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Low versus high activity radioiodine remnant ablation for differentiated thyroid carcinoma with gross extrathyroidal extension invading only strap muscles

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A B S T R A C T

Objectives: The efficacy of radioiodine remnant ablation (RRA) for patients with differentiated thyroid carcinoma (DTC) with gross extrathyroidal extension (ETE) is well described in observational studies. However, its role in gross ETE invading only strap muscles, T3b category in the newly proposed eighth edition of the TNM staging system, is currently unknown.

Methods: This study retrospectively analyzed 260 DTC patients with ETE invading only strap muscles who underwent thyroidectomy at a tertiary Korean hospital between 1994 and 2005. Cancer-specific survival (CSS) and recurrence-free survival (RFS) in the no RRA (n = 13), low RRA activity (< 3.7 GBq, n = 80), and high RRA activity (≥ 3.7 GBq, n = 167) groups were studied.

Results: No significant differences were observed between low and high activity RRA groups in terms of 10-year CSS (97.3% versus 99.3%; HR 0.23, 95% CI 0.02–2.57; p = .235) and RFS (86.8% versus 88.8%; 0.90, 0.40–2.03; p = .804). In the no RRA group, no patients died of cancer, and only one developed structural recurrence. In Cox regression analyses with inverse probability of treatment weighting adjusted for clinicopathologic risk factors, high activity RRA was not related to recurrence outcomes compared to low activity (HR 0.60, 95% CI 0.26–1.35; p = .214).

Conclusions: Long term oncologic outcomes did not significantly differ between low versus high activity RRA groups, which suggests that low activity RRA might be sufficient in patients with DTC with gross ETE invading only strap muscles. Further studies are needed to clarify the optimal activity of RRA in these patients.

Introduction

In decades, radioiodine therapy has been a cornerstone in managing differentiated thyroid carcinoma (DTC) [1]. Recent paradigms on the use of radioiodine therapy have changed, and selective use of radioiodine therapy as postoperative adjuvant therapy is being considered [2]. Although radioiodine therapy is considered reasonably safe compared to other cancer treatment modalities, potential complications cannot be completely eliminated. In addition to early onset adverse effects, there are increasing reports of late onset adverse effects in long term survivors previously treated with radioiodine therapy, including second primary malignancies [3,4]. Appropriate postoperative radioiodine decision-making is important for balancing benefits and risks.

The efficacy of postoperative radioiodine remnant ablation (RRA) in

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long term survival and recurrence for patients with DTC with distant metastasis or gross extrathyroidal extension (ETE) has been well described in several studies [5,6]. Most guidelines have also agreed that RRA is not indicated for patients with DTC with tumors < 1 cm without ETE and other poor clinicopathologic features [7,8]. However, the efficacy of RRA remains controversial in intermediate risk patients, including those with minimal ETE. Some reports found benefits of RRA with minimal ETE [9,10], while others did not [11,12]. Without a clear conclusion on RRA efficacy in patients with minimal ETE, recommendations for RRA in smaller tumors with microscopic ETE remain a “grey area”.

In the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system [13], because minimal ETE has no prognostic significance, it does not constitute a T3b category. Instead, gross ETE invading only strap muscles is designated as the new T3b category. Until now, the efficacy of RRA for gross ETE invading only strap muscles has not been analyzed. We aimed to determine whether low activity RRA could be used instead of high activity RRA.

Materials and methods

Study subjects

Among patients with histologically confirmed DTC who underwent total thyroidectomy at a tertiary Korean hospital between 1994 and 2005, patients with gross ETE invading only strap muscles were retrospectively analyzed. Only one patient with distant metastasis at initial diagnosis was excluded from this study. The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2016-05-053). The committee waived patient consent in some cases because this study was of retrospective design and used only deidentified clinicopathologic information.

Postoperative RRA

Radioiodine therapy strategy at our institution has changed with time. In this cohort period, the majority of patients with gross ETE invading only strap muscles received RRA, except for those with comorbidities or refusing therapy. Our institute recommended 1.1 GBq for patients with low risk disease like small tumor without lymph node metastasis. An activity of 3.7 or more was recommended for patients with high risk disease defined by incomplete tumor resection, extensive gross extrathyroidal extension or distant metastasis. Otherwise, 1.1–3.7 mCi was used for patients with low to intermediate risk disease. Individual cumulative ablation activity was finally determined by an endocrinologist based on the initial postoperative cancer stage and clinicopathologic factors, as well as adjustments based on the clinical judgement of the responsible physician. To reflect cumulative ablation activities administered at different clinical situations, patients were categorized into 3 groups: no RRA, low activity RRA (< 3.7 GBq [100 mCi]), and high activity RRA (≥ 3.7 GBq). As most contemporary studies have defined low versus high radioiodine activities of 1.1 GBq (30 mCi) or 3.7 GBq, our study empirically categorized patients based on cumulative radioiodine activity of 3.7 GBq.

Data collection and outcomes

Clinicopathologic information was obtained from our thyroid cancer database, with data collected regularly. Collected data includes age at diagnosis, gender, histologic subtype, primary tumor size, presence of ETE, pathologic lymph node involvement status, presence of distant metastases at diagnosis, extent of surgery, and cumulative activities of initial RRA. The same patient dataset was reviewed and reclassified based on the eight edition of the AJCC TNM staging system.

Time to recurrence or disease status at last follow up was obtained from the medical record. All patients were followed-up every 6–12 months with physical examination and measurements of thyroid function tests, serum thyroglobulin and anti-thyroglobulin antibody. Ultrasonography was performed within 6–12 months after initial therapy and followed by every 12–24 months at a minimum. Additional imaging studies including diagnostic whole-body scan, computed tomography (CT) and fluorodeoxyglucose-positron emission tomography (FDG-PET) were performed to detect recurrence if suspected. Patient survival status and cause of death were ascertained by linkage to national death certificate data from the Korea National Statistical Office. Thyroid cancer-specific survival (CSS) was defined as time from initial surgery to last follow-up or death caused by DTC. Recurrence-free survival (RFS) was defined as time from initial surgery to last follow-up or development of first evidence of structural recurrence. Disease recurrence in this study referred to structural recurrence confirmed as existence of physical tumors of recurrent or persistent disease by standard cytologic, histologic, and radiographic criteria.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD), while categorical variables were presented using numbers and percentages. Kruskal-Wallis test, Wilcoxon rank sum test, and Fisher's exact test were used to compare baseline characteristics between the groups. Thyroid cancer-specific survival and recurrence-free survival were estimated by Kaplan-Meier curves and compared with log-rank tests. Cox regression analysis and Weighted Cox regression analysis with inverse probability of treatment weighting (IPTW) using propensity score were applied to evaluate the effect of RRA on recurrence outcomes after adjusting for risk factors, including age at diagnosis, gender, primary tumor size and lymph node involvement status. Variables with P-value < 0.1 in univariable analysis were selected as candidates for the multivariable analysis. Statistical analysis was executed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) and R 3.4.2 (Vienna, Austria; http://www.R-project.org). A P-value < 0.05 was considered statistically significant.

Results

Patient demographics

A total of 260 patients (227 women and 33 men) with a mean age of 49.2 years were analyzed. Of these patients, 13 did not receive RRA, 80 received low activity RRA (< 3.7 GBq), and 167 received high activity RRA (≥ 3.7 GBq). Mean (SD) radioiodine activity was 2.39 (0.66) GBq [64.5 (17.8) mCi] in the low RRA group and 6.84 (3.89) GBq [184.9 (105.0) mCi] in the high RRA group. After ablation, no remnant uptake was found in 92.5% of the low RRA group and 87.4% of the high RRA group. Comparison of clinicopathologic characteristics among the three groups is described in Table 1. Gender, age at diagnosis, and lymph node involvement status did not differ among groups. However, the high activity RRA group tended to have larger tumors (p = .001) and more lymph node metastases (p = .019) compared to the low activity RRA group. In the no RRA group, the follow up period was shorter than in the other groups (p = .009). Overall mean follow up period from initial surgery to death, recurrence, or censoring was 10.6 years.

Long term survival outcome according to RRA activity

Of 260 patients, 4 (1.5%) died of thyroid cancer (Table 2); none in the no RRA group, 2 patients in the low activity group, and 2 patients in the high activity RRA group. The 10-year CSS was not significantly different between low and high activity RRA groups (97.3% versus 99.3%; p = .235). CSS curves for low and high activity RRA groups are presented in Fig. 1, and they did not significantly differ (P value by log-rank test = 0.200).