma, RAI, Recurrence, Prognosis

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INTRODUCTION

Papillary thyroid carcinoma (PTC) is an indolent disease with minimal mortality in low-risk patients.[1,2] Approximately 60-90% of patients with PTC had microscopic regional lymph node metastases at the time of thyroidectomy.[3,4] The clinical significance of the presence of microscopic infiltrated lymph nodes remains controversial.[5] Prophylactic central compartment lymph node dissection (PCCLND) is the dissection of clinically uninvolved cervical lymph nodes of the central compartment.[6] According to the 2015 ATA guidelines, PCCLND is not recommended in patients with PTC and small noninvasive tumors (T1 and T2), nor in clinically node-negative and most follicular cancers.[7] In addition, these ATA guidelines for initial risk stratification suggest the need to identify more than 5 small volume cervical lymph node metastases to upgrade the classification of low-risk of recurrence in PTC patients. However, in patients older than 45yr, the identification of even one microscopic metastatic lymph node changes the classification of these patients from stage I to stage III if the infiltrated lymph node is located in the central department, or to stage IVa if it is laterally located.[7]

Recent reports have demonstrated that the risk of persistent disease or local recurrence in PTC patients with metastatic lymph nodes is increased if there are more than 5 positive nodes or if extranodal extension exists.[5,8,9] Most suspicious lymph nodes detected after thyroidectomy for papillary thyroid carcinoma remained stable over several years with only a small proportion (20%) experiencing slow growth of 3-5 mm during 3 to 5 years observation without causing any apparent local complications.[10] These data indicate that the identification of a few microscopic lymph nodes during prophylactic central lymph node dissection may overestimate recurrence risk and mortality, also leading unnecessarily to more aggressive management and intensive follow-up of these patients.[11] Moreover, patients treated by means of total thyroidectomy and PCCLND, when compared to those treated only via total thyroidectomy, exhibited more complications, which included temporary or permanent hypocalcemia or recurrent laryngeal nerve dysfunction.[12,13]

Studies suggest that the dose as well as the potential benefits of postoperative RAI administration in low-risk patients with differentiated thyroid cancer (DTC) is a matter of debate. Two randomized controlled multicenter trials have found that low-dose radioiodine ablation with 30mCi with recombinant TSH, when compared to higher doses of 100mCi RAI with thyroid hormone withdrawal, in low- to intermediate-risk DTC patients had similar outcomes of successful ablation within 1 year.[14,15] In an extensive literature review it was also found that low-risk DTC patients treated with RAI ablation did not experience improved disease-specific survival.[16] It is possible, however, that RAI ablation may be beneficial in decreasing disease recurrence.[17] Post-surgical RAI ablation after thyroidectomy is not routinely recommended for low-risk patients by the current ATA guidelines. These guidelines indicate that low-risk PTC patients, defined as those with intrathyroidal PTC of any size without aggressive histology of up to 5 small volume metastatic cervical lymph nodes, are not candidates for post-surgical RAI ablation following thyroidectomy.[7]

Currently, the number of low-risk PTC patients has been dramatically increased due to the widespread availability of improved diagnostic strategies that include high-resolution ultrasound screening.[18] It appears that the current trend for managing these patients is the minimal intervention approach. Our main aim was to retrospectively investigate the long-term outcomes of low-risk patients with PTC who were treated with minimal intervention, such as near-total thyroidectomy without PCCLND and ablated with a low dose of 50mCi RAI.

PATIENTS AND METHODS

We retrospectively analyzed 137 patients (26 men; 111 women) with a mean age of 46.9±11.9 years who were diagnosed with low-risk PTC (stages I n=77 & II n=60, according to the 7th edition AJCC/TNM classification system for DTC) while visiting our outpatient clinic from 1985 to 2010 and who were followed clinically until 2014. All patients were followed for a median of 10 years, with a range of 3-30 years. Eligibility criteria included the following: 1) near-total or total thyroidectomy without PCCLND, 2) no clinical evidence of cervical nodal metastasis preoperatively or intraoperatively or by imaging, 3)

no evidence of distant metastases, 4) no extrathyroidal invasion of the tumor and no aggressive histological subtypes, 5) normal titers of autoantibodies against thyroglobulin (anti-Tg). Out of our total sample, 107 patients received ablation with 50mCi RAI under thyroid hormones withdrawal and were then given suppression TSH therapy (Group1) (Table 1). The remaining 30 patients were diagnosed with micropapillary thyroid carcinoma (MPTC) and were not ablated (Group 2) (Table 1). Group 2 was followed for a median of 6.5 years (range 2-16 years). The evaluation of the response to the initial therapy as excellent or biochemically/structurally incomplete or indeterminate was done according to the recently published ATA guidelines 2015.[7] Briefly, excellent response denoted that 1 year following postoperative RAI administration the patient had negative imaging and either suppressed levels of thyroglobulin (Tg) <0.2ng/mL, or stimulated (by withdrawal or with recombinant TSH) to <1.0ng/mL with anti-Tg within normal range; biochemically incomplete denoted the presence of suppressed Tg ≥1ng/mL or stimulated Tg ≥10ng/mL or rising anti-Tg antibodies levels; structurally incomplete denoted the presence of structural or functional evidence of disease; indeterminate response denoted that there were nonspecific findings on imaging studies, faint uptake in the thyroid bed on RAI scanning, non-stimulated Tg detectable, but <1ng/mL and stimulated Tg detectable but <10ng/mL or anti-Tg antibodies stable or declining in the absence of structural or functional disease.

Group 1 patients were clinically assessed at 6-month intervals for the first 3 years and were then assessed annually for T4, TSH, serum Tg and anti-Tg, and underwent neck ultrasound. During follow-up, if Tg remained suppressed we did not carry out a stimulation test for Tg. After 2003, we considered Tg levels suppressed if they were less than <0.2ng/mL.

Group 2 patients were followed by measuring serum Tg and anti-Tg and neck ultrasound annually: evaluation 'recurrence' denoted those cases where the patients were found to have a progressive increase in serum concentration of Tg or a finding of pathological neck ultrasound.[7]

Table 1. Clinicopathological features of low-risk PTC patients of Group 1 (with macro-PTC and ablated with 50mCi RAI) and Group 2 (with micro-PTC and non-ablated)

	Total	Group 1	Group 2
n	137	107	30
Age, mean±SD (years)	46.9±11.9	46.6±12.4	47.7±10
Male/Female	26/111	19/88	7/23
Stage I	77	47	30
Stage II	60	60	0
Tumor size, mean±SD (mm)		24.1±14.5	5±2.6

Assays

Until 2003, serum Tg and anti-Tg were measured by the commercial IRMA radioimmunoassay kit (DiaSorin, Inc., Saluggia, Italy). The detection limit of the assays was 0.8 ng/ml for Tg and 5 IU/ml for anti-Tg. The CVs for the Tg ranged from 2.6% to 3.5% (intra-assay) and 5% to 7.8% (inter-assay) and for the anti-Tg from 3.6 to 4.4% (intra-assay) and 6.7% to 11.6% (inter-assay), respectively.

From 2004 until today, Tg and anti-Tg have been measured by electrochemiluminescencent technology (ECL) with an automatic immunoassay analyzer (Roche Diagnostics Modular E170 Immunoassay System, Hitatchi). The detection limit of the assays was 0.04 ng/ml for the Tg hormone and 10 IU/ml for the anti-Tg Abs. The CVs for Tg ranged from 1.0% to 13.9% (intra-assay) and 1.1% to 21.0% (inter-assay), and for anti-Tg antibodies from 1.2% to 5.5% (intra-assay) and 2.6% to 9.2% (inter-assay), respectively.

Statistics

All values are expressed as mean±SD or median (range). The endpoints of the study were the response of low-risk DTC patients to initial therapy and the rate of recurrence or death during the follow-up period. The response to the initial therapy was examined in the first year of evaluation. None of our patients died during follow-up but some of them had a recurrence. The probability of recurrence during follow-up was examined by the Kaplan-Meier survival analysis. In the survival curve, the horizontal axis shows the time to event; the vertical axis shows the probability of recurrence. Any point on the survival curve shows the probability that a patient will not have experienced

the recurrence by that time. For the statistical analysis IBM SPSS statistics 20 was used.

RESULTS

The median follow-up for Group 1 patients was 10 years (range: 3-30 years). In Group 1, 99 patients (92.5%) had excellent response to therapy 1 year after RAI administration. The remaining 8 patients had either biochemically and/or structurally incomplete response or indeterminate response to therapy. Four out of 8 had only biochemically incomplete (n=1) or indeterminate response (n=3) and received an additional dose of 100mCi RAI (Table 2). The remaining 4 had locoregional structurally incomplete response and biochemically either incomplete (n=3) or indeterminate response (n=1). Of these 4 patients, 3 received only an additional dose of 100mCi RAI and 1 underwent cervical lymph nodes dissection and received 100mCi RAI (Table 2). These 8 patients have been continually followed until the present time, with no recurrence or deaths (median follow-up: 17.5; range: 3-30 years). At 15 years only 2 patients of Group 1 had local recurrence and received 100mCi RAI (Table 3, Figure 1). None of the Group 1 patients developed distant metastases or died during the follow-up period.

Patients of Group 2 were followed for a median follow-up of 6.5 years (range: 3-15 years). Of the 30 patients in this group, 3 had progressively increas-

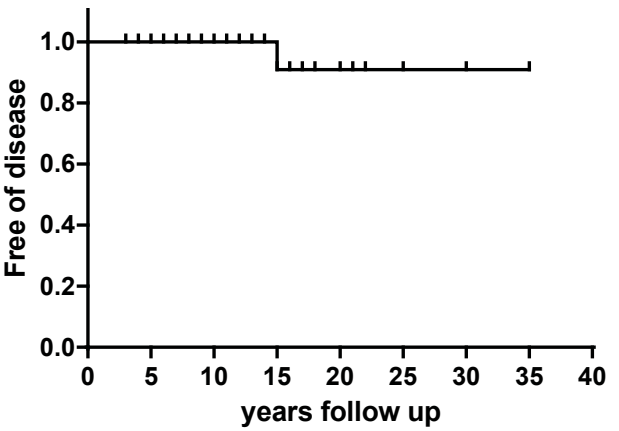

Figure 1. Survival Curve for recurrences among the 107 low-risk DTC patients, from the Kaplan-Meir survival analysis.

Table 2. Stimulated Tg levels and imaging findings of the 8 patients of Group 1 with incomplete or indeterminate response to therapy 1 year post ablation with 50mCi RAI

	Stage	Stimulated Tg (ng/mL) during ablation with 50mCi RAI	Stimulated Tg (ng/mL) during follow-up	Cervical U/S or WBS	Management
1	II	3.35	7	(-)	100mCi RAI
2	II	9.7	18	(+)	Cervical Lymph node Dissection &100mCi RAI
3	I	12.8	16.3	(+)	100mCi RAI
4	II	16.4	3.4	(-)	100mCi RAI
5	II	35.2	15	(-)	100mCi RAI
6	II	8.3	2.84	(-)	100mCi RAI
7	II	12.4	2.7	(+)	100mCi RAI
8	I	9.4	13.3	(+)	100mCi RAI

Table 3. 10 years follow-up of 107 low risk PTC patients of Group 1

	Indeterminate or incomplete response	Recurrence	Distant metastases	Death
1st year, n=107	8	0	0	0
3rd year, n=100	0	0	0	0
5th year, n=82	0	0	0	0
10th year, n=55	0	0	0	0

ing serum Tg levels, of whom 2 had normal neck ultrasound and received 50mCi RAI. The remaining 1 patient had infiltrated lymph nodes appearing in the neck ultrasound and underwent lymph node dissection and received 50mci RAI. Of all the operated patients (n=137), 9 had permanent hypoparathyroidism (6.5%), while none had signs of permanent recurrent nerve injury.

DISCUSSION

The results of this retrospective study demonstrate that low-risk macro-PTC patients who did not undergo central compartment lymph node dissection and received postoperatively a low dose of 50mCi RAI had excellent 10 years prognosis. The low dose of 50mCi RAI appears to be sufficient in 93% of patients for the successful ablation of thyroid remnants and possibly remaining microscopic metastatic lymph nodes. During the follow-up period, none of these patients died or developed distant metastasis and only 2 of them had biochemical recurrence 15 years later and received an additional dose of 100 mCi RAI. The remaining patients (7%) had incomplete or indeterminate response to therapy at 1 year evaluation and only a single patient underwent therapeutic lymph node dissection, while the others received an additional dose of 100mCi RAI, after which none had relapse or distant metastasis or died during the follow-up period. Our data are in accordance with those in the literature. Even low-risk DTC patients who underwent total thyroidectomy and were ablated have 11-15% biochemically and 2-7% structurally incomplete response to initial therapy.[7]

Prophylactic lymph node dissection demands removal of apparently normal cervical lymph nodes due to the high probability of microscopic infiltration.[5] However, the clinical significance of metastatic cervical lymph nodes, especially as regards microscopic lymph nodes, remains controversial. There are several reasons for this discrepancy. One reason is the lack of well-designed prospective studies as well as the absence of an in-depth evaluation of such parameters as patient's age, the number of metastatic lymph nodes, the extent of lymph node infiltration, as well as the presence of extranodal extension which seems to influence the impact of nodal disease on the rate of recurrence and mortality.[5,9] Additionally, most large studies that examine the outcome of patients with differentiated thyroid carcinoma according to the treatment analyze only the effect of the extent of surgery and not the impact of lymph node dissection.[19] Three Surveillance, Epidemiology and End Results (SEER) registry studies found that the involvement of cervical lymph nodes metastases increases mortality in PTC patients, particularly for those older than 45 years, but it was not evident from these studies if the lymph node metastases were clinically evident or unapparent.[20,21] There are only a few prospective, randomized, controlled studies regarding PCCLND and recurrence. One of these studies analyzed the data of 181 patients with PTC, including those with stage III, or extrathyroid extension, or aggressive histology. It was found that in a median 5-years follow-up, the rate of persistent disease was similar among patients who underwent PCCLND and those who did not (8% vs 7.5%). The former had a reduced necessity to repeat RAI treatments but had higher prevalence of permanent hypoparathyroidism.[22] Another prospective, controlled study that included 257 low-risk PTC patients who were followed for approximately 4 years had similar results, with no difference in the recurrence rate between patients treated either via total thyroidectomy or via thyroidectomy and central lymph node dissection (3.9% vs 3.3%), although more perioperative complications were observed in the latter group of patients.[23] In a contrasting finding, a retrospectively controlled (but non-randomized) study of PTC in low-risk patients who underwent total thyroidectomy or also PCCLND, the rate of permanent surgical complications was similar between the two groups.[24] Finally, in a systematic review and meta-analysis including 14 non-randomized studies of which 13 were retrospective, it was found that patients treated with total thyroidectomy and PCCLND were more likely to have postoperative RAI ablation and temporary hypocalcemia but had a 35% reduction in risk of locoregional recurrence in the short term (<5 years). However, the authors were unable to determine how much of this reduction was due to postoperative RAI ablation (71.7% vs 53.1%) and how much to potential selection bias in some of the studies examined.[12] The results of our retrospective study are in agreement with those studies which maintain that the avoidance of PCCLND in low-risk

PTC patients does not alter the excellent outcome of these patients.

Postoperative RAI is used either to destroy normal or remaining cancerous thyroid tissue and to facilitate follow-up of these patients, or to serve as adjuvant therapy.[7] During the last decade there has been an increasing trend to treat low-risk PTC patients less aggressively with lower doses of RAI, or even by withholding RAI treatment.[1,16,25] The overall mortality in low-risk DTC patients for a median follow-up of 10 years is approximately 5%, either with or without RAI ablation.[26] Furthermore, several studies and meta-analyses have demonstrated that postoperative RAI administration in low-risk DTC patients fails to improve the overall survival rate.[1,16,26] The role of postoperative RAI administration in recurrence in low-risk DTC patients is less clear due to the lack of randomized, controlled studies. One recently published retrospective controlled study with 1,298 low-risk macrocarcinoma DTC patients failed to demonstrate any benefit as regards the structural recurrence rate or overall survival during a median follow-up duration of 10.3 years. The mean dose of RAI used was 90mCi.[26] Another retrospective study assessing low-risk PTC patients, of whom only 55% had macrocarcinoma and who were not treated with RAI, found a structural recurrence rate of 2.3%.[27] The current ATA guidelines report that "RAI remnant ablation is not routinely recommended after thyroidectomy for ATA low-risk DTC patients. Consideration of specific features of the individual patient that could modulate recurrence risk, disease follow-up implications, and patient preferences are relevant to RAI decision-making". Our main finding regarding post-operative RAI administration is that in low-risk macro-PTC patients, even without PCCLND, the low dose of 50mCi RAI effectively destroyed thyroid remnants and possibly microscopic metastatic lymph nodes. It is also important to consider that this dose has been found safe for leukemia and other malignancies.[28] Our results are in agreement with the current literature which advocates minimal intervention with regard to type of surgery and the administered dose of RAI in the management of low-risk PTC patients.

A limitation of our study is the lack of a control group either with PCCLND or ablated with 100mCi RAI. However, we believe that this limitation does not influence our conclusion regarding the prognosis of these patients, taking into consideration that the results were clear.

We conclude that patients with low-risk macro-PTC who are treated by means of near-total thyroidectomy without prophylactic central lymph node dissection and who receive postoperatively a low dose of 50mCi RAI have an excellent long-term prognosis.

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