REVIEW ARTICLE

MANAGEMENT OF WELL DIFFERENTIATED THYROID CANCERS: CONTROVERSIES AND WAY FORWARD

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ABSTRACT

The American Thyroid Association (ATA) 2015 guidelines favor lobectomy for tumors 1-4 cm, recommend use of contrast enhanced CT/MRI examination for high risk patients and low or no radioiodine-131 therapy for low to intermediate risk patients. However, these guidelines have been declined by European Association of Nuclear Medicine (EANM) on a plea that these are based on conflicting weak retrospective studies and skewed interpretation of existing database. Lack of valid prospective randomized clinical trials due to tumor biology and exceedingly low event rate which need longer follow-up is the primary reason for these controversies. Currently three prospective randomized clinical trials upon low risk DTC patients are underway and hopefully their results would clarify dense smokescreen to a greater extent in years to come.

Key Words: Differentiated thyroid cancer; lobectomy; thyroidectomy; iodinated contrast; radioiodine-131 treatment; prospective trials

Differentiated thyroid cancers (DTC) include papillary and follicular (including Hurtles cell type) carcinomas. It is a fascinating disease as it is both frustrating and heartening to treat patients with DTC.[1] Over the last two decades there has been an increase trend in detection of small size nodules (less than 1-2 cm) due to overwhelming use of ultrasound (US) and fine needle aspiration cytology (FNAC).[2] The management of patients with low to intermediate risk disease is a matter of great controversies. The major controversies are extent of thyroid surgery, use of preoperative cross sectional neck imaging and use of radioactive iodine-131 (RAI) post-operatively.[3] The sentinel reason is lack of valid prospective randomized clinical trials. In this review we will discuss these areas of controversies and expected way forward.

Extent of thyroid surgery: There was a consensus among various thyroid societies for DTC less than 1 cm (micro-carcinoma) lobectomy and for tumor larger than 1cm total or near total thyroidectomy are the preferred surgical options.[4] However, the recommendation 35-B in ATA 2015 guideline allows lobectomy for patients with tumor size 1-4 cm without extra-thyroidal extension or distant metastasis.[4] This is a major shift from its previous recommendations favoring total thyroidectomy for lesion > 1cm[5] and will impact the use of state of the art test like thyroglobulin for follow-up in clinical practice. This recommendation was based on large body of data showing no significant survival benefit in patients having 1-4 cm tumors who had either lobectomy or total thyroidectomy.[3] However in 2016, European Association of Nuclear Medicine (EANM) declined to endorse ATA 2015 guidelines. The EANM believes that this major change in surgical practice would undermine adjuvant use of

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RAI and use of serum thyroglobulin to follow-up these patients.[6] However, recommendation 35-B of ATA-2015 also allows treatment team to consider total thyroidectomy to enable adjuvant RAI or to enhance follow-up based on disease features and/or patient preferences.[4] Lobectomy may be followed by early completion thyroidectomy in up to 20% of patients having a non-favorable final histopathology report.[7,8]

Use of CT with iodinated contrast: The ATA 2015 guidelines (recommendation 33-A) endorse use of contrast enhanced cross sectional imaging (CT or MRI) as an adjunct to ultrasound in patients with suspected or known high risk disease. This will definitely result in delay in adjuvant RAI treatment for several weeks. However, ATA feels that benefits outweigh the risk of delaying RAI for several weeks.[4] ATA recommends a delay of 4-8 weeks after contrast examination as urinary iodine level usually returns to normal.[9] However, there remains concern that residual iodine in thyroid tissue could impair the effectiveness of RAI despite of having normal urinary iodine. Although ATA assumes that a delay of few months in RAI after iodinated contrast has no potential hazard, there are published studies which have shown poor survival in patients having a delay more than 180 days after thyroidectomy.[10]

Radioactive Iodine-131 (RAI) treatment post-operatively: The ATA 2015 guidelines have significantly curtailed the applications of RAI in the management of low and intermediate risk patients. The ATA has placed patients with nodal metastasis into low, intermediate and high risk for loco-regional recurrence or distant metastasis rather than placing into intermediate risk group.[11] It has categorized RAI use as remnant ablation (ablation of normal thyroid tissue), adjuvant therapy (having no known residual disease but having risk of recurrence) and therapy to treat known loco-regional or metastatic disease.[4] ATA recommends observation in low risk patients having no evidence of residual disease after surgery.[4] For high risk patients, RAI is recommended for adjuvant therapy or treatment of known disease.[4] For intermediate risk group, RAI is recommended based on risk of recurrence, disease specific mortality and post-operative evaluation.[4] Patients with proven persistent disease or raised serum thyroglobulin are candidates for treatment of known persistent disease. Patients in intermediate risk group having no post-operative structural or biochemical evidence of disease are recommended for remnant ablation or adjuvant therapy.[4] The ATA endorses 30 mCi of Iodine-131 for remnant ablation, 30-150 mCi for adjuvant therapy and 100 - 200 mCi for therapy of persistent or recurrent disease, except in elderly in whom dose should not exceed 150 mCi due to potential side effects in them.[4]

The British Thyroid Association (BTA) guidelines endorses the ATA guidelines but used the term selective use instead of may be considered.[2] However, EANM has declined to endorse ATA recommendation about RAI. The EANM argues that US National Cancer Database from 1998 -2006 and US Surveillance Epidemiology and End Result (SEER) from 1973-2009 and other published studies, clearly favor the benefit of RAI for disease specific mortality.[12,5,13] It further argues that data published 2016 onward support beneficial role of RAI in intermediate risk patients with nodal involvement[14,15,16] and expect these would be given due consideration in future version of ATA guidelines.

For papillary micro-carcinoma (less than 10 mm; PMC) ATA recommends lobectomy, no RAI but serial follow up with serum thyroglobulin and ultrasound as the best option.[4] However, BTA argues that PMC is associated with loco-regional recurrence in 2.5%, regional nodal metastasis in 12.3-50% and distant metastasis in 0.4% cases.[2] Based on these facts, BTA designed a risk adopted strategy to decide the radioiodine therapy in PMC. Risk factors are nodule having size 6-10 mm, multifocal, unfavorable histology, nodal involvement and FDG avid incidentaloma on PET imaging.[17]

Risk of second primary malignancy after Radio-iodine-131 therapy: Second primary malignancy (SPM) has been a matter of great concern for patients undergoing radioiodine treatment but data is contro-versial regarding incidence, latent period and threshold dose of RAI. Study by Rubino et al. revealed small risk of SPM for a cumulative dose of RAI greater than 200 mCi.[18] However, SEER database is difficult to assess as most of SPMs were detected within 1 year after RAI and likely due to use of high end diagnostic modalities.[5] Study by Hirsch et al. reported no signi-ficant difference in incidence of SPMs in patients

either treated with RAI (80% had >200 mCi) or not-treated with RAI . However, study by Seo et al. claimed a dose dependent risk between RAI and leukemia . They found that 1 in 20,000 patients treated with RAI >100 mCi has developed leukemia but no rise is seen in patients treated with <100 mCi of RAI.[20] Importantly the latent period before the leukemia appears was 8 months which is much shorter than previously reported period.[20]

Reasons of controversy and way-forward: The primary reason for controversy associated with management of thyroid cancer is lack of prospective randomized trials. Slow growth of DTC with exceedingly low event rate makes it difficult to follow these patients for longer duration. Researchers have estimated that a prospective trial having sample size of 1500 thyroid cancer patients treated with RAI with a follow-up greater than 10 years will have good statistical strength.[21] A prospective randomized control trial to observe the outcome of prophylactic central neck dissection in cN0 (clinically non-palpable nodes) patients would require a sample size of about 5800 to get good statistical strength, hence not feasible.[22] To study the role of RAI in low risk group, three prospective randomized trials are currently underway, comparing patients treated with and without RAI. These are French *ESTIMBAL-2* (Etude Stimulation Ablation-2), British *IoN* (Iodine or Not) and German *CLERAD-PROBE* (I-124 PET/CT based decision making) trials.[5] However, these trials have shorter follow-up period of 3-5 years which could affect the strength of these trails and results are expected beginning in 2020.[5]

We feel that recent ATA 2015 guidelines have further shaken the settling muddy water by limiting the extent of surgery and use of RAI in low and intermediate risk patients. The EANM has declined to endorse these guidelines as they feel that these are based on biased retrospective studies and non-realistic interpretation of US National Cancer and SEER database. Lack of valid prospective randomized clinical trials due to tumor biology and exceedingly low event rate which need longer follow-up is the primary reason for these controversies. Currently three prospective randomized clinical trials upon low risk DTC patients are underway and hopefully their results would minimize the dense smokescreen.

Conflict of Interest: Authors declare no conflict of interest.

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