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The Use of Low Dose in Radioiodine Ablation of Well-Differentiated Thyroid Cancer

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Abstract

Remnant thyroid ablation after thyroidectomy with radioiodine (RAI, I-131) is considered the standard of care for low risk patients with well-differentiated thyroid cancer (WDTC). The choice of activity for therapy is usually empirically determined according to the tumor characteristics and the patient's age. Many guidelines recommend a range of 1.1 to 3.7 GBq (30 to 100 mCi), although the choice between the extremes of this range remains controversial. Many studies, including retrospective systematic reviews and randomized multicenter trials, have compared results from using low versus high RAI doses. Data demonstrated similar successful ablation and recurrence rates in these groups, although there are no randomized trials to evaluate long-term outcomes. Until this has been addressed, the choice between 1.1 and 3.7 GBq dose for remnant ablation must be made according to the risk of each patient to maximize the efficacy of treatment, while minimizing unnecessary radiation.

Keywords: Low dose; 30 mCi; High dose; 100 mCi; Radioiodine ablation; Thyroid cancer

Introduction

Radioactive iodine (RAI) ablation refers to the use of iodine-131 to destroy functioning remnant thyroid tissue after total or near total thyroidectomy for well-differentiated thyroid cancer (WDTC). The rationale for remnant thyroid ablation following thyroidectomy is to destroy subclinical, microscopic foci of remaining disease, thus facilitate the use of serum thyroglobulin as a tumor marker to monitor the presence of disease, and to increase the sensitivity and specificity of I-131 whole body scanning in detection of recurrent or metastatic disease. Thyroid tissue has the unique ability to extract and retain iodine from blood. Similarly, radioiodine is taken up and concentrated in thyroid follicular cells by the membrane sodium-iodide transporter [1]. Compared to normal cells, thyroid cancer cells have reduced expression of the transporter, which may account for the low radioiodine uptake in thyroid cancer tissue. Hence, a larger dose of RAI is needed for successful ablation, and with it, side effects, such as transient sialadenitis that may affect a patient's quality of life. Arguably, a lower dose such as 1.1 GBq (30 mCi) should lessen these effects. The recommended radiation dose for ablation of remnant thyroid tissue by the Society of Nuclear Medicine is 300 Gy [1]. However, the dose to the whole body should not exceed 2 Gy, which is the maximum permissible dose to the bone marrow. For this reason, estimated whole-body retention at 48 hours post-administration of I-131 should not exceed 4.44 GBq (120 mCi). The American Thyroid Association (ATA) guidelines recommend the use of minimal radioactivity (1.1 to 3.7 GBq) in order to achieve successful ablation. In this range, complete destruction of thyroid remnant has been successful in 90% of the cases, when uptake in the neck was <2% [1]. In this article, we will provide a brief review of the literature for low-risk patients.

Multiple professional societies have published guidelines for the appropriate use of RAI for remnant thyroid ablation. The American Thyroid Association (ATA) Guidelines for Patients with Thyroid Nodules and WDTC (2009) recommend the routine I-131 ablation for selected patients with T1-T2 disease stage confined to the thyroid with documented metastatic lymph node or demonstration of higher risk features (age, tumor size, lymph node status, tumor histology). ATA does not recommend ablation for patients with unifocal cancer <1 cm and those with multifocal cancer when all foci are <1 cm, in the absence of other high risk features [2]. The European Thyroid Association (ETA) consensus report and guidelines advise RAI ablation for T3-T4, N1, or M1 stage of the disease only as a relative indication in young patients (<18 years) and in those with primary tumors between 1 and 2 cm without lymph node or distant metastatic disease. RAI ablation therapy is not recommended in patients with differentiated thyroid cancer (DTC) which are <1 cm in size with no metastatic disease [3]. The Society of Nuclear Medicine (SNM) Procedure Guideline for The Therapy of Thyroid Disease (2005) stated that treatment of WDTC with RAI should be considered postsurgically in patients with: tumor size >1.5 cm; tumor size <1.5 cm with unfavorable histology; metastatic lymph node(s); multifocal disease, which may represent intra-thyroidal metastatic lesions; lymphatic, vascular, or capsular invasion, including into peri-thyroidal soft tissue; or distant metastatic disease [4]. The Guidelines for RAI ablation of WDTC published by the European Association of Nuclear Medicine (EANM) in 2008 stated that RAI ablation after total or near total thyroidectomy is a standard procedure in patients with DTC, with the only exception being patients with unifocal thyroid carcinoma ≤1 cm in diameter without evidence of metastatic disease, thyroid capsule invasion, history of radiation exposure, or unfavorable histology (tall-cell, columnar cell, or diffuse sclerosing subtypes). They also concluded that RAI ablation should be considered when potential risk factors for recurrence or mortality, including family history of WDTC,

presence of vascular invasion, and closeness of the tumor to the thyroid capsule [5].

A wide range of activities is used for I-131 remnant ablation of WDTC with the papillary, papillofollicular, follicular, and Hürthle-cell histology, depending on the risk of the disease. Typical dosing is between 1.1 and 5.6 GBq (29 and 150 mCi) [4-10]. The higher radioactivity may have tumorcidal effects on occult metastases that may not be detected on low dose I-131 whole body surveillance scans. However, recent studies suggest that higher doses are not necessarily associated with a lower risk of disease recurrence [9,11]. It has been suggested that for lower risk patients, such as those under the age of 45 with tumors <2 cm confined within the thyroid gland, a dose in the range of 1.1 to 1.8 GBq (30-50 mCi) may be adequate [12]. For intermediate-risk patients, radioactivity in the range of 2.8 to 3.7 GBq (75-100 mCi) can be used, while high-risk patients may require a dose of 5.6 to 7.4 GBq (150-200 mC) [12]. Experts are now in favor of lower dosing, such as 1.85 GBq (50 mCi), without a pretherapy radioiodine scan in low-risk patients [13].

In a systematic literature review by Hackshaw et al. [6], 41 retrospective studies, 12 prospective cohorts, and 6 randomized trials were examined that compared 1.1 with 3.7 GBq (30 mCi vs 100 mCi). They concluded that the 100 mCi dose was associated with a high success rates (~80%, some studies even >90%), with a pooled success rate of 10% higher than the 1.1 GBq dose [6]. Unfortunately, limitations of the analysis include heterogeneity in the criteria for successful ablation, where some studies used visual inspection on a follow-up iodine scan, some used a threshold of uptake in the neck, while others used a threshold in serum thyroglobulin level. In addition, study protocol differences include the extent of surgery, the method of stimulation (i.e. hormone withdrawal versus recombinant TSH or Thyrogen), dietary restrictions (low iodine versus unrestricted diet), use of a pretherapy whole body iodine scan, and the length of time between therapy and the follow-up scan. The lack of blinding/non-randomization of doses may further confound the reported rates. Hence, the conclusions drawn from this review that the higher doses are more effective should be taken with caution.

A randomized, single-center trial involving 160 patients by Maenpaa et al. [14] compared 1.1 with 3.7 GBq (30 vs 100 mCi). [14]. Criteria for successful ablation included serum thyroglobulin <1 ng/mL with no appreciable uptake on the I-131 scan. The success rates for 1.1 and 3.7 GBq (30 and 100 mCi) dosing were 42/81 (52%) and 43/77 (56%), respectively, with no statistical differences. However, the higher dose group experienced greater side effects, including nausea and taste disturbances, and a longer period of isolation.

A multicenter trial from France by Schlumberger et al. [15] randomly assigned 752 patients with low-risk WDTC to 1.1 versus 3.7 GBq (30 versus 100 mCi) [15]. They defined successful ablation as an ultrasound showing normal post-operative thyroid bed with no suspicious lymph nodes, and a Thyrogen-stimulated thyroglobulin level ≤1 ng/mL. If the patient was found to have thyroglobulin antibodies, successful ablation in these patients was defined by a posttherapy I-131 total body scan showing <0.5% uptake in the thyroid bed. Complete ablation rates in both the 1.1 and 3.7 GBq (30 and 100 mCi) group were 89%, with similarly high rates at follow-up diagnostic scan in 6-10 months posttherapy (91% for 30 mCi and 93.5% for 3.7 GBq (100 mCi), not statistically different). They also found that lacrimal complications were more frequent in patients receiving the higher dose than the lower dose, although there was no statistical differences for hypothyroidism or quality of life. The authors concluded that a low dose of I-131 for ablation is an effective option for low-risk WDTC patients, with the benefit of a lower whole-body irradiation and without a compromise in the quality of life.

In a parallel study, Mallick et al. [16] enrolled 438 patients with low-risk WDTC into a randomized multicenter trial in the United Kingdom [16]. Successful ablation was defined as having both a post therapy iodine scan with <0.1% uptake and a Thyrogen-stimulated thyroglobulin level <2 ng/mL at 6-9 months post treatment. For patients with anti-thyroglobulin antibodies or if the antibody status was unknown, unavailable or discordant, a negative I-131 scan was used as the sole determinant for successful ablation. Comparable to the Schlumberger study, the rates of successful ablation were similar with both dosing (85% at 1.1 GBq (30 mCi) and 89% at 3.7 GBq (100 mCi)). They also found a significantly lower incidence of side effects (21% in 1.1 GBq (30 mCi) versus 33% in 3.7 GBq (100 mCi) groups). As expected, low dose therapy patients had a shorter hospital stay and reported a better quality of life. Interestingly, although there is an odds ratio of 1.02 for ablation failure per 0.5 ng/ml serum thyroglobulin, the authors noted a slightly larger odds ratio of 1.09 in the low-dose combined with Thyrogen stimulated group, hinting that there may be room for improvement with higher dosing. In addition, their low-dose data showed a -2.7% decrease in success rate on the basis of scanning results and a -3.8% decrease in success rate on the basis of scanning results and thyroglobulin level, although within the allowable difference of +10% between the groups [16].

A randomized study of 309 patients were treated with 1.1 GBq (30 mCi), 2.2 (GBq 60 mCi), or 3.7 GBq (100 mCi) I-131 and followed >5 years [17]. Disease status was assessed by sonography, radiological examinations and serum thyroglobulin measurements. Within the 5 year period, local relapse was found in 2.4% of the 1.1 GBq (30 mCi) group, 3% of the 2.2 GBq (60 mCi) group and 3% of the 3.7 GBq (100 mCi) group, without statistical differences between the groups. However, patients treated initially with 1.1 GBq (30 mCi), required a second dose of RAI in 22%, while only in 13% and 11% needed a second treatment in the 2.2 GBq (60 mCi) and 3.7 GBq (100 mCi) groups, respectively.

In a retrospective study of 140 patients, Rosario et al. compared patients treated with 1.1 and 3.7 GBq (30 and 100 mCi) of I-131 with a 5 year follow-up [9]. Relapse was defined by a stimulated thyroglobulin level >2 ng/ml. Follow-up consisted of annual clinical examination, serum thyroglobulin level and neck ultrasounds. At the end of the 5 year period, the recurrence rates were very similar with 3.4% in the 1.1 GBq (30 mCi) and 3.6% in the 3.7 GBq (100 mCi) groups.

Mazzaferri et al. [11] compared 100 patients treated with low doses (1.1-1.8 GBq or 29-50 mCi) with high doses (1.8-7.4 GBq or 51-200 mCi) for remnant thyroid ablation over a mean period of 14.7 years [11]. During this time period, 3 of the 43 patients (7%) in the low dose group developed recurrent disease compared to 5 out of 57 patients (9%) who were found to have recurrence in the high dose group (p=0.7), suggesting equal efficacy in controlling tumor recurrence.

In summary, the survival outcome between using either 1.1 GBq or 3.7 GBq (30 mCi or 100 mCi) in RAI ablation for WDTC patients appears to be comparable with a slight benefit in side effect profile using the lower dose. However, one cannot ignore that there is better, albeit by very small amount, success using the standard dose. More focused data are needed to delineate the small benefit exhibited in using the established higher 3.7 GBq (100 mCi) ablation dose.

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