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Adjuvant I-131 therapy for T0–3 N1b M0 differentiated thyroid cancer with many (≥ 5) positive nodes

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ABSTRACT

Background: In patients with well-differentiated thyroid cancer, there is controversy about the prognostic importance of a large number of positive neck nodes and the potential value of radioiodine therapy. The purpose of this study was to evaluate this issue in the group of patients for whom it is most clinically important — those with classic histology and favorable T and M stage.

Materials and methods: Twenty-five patients met the following inclusion criteria: classic histology of papillary or follicular thyroid carcinoma treated with total thyroidectomy and neck dissection followed by adjuvant I-131 treatment in our department between January 1, 2003, and December 31, 2013; adult age of > 21 years; and American Joint Committee on Cancer (AJCC) stage (8th edition) of T0–3, N1b with ≥ 5 positive nodes, and M0.

Results: The median positive node number was 10 (range, 5–31). The median adjuvant I-131 dose was 158 mCi (range, 150–219 mCi). The median follow-up in patients without recurrence after treatment was 7.3 years. The 10-year actuarial rates were favorable: overall survival, 100%; freedom from visible recurrence, 82%; and visible or biochemical recurrence, 72%.

Conclusion: Recurrence was infrequent in our study population with ≥ 5 positive nodes following moderate-dose adjuvant I-131 treatment. These results are valuable in directing initial adjuvant therapy and follow-up intensity. Our results do not inform the question of the use of postoperative thyroglobulin (Tg) level to select N1b patients for low-dose I-131 treatment.

Key words: radiation oncology; thyroid; head and neck; outcomes

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Introduction

In patients with well-differentiated thyroid cancer, there is controversy about the prognostic importance of a large number of positive neck nodes [1–6]. The limitation of published studies on this subject is that they include patients with advanced T stage (pT4), distant metastases (M1), low node number (< 5), inconsistent radioiodine therapy, and/or short follow-up. Our department has a long history of treating thyroid cancer with a standardized policy of moderate-dose radioiodine soon after total thyroidectomy and neck dissection to clear gross disease. The purpose of this report is to document long-term outcomes in a relatively homogenous study population for whom the issue of a high node number is most clinically important: those with AJCC stage T0–3, N1b disease with ≥ 5 positive nodes and M0.

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Materials and methods

With approval from our institution's review board (IRB201500689), we reviewed the medical records of the 25 patients who met the inclusion criteria of this study: classic histology papillary or follicular thyroid carcinoma treated with total thyroidectomy and neck dissection followed by adjuvant I-131 treatment in our department between January 1, 2003, and December 31, 2013; adult age of > 21 years; and American Joint Committee on Cancer (AJCC) stage (8th edition) of T0–3, N1b with ≥ 5 positive nodes, and M0. Study population characteristics are detailed in Table 1.

Although we did not exclude older patients, all patients in our study were < 50 years old at the time of thyroidectomy. All patients were pathologic stage N1b based on positive nodes in the lateral neck, with or without nodes also in the central compartment. During the years of treatment in this study, we did not check serum thyroglobulin (Tg) level after thyroidectomy to determine the need or dose of I-131 treatment. All I-131 treatments were delivered by the senior author of this paper (RJA) with a standard protocol for iodine depletion. Following adjuvant I-131 treatment, patients where followed by an endocrinologist with neck ultrasound and unstimulated serum Tg level. Abnormal findings were further evaluated with additional imaging studies, as indicated.

Table 1. Study population characteristics (25 patients)

Characteristic	Value
Age at the time of thyroidectomy, median (range)	28 years (19–48 years)
Sex	
Male	40% (10 patients)
Female	60% (15 patients)
Pathological T stage (AJCC 8th ed.)	
T1	28% (12 patients)
T2	72% (13 patients)
Primary tumor size, median (range)	2.1 cm (range 0.3–10.5)
Pathologic N stage (AJCC 8th Ed.), N1b	100% (25 patients)
Number of positive lymphnodes, median (range)	10 (5–31)
Adjuvent I-131 activity, median (range)	162 mCi (150–219)
TSH elevation program	
rhTSH	84% (21 patients)
T4 deprivation	12% (4 patients)
Serum thyroglobulin level prior to adjuvant I-131	Not tested

AJCC — American Joint Committee on Cancer; TSH — thyroid-stimulating hormone; rhTSH — recombinant human TSH; T4 — thyroxine

Statistics

SAS and JMP software were utilized for statistical analyses (SAS Institute, Cary, NC). The Kaplan-Meier product limit method provided actuarial outcome estimates. Primary endpoints in this study included overall survival with an event being death from any cause, cause-specific survival (CSS) with an event being death from thyroid cancer or complications of treatment, visible recurrence-free survival with an event being recurrent cancer that was visible on ultrasound or computer tomography (CT) scan, and Tg-only recurrence-free survival with an event being rising Tg with no visible evidence of tumor on ultrasound or CT scan.

Results

The median Tg follow-up for patients without disease recurrence after initial radioactive iodine was 73 months and the median clinical follow-up was 88 months. Seven (28%) patients demonstrated a tumor recurrence after adjuvant I-131 treatment: 5 with visible tumor in the neck and 2 with the only evidence of recurrence being rising serum Tg. Of the 7 patients with a tumor recurrence, 6 underwent salvage therapy with curative intent with neck surgery, external-beam radiotherapy, and/or repeat I-131 treatment. At last follow-up, 92% of the 25 patients (23/25) had no evidence of disease and no patient had died of thyroid cancer. Figure 1 shows actuarial plots for the main outcome endpoints.

There was no significant association between number of nodes and tumor recurrence (visible plus Tg-only): ≤ 10 nodes, 23% *vs.* > 10 nodes, 33%; and no significant association between the presence of extra nodal extension (ENE) and tumor recurrence: yes ENE, 31% vs no ENE, 25%; all comparisons had a p-value > 0.5.

Discussion

Table 2 lists the major published series that analyzed the prognostic importance of a high number of positive nodes. Most of these studies conclude that a higher positive node number is a major prog-

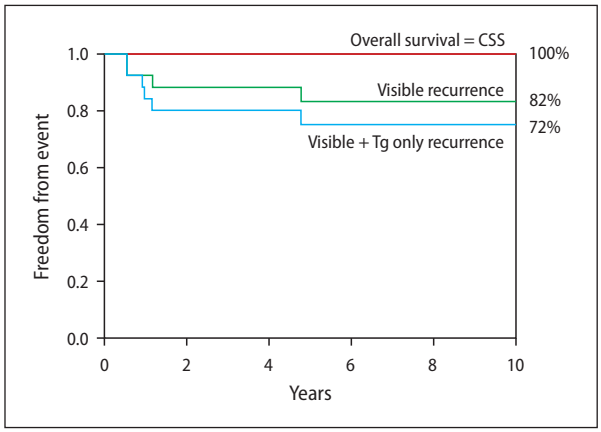

Figure 1. Outcome following adjuvant radioiodine therapy. CSS — cause-specific survival where the only event is death from thyroid cancer

nostic factor — some with the cutoff at 5 positive nodes and others with it at 10 positive nodes. The limitation of these studies is that most include patients with advanced T stage (pT4), distant metastases (M1), low node number (< 5) of nodes, inconsistent radioiodine therapy, and/or short follow-up. Moreover, most of these studies show high recurrence rates in patients with a high number of positive nodes. For example, the recent series from the University of Alberta reported a 10-years relapse-free survival rate of only 40% in node-positive patients [5].

The value of our small series is in its relatively homogenous study population in terms of those factors for which the issue of node number influences the decision for I-131 treatment. Using a standardized program of near-total thyroidectomy, neck dissection to clear gross adenopathy, and 150–200 mCi I-131, we achieved excellent long-term outcomes in patients with a high number of positive nodes (minimum 5, median 10).

Our series has two major limitations: First is its inability to compare I-131 doses and lack of postoperative serum Tg levels. Our results suggest that 150–200 mCi adjuvant I-131 produces high cure rates, but we are unable to say if lower doses would be equally efficacious. Similarly, beyond positive node number, measuring serum Tg levels at least 4 weeks after thyroidectomy can inform the risk to our patients.

Conclusion

Recurrence was infrequent in our study population with ≥ 5 positive nodes following moderate-dose adjuvant I-131 treatment. These results are valuable in directing initial adjuvant therapy and follow-up intensity. Our results do not inform the question of the use of postoperative Tg level to select N1b patients for low-dose I-131 treatment.

Table 2. Review of major published series and guidelines related to the prognostic value of number of positive nodes (usually after adjuvant I-131)

Published series	
Series, year	**Outcome**
University of Ulsan, South Korea 2019 [6]	Local regional recurrence high with > 10 positive nodes
University of Alberta, 2018 [5]	10-year relapse-free survival 40% when the only risk factor was positive nodes; number not analyzed
SEER study of DTC in < 45-year olds, 2015 [4]	Overall survival decreased with increasing number of positive nodes up to 6
Kuma Hospital, Japan, 2009 [3]	≥ 5 positive nodes associated with worse disease-free survival
Gustave Roussy, France, 2005 [2]	10-year disease-specific survival worse with ≥ 10 positive nodes
Japan Cancer Institute, 2004 [1]	10-year disease-specific survival worse with ≥ 5 positive nodes
Guidelines	
Guidelines, year	**Outcome**
American Thyroid Association, 2015 [7]	I-131 "generally favored" with N1b; number of positive nodes not mentioned
National Comprehensive Cancer Network v2, 2019 [8]	I-131 "typically recommended" for > 5 positive nodes
Randomized Trials of 30 *vs.* 150 mCi I-131, 2019 [9, 10]	Both included N1b without limit to the number of positive nodes (outcome equivalent with 30 mCi I-131

DTC — differentiated thyroid carcinoma; I-131 — radioactive iodine 131

Conflict of interest

The authors have no conflicts of interest to declare.

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Statement of ethics

All subjects gave their written informed consent and this study protocol was approved by the University of Florida's Institutional Review Board (IRB 201500689).

Submission declaration

This publication has not been published previously and not under consideration for publication elsewhere.

Authors' contributions

E.Ch.F. collected data, interpreted data, wrote first draft of manuscript, incorporated coauthor revisions, approved the final draft; C.E.M. collected data, interpreted data, approved the final draft; P.A.D. collected data, interpreted data, approved the final draft; Ch.G.M. collected data, contributed to study design, interpreted data, approved final draft; R.J.A. conceived study, collected data, interpreted data, revised manuscript, approved final draft.

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