MINI-REVIEW

Controversies about Radioactive Iodine-131 Remnant Ablation in Low Risk Thyroid Cancers: Are We Near A Consensus?

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Abstract

Well differentiated thyroid cancers (WDTC), including papillary (80%) and follicular (10%) types, are the most common endocrine cancers globally. Over the last few decades most the diagnosed cases have fallen into low risk categories. Radioactive iodine-131 (RAI) has an established role in reducing recurrence and improving the survival in high risk patients. In patients with primary tumor size <1 cm, RAI is not recommended by many thyroid societies. However, low risk WDTC has been an arena of major controversies, most importantly the role and dose of adjuvant RAI for remnant ablation to minimize chances of recurrence and improving survival. This review is an attempt to update readers about the previous and existing practice based on results of non-randomized trials and evolving trends fueled by recently published randomized studies.

Keywords: Papillary thyroid cancer - follicular thyroid cancer - low dose iodine - remnant ablation

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Introduction

Thyroid carcinoma is the most common endocrine malignancy around the globe and papillary cancer (80%) followed by follicular (10%) carcinoma are the vast majority and collectively termed as well differentiated thyroid cancers (WDTC). Over the last few decades, there has been an increased incidence of WDTC (primarily papillary carcinoma) with a significant rise from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002 in United States (US), a 2.4-fold increase ($p<0.001$ for trend) with a crescendo pattern (Davies and Welch, 2002). Similar increases have also been reported in Europe (Elisei et al., 2010). Importantly most of these tumors were diagnosed at a smaller size (49% tumors were ≤1cm and 87% were ≤2cm) and 58% of patients were aged <50 years (median age=46 years) (Edwards et al., 2002). The sentinel reason for this increase incidence of low risk cases is frequent detection on ultrasound and subsequent fine needle aspiration cytology (FNAC) of small thyroid nodules. Low risk WDTC with reported 10-year mortality rate of 1.7% for papillary and 3.4% for combined papillary and follicular studies (Sawka et al., 2004), has been a major domain of therapeutic controversies. These controversies have been focused upon the extent of surgery, option of using and optimal dose of radioactive iodine-131 (RAI) after surgery (adjuvant therapy), appropriate use of thyroxin suppression therapy and role of human recombinant thyrotropin (rhTSH). In this review the term ablation means use of RAI to completely destroy residual macroscopically normal thyroid tissue after gross surgical resection of cancer. This review will be focusing upon: *i*) whether RAI should be used or not for ablation in low risk group? *ii*) If so, than what should be the dose of adjuvant RAI?

Radioiodine-131 (RAI)

Historical Background, it was Seidlin et al. (1948) who published their experience of RAI for treating pulmonary metastasis in a patient with thyroid cancer and in subsequent 10-12 years it was evident that RAI increased survival of patients with metastatic thyroid carcinoma. In 1970's concept of using RAI for ablation got popularity and Mazzaferri and Young (1981) published 10 years follow-up data of 576 patients revealing efficacy of RAI in reducing mortality and recurrence. However, Hay et al. (2002) presented data of 2444 patients treated during 1940-1999 showing no significant impact of RAI upon mortality and tumor recurrence in low risk thyroid cancer patients. Despite of these conflicting findings from these retrospective studies, during this period in US, approximately 38% of patients with WDTC are reported to have received RAI ablation or therapy (Edwards et al., 2002). Similarly a survey conducted by American Thyroid Association published in 1996, 61% of respondents recommended RAI ablation for a hypothetical low-risk papillary cancer case (Solomon et al., 1996).

Biophysical Properties of RAI: It's a reactor produced isotope having a physical half-life of 8.02 days and emits beta particles with a maximal energy of 0.6 MeV (about 2mm tissue penetration and 90% of total absorbed

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dose) and gamma rays of 364 and 674 KeV (10% of total absorbed dose) which are primarily responsible for radiation exposure to caregivers and public.

RAI is taken up and concentrated in thyroid follicular cells via sodium-iodide transporter (membrane transporter protein, NIS) which is also found in several other tissues that concentrate iodine such as the salivary and lacrimal glands, nasal mucosa, stomach, thymus, lactating breast and placenta (Shen et al., 1996). WDTC have thyroid stimulating hormone (TSH) receptors and do produce thyroglobulin (Tg). A serum TSH level of 25-30mU/L is necessary to stimulate adequate RAI uptake by the residual normal follicular and tumor cells (Carballo and Quiros, 2012). However, compared with normal thyroid tissue, thyroid cancer tissue has low expression of NIS (rather undetectable in one third cases), reduced iodine organification and shorter effective half-life of RAI. However, the cancer cells do respond to TSH stimulation, even in the absence of clinically evident RAI uptake (Robbins and Schulmberger, 2005). Successful ablation is characterized by an undetectable stimulated Tg level (<2ng/ml) with negative antithyroid antibodies, negative whole body iodine scan or <0.5% tracer uptake over thyroid bed and a negative neck ultrasound.

Controversies in use of RAI for Remnant Ablation in Low Risk WDTC

In last few decades, >80% of WDTC are <2cm and in these low risk patients, a low recurrence without RAI after total thyroidectomy (4%) (Vaisman et al., 2011) and 10 year cause specific mortality of 1.7% has been documented. Furthermore, in recent years, there has been an increasing concern over RAI induced second primary malignancy (SPM) and its other side effects which have fueled ongoing debate about the role of RAI ablation and ablation dose in low risk patients with WDTC.

In patients with follicular cell origin thyroid cancers (i.e. WDTC) who had total or near thyroidectomy, RAI is used to destroy macroscopically residual normal thyroid tissue (adjuvant ablation). The theoretical goals of adjuvant ablation are: *i*) to destroy any residual microscopic disease; *ii*) to enhance sensitivity of diagnostic whole body iodine scan (WBIS) and specificity of serum Tg which facilitate follow up and early detection of recurrence or metastatic disease; and *iii*) use of post ablative WBIS which is more sensitive than diagnostic WBIS for detection of nodal or distant functioning metastases (Carballo and Quiros, 2012).

Remnant Ablation or Not in Low Risk WDTC?

There is large number of proponents of RAI ablation in high and intermediate risk patients with a tumor >4cm, gross extrathyroidal extension, aggressive histology, and presence of distant metastases due to its established role in reducing the recurrence and improving the survival (Mazaferri and Young, 1981; Yamashita et al., 1997; Pacini et al., 1994; AACE, 2001; Brierley et al., 2005). Similarly, there seems to be a consensus among major stake holders regarding not using adjuvant RAI ablation for tumor <1cm including multifocal microcarcinoma without any high risk features (British Thyroid Association Guidelines, 2007; Cooper et al., 2009). For patients in between these extremes, evidence for RAI effectiveness is largely inconclusive, conflicting or lacking (Maenpaa et al., 2008). However, despite the lack of robust evidence, use of RAI has been increasing in low risk patients which raise concern that these patients are being over-treated (Haymart et al., 2011) with an undeniable chances of radiation induced SPM and other long term side effects (Iyer et al., 2011). The absolute risk for radioiodine-induced cancers has not been well established, but the risk of any SPM after initial diagnosis of thyroid cancer is increased approximately 30% over that of the general population (Sandeep et al., 2006) and the risk appears to increase with increasing cumulative administered activity (Rubino et al., 2003). Radioiodine treatment may be associated with nausea, taste disturbance, transient hypospermia and amenorrhea; permanent gonadal damage has been observed with cumulative activities exceeding >500 mCi (18500 MBq) (Maenpaa et al., 2008).

A land mark retrospective study (576 patients) published by Mazzaferri and Young (1981) revealed lowest recurrence and mortality in patients who had near total thyroidectomy, RAI and thyroxin therapy while in tumor <1.5cm, RAI did not have significant impact. Mazaferri and Kloos (2001) published findings based on 1510 patients (without distant metastases at the time of initial therapy) who were followed-up for 40 years, that RAI ablation to be an independent variable that reduced locoregional recurrence, distant metastases, and cancer death. However, these findings were not confirmed in an analysis performed in an identical fashion on a series of 1542 patients treated at Mayo clinic (Grebe and Hay, 1997). In 2002, Mayo Clinic again presented data of 2444 patients and claimed that RAI ablation had not improved already excellent cause specific mortality (CSM) and tumor recurrence (TR) in low risk patients managed by near total thyroidectomy and conservative nodal excision (Hey et al., 2002). Schlumberger and Hay argued that extent and completeness of thyroidectomy (adequacy of surgery) was the seminal reason of different results in these studies (Wartofsky et al., 1998). This notion was further supported by a multicenter Canadian trial upon 1578 patients revealed low TR and CSM in patients with residual microscopic disease treated postoperatively with either RAI ablation or external beam radiotherapy or both together than those treated with thyroid hormone alone. While in patients without obvious residual disease, RAI ablation did not significantly improve survival (Simpson et al., 1998). However, National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) published data of 4,767 patients with >5 year follow-up in 2010 with a revised conclusion of no significant impact of RAI ablation upon survival of low risk patients (Jonklaas et al., 2010). NTCTCSG also ruled out its previous findings published in 2006 showing adverse effect of RAI on over-all survival in low risk patient (Schvartz et al., 2012). Schvartz et al. (2012) published a retrospective study accrued 1298 low risk patients with a median follow up of 10 years which

failed to prove any survival benefit of RAI after surgery in low risk group with WDTC. So the controversy is still on about the use of RAI in low risk patients with WDTC as available data are fueled by retrospective and non-randomized clinical studies. Due to very low long-term mortality rate in low risk patients, even without ablation, raises serious doubts whether it can be reduced further and whether a study with sufficient power could in fact be designed to detect a meaningful difference in mortality. To reach a consensus whether RAI can safely be omitted in low risk patients with WDTC and avoiding these patients from possible SPM and other side effect of RAI, we must wait for the results of the non-inferiority randomized trial currently underway in United Kingdom (Mallick et al., 2012).

Low or High Dose of RAI for Remnant Ablation?

Another area of ongoing controversy is the optimal dose of RAI required to successfully ablate remnant tissue after total or near total thyroidectomy with a single administration in low risk group. This can be achieved by either dosimetry method introduced by Benua et al. (1962) or by fixed empiric activity of RAI. According to Maxon et al. (1983), about 30,000 rad (300Gy) radiation dose to thyroid bed was required for successful ablation and Bal and Padhy (1996) found 50mCi (1850MBq) of RAI to deliver this required dose to thyroid bed after total thyroidectomy. However, due to cumbersomeness of dosimetry method, majority of treating physicians have adopted fixed empiric activity of RAI (30-200mCi or 1110-7400MBq) with no consensus about adequate ablative dose in low risk patients. Some are proponents of low dose like 30-50mCi (1110-1850MBq) of RAI (Leung et al., 1992; Bal et al., 1996) while others believe that a higher dose like 100-150mCi (3700-5550MBq) is more effective in ablating the remnant thyroid tissue (Doi et al., 2000; Doi and Woodhouse 2000; Sawka et al., 2004). The basic reason of this disagreement is due to lack of reliable evidence from retrospective and non-randomized nature of most of studies, different selection criteria, variation in adequacy of surgery and different criteria used for successful remnant ablation. Advantages of low dose of RAI are shorter stay in hospital, fewer side effects, lower risk of SPM and reduced cost of treatment (Mallick et al., 2012). While proponents of high RAI dose give more weightage to benefits of complete ablation rather than insignificant side effects of higher doses of RAI. A historical large clinical trial was conducted by Bal et al. (2004) from India including 509 patients with WDTC who were divided into 8 treatment groups [received RAI from 15-50mCi (555-1850MBq)] to find out the optimal ablative dose. They concluded that a RAI of at least 25mCi (925MBq) had better chance of remnant ablation and any activity between 25-50mCi (925-1850MBq) of RAI was found adequate for remnant ablation (Bal et al., 2004). However, this study was criticized due to inadequate surgery in 28% patients resulting in higher neck uptake of RAI, variable time between ablation and surgery and low number of patients in groups who received least RAI.

A systematic review of randomized and observational studies (predominantly with small sample sizes) was inconclusive as to whether low dose RAI (30mCi or 1110MBq) was associated with rates of ablation success that were similar to or lower than rates with high-dose radioiodine (100mCi or 3700MBq) (Hackshaw et al., 2007). However, a recently published metaanalysis of nine randomized studies including 2569 patients revealed 30mCi (1110MBq) RAI ablative dose as effective as 100mCi (3700MBq) with similar quality of life, less common adverse effects, and a shorter hospital stay (Cheng et al., 2013). But a metaanalysis including 13 studies comparing outcomes in 967 patients (518 treated with low dose and 449 treated with high dose RAI) revealed better efficiency of high RAI dose than low dose in achieving successful ablation (Doi and Woodhouse, 2000). Due to these variable results, there has been a lack of consensus among various thyroid organizations on the optimum RAI dose for remnant ablation in low risk group. The British Thyroid Association's 2007 guidelines recommend the use of high dose (BTA Guidelines, 2007). National Comprehensive Cancer Network (NCCN guidelines. 2010), the American Thyroid Association (ATA guidelines, 2009) and European Thyroid Cancer Task Force consensus report (ETCTF consensus report, 2006) advise that clinicians can choose between the low dose and the high dose due to lack of reliable evidence from large randomized studies (Mallick et al., 2012). In 2008 a prospective randomized open label trial from Finland was published which compared the efficacy of low [30 mCi (1110 MBq) of I-131] and high dose [100 mCi (3700 MBq) of I-131] in 160 patients with total or near total thyroidectomy (Maenpaa et al., 2008). The results of this trial showed that low ablative dose has similar efficacy to higher dose with lesser side effects (Maenpaa et al., 2008). Meltem Caglara et al. (2012) from Turkey conducted a prospective randomized trial upon 108 low risk patients and found equal successful ablation rates in patients treated with 21.6mCi (800MBq) and 100mCi (3700MBq) of RAI. Schlumberger et al. (2012) published multicenter randomized French trial including 752 low risk patients (pT1 or pT2 with or without nodal metastasis but no distant metastasis) who had total thyroidectomy for WDTC and given 30mCi (1110MBq) and 100mCi (3700MBq) of RAI. They found similar successful ablation rates in low and high dose groups and similar ablation efficacy in patients pretreated with rhTSH or thyroid hormone withdrawal (Schlumberger et al., 2012). Mallick et al. (2012) published findings of a similar and carefully designed randomized, non-inferiority multicenter British trial (HiLo Trial) including 421 patients with WDTC (T1-3, N0/N1/Nx, Mo). They also inferred that 30mCi (1110MBq) radioiodine was as effective as 100mCi (3700MBq) dose with a lower rate of adverse events. The plausible reason of cascade of these recent studies favoring low ablative dose of RAI in patients with WDTC is adequacy of total or near thyroidectomy leaving little tissue over thyroid bed translated into low baseline serum Tg levels. This notion is supported by an ancillary observation in a study which revealed unsuccessful ablation in all 18 patients with serum Tg≥20ng/mL at baseline regardless of dose of

RAI administered, whereas it was successful in 83 (61%) of patients who had a serum Tg concentration <20ng/mL (Maenpaa et al., 2008). Similarly the baseline stimulated serum Tg level with negative antithyroid antibodies was <2ng/ml in 111/438 patients in HiLo Trial (Mallick et al., 2012) and ≤1ng/ml in 315/652 patients of French Trial (Schlumberger et al., 2012). This important observation from these randomized trials draws our attention towards "completeness" of total or near total thyroidectomy and importance of high volume thyroid surgeons. Therefore, a good surgery helps nuclear physicians in treating these low risk patients using low dose RAI for remnant ablation which is cost effective, requires shorter hospital stay [or no stay in countries where 30mCi (1110 MBq) can be given on out-patient basis] with lower short and long term adverse effects. Furthermore, inclusion of these patients with adequate thyroid surgery in ongoing randomize trials would certainly help to ascertain the role of adjuvant RAI in patients with low risk WDTC.

We conclude that in low risk WDTC, an adequately performed total or near thyroidectomy ensures use of either low or no adjuvant RAI and minimizing the probabilities of second primary malignancy and adverse effects. The evolving results of ongoing randomized trials upon low risk patients may shift the burden from nuclear physicians to high volume thyroid surgeons and endocrinologists.

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