Editorial

Low and High Radio-Iodine-131 Doses in Postoperative Ablation in Differentiated Thyroid Carcinoma

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The goals of post-surgical RAI therapy in patients with differentiated DTC are to ablate residual normal thyroid tissue that may facilitate surveillance,) Also the potential tumoricidal effect on residual microscopic RAI-avid disease, and to provide a post-treatment whole-body scan that may reveal undetected local or distant metastases.Although, these goals are important, the ultimate endpoint of post-surgical ablation is to minimize DTC recurrence and death by eliminating residual normal thyroid tissue or residual microscopic disease that could be a focus for future recurrence***(1).***

Successful RAI-131 thyroid remnant ablation is associated with better prognosis with regard to both recurrence-free and overall survival, lower rates of distant metastases, and reduced cancer mortality rates, compared with only surgery or surgery and L-thyroxin therapy alone ***(2).*** It also facilitates long-term follow up of patients with DTC. It was shown by ***Verburg et al***. that a successful ablation itself seems to be a highly important prognostic factor for long-term outcome. They found that the patients with a successful ablation, 87% were still free of the disease after 10 years, whereas of the patients with an unsuccessful ablation, only 50% were free of disease with thyroid cancer-related survival was (93% versus 78%) ($P > 0.001$)***(3).***

After four decades of follow-up, based on regression modeling of 1510 patients without distant metastases at the time of initial therapy, **Mazzaferri** and ***Kloos*** found thyroid remnant ablation to be an independent variable that reduced loco regional recurrence, distant metastases, and cancer death. A similar observation has also been made by the National Thyroid Cancer Treatment Cooperative Study group ***(4),*** they had reconfirmed that postoperative RAI treatment was associated with improved cancer-specific mortality rates and reduced disease progression in both papillary and follicular cancer***(5).***

Side effects and risks of radioactive iodine therapy have been reported, including salivary

gland problems (dry mouth, alterations in taste, or salivary gland pain),

Lacrimal problems (watery eyes, and tear duct blockage) ***(6),*** risk of dental caries and oral problems (post-RAI xerostomia). Loss of taste that can become permanent) ***(7),*** as well as increased risk of secondary primary malignancies from high-dose RAI therapy ***(8, 9).***

All previous data suggests that it is important to achieve complete ablation after diagnosis in order to ensure the best possible prognosis for a patient. And to reduce the ablative RAI131 dose as much as possible to reduce the incidence of the side effects.

ATA guidelines for RAI dose selection is based on patient risk factors. It states that low-risk patients receive 80-120 mCi, according to the risk of patients. The ATA guideline states that patients should receive the least dose that could achieve complete ablation ***(10).***

Regarding administered activities, published guidelines give no strong conclusions on the level of activity to administer for an ablation, which can vary from 30 to 100 mCi for remnant ablation that generally may show similar rates of successful remnant ablation and recurrence rates. However, the goal is to administer the lowest activity possible that will effectively eliminate the residual normal thyroid tissue ***(10-12).***

Many studies done to evaluate the effect of therapeutic dose concluded showed that there is no significant difference regarding the ablation outcome between the high and the low RAI-131in low risk group (2, 12-23).

In patients defined as high risk according to ATA and ETA guidelines ***(10, 24),*** high RAI activities are recommended. Much debate still exists regarding the activities administered in intermediate risk (microscopic invasion of tumor into the peri-thyroidal soft tissues, aggressive tumor histology, and node positive). In this context, no evidences are provided regarding the optimal RAI activity to be administered and current recommendations, advocating the use of high RAI activities, are based mainly on the expert opinion rather than clinical evidence***(10, 24).***

Low Dose Ablation:

Elrasad et al.(2014), a prospective, randomized trial ever performed that involved 88 patients of low and intermediate risk with complete tumor and pathologic LN excision, and no evidence of residual disease in post-operative evaluation by ultrasonography. Patients were randomized into two groups then we prospectively compared the overall response rate in each group. They found that 23 patients in group 1 from a total of 39 (58.9%) included in Low RAI131-dose group, have achieved successful ablation with no significant residual functioning thyroid tissue

in the first follow-up DxWBS scan done after 6-9 months, TG level <2ng/ml, and no cervical

LN's on follow up US. The response rate in group II was (75.5%) (37 patients from a total of 49) (P value = 0.098). Although no significant difference in ablation rate between the two groups.However, Limitations of this study were; small number of patients and short follow up duration (6-18 months)***(25).***

Similar results were reported by ***Castagn et al***. in a retrospective study, involved 225 DTC patients classified as intermediate risk. They stratified DTC patients in two homogenous groups, according to the RAI activity given for remnant ablation: 85/225 patients (37.8%) were treated with low RAI activities (1110–1850 MBq) and 140/225 (62.2%) with high RAI activities (>3700 MBq). All patients had been treated with near total thyroidectomy; all patients received RAI therapy after thyroid hormone withdrawal (THW) or after recombinant human TSH. At 6–18 months (median 9 months) after initial therapy, patients were evaluated to define the clinical status. When stimulated serum TG was undetectable (<1.0 ng/ml) and neck US (and diagnostic WBS when performed) were negative, patients were defined as in remission. 56(40%) patients treated with low and 84/140 (60%) patients treated with high RAI activities fulfilled the criteria for remission No difference in clinical status was found between patients treated with low or high RAI-131 activities (P value= 0.56). Biochemical disease (detectable serum TGwith no evidence of disease) was found in 16/85 (18.8%) patients treated with low and in 20/140 (14.3%) patients treated with high RAI-131 activities. Metastatic disease was found in 18/85 (21.2%) patients treated with low and in 36/140 (25.7%) patients treated with high RAI-131 activities ***(11).***

Also, ***Mallick et al.,*** 2012 also concluded that low-dose radioiodine plus thyrotropinalfa was as effective as high-dose radioiodine, with a lower rate of adverse events in their randomized study that was conducted at 29 centers in the United Kingdom involving 438 patients comparing low-dose and high-dose radioiodine, each in combination with either thyrotropinalfa or thyroid hormone withdrawal before ablation. Ablation success rates were 85.0% in the group receiving low-dose radioiodine versus 88.9% in the group receiving the high dose and 87.1% in the thyrotropinalfa group versus 86.7% in the group undergoing thyroid hormone withdrawal. Similar results were found for low-dose radioiodine plus thyrotropinalfa (84.3%) versus high-dose radioiodine plus thyroid hormone withdrawal (87.6%) or high-dose radioiodine plus thyrotropinalfa (90.2%). They suggested that high-dose group needs patient hospitalization for at least 3 days (36.3% vs. 13.0%, P<0.001). The proportion of patients with adverse events were 21% in

the low-dose group versus 33% in the high-dose group (P=0.007) and 23% in the thyrotropin alfa group versus 30% in the group undergoing thyroid hormone withdrawal (P=0.11) ***(12).***

In the study of ***Schlumberger, et al,***(2012) they stated that the use of recombinant human thyrotropin and low-dose 30 mCi postoperative RAI-131 ablation may be sufficient for the management of low-risk thyroid cancer. It was randomized trial of 715 patients, comparing 30mCi versus 100mCi Inclusion criteria were an age of 18 years or older; total thyroidectomy for DTC; absence of distant metastasis; and no iodine contamination. Thyroid ablation was assessed 8 months after radioiodine administration by neck ultrasonography and measurement of recombinant human thyrotropin–stimulated thyroglobulin. Ultrasonography of the neck was normal in 652 (95%), and the stimulated thyroglobulin level was 1.0 ng per milliliter or less in 621 of the 652 patients (95%) without detectable thyroglobulin antibodies. Thyroid ablation was complete in 631 of the 684 patients (92%). The ablation rate was equivalent between both ^{131}I doses ***(23).***

Furthermore,***Bal, et al.*** 2012, reported that first-dose ablation rates at 6 months in the stratified randomized trial conducted on 450 patients to compare between lower RAI-131 activities (25 and 50 mCi) and activities as high as 100 mCi. All patients underwent pre-ablation RAI-131 whole-body scan, 48-h radioiodine neck uptake measurements and post-therapeutic scans. Evaluation was performed after 6 months. First-dose ablation success rate was 81.5, 84.9, 88.5, and 84.2% in the 25, 50, and 100mCi groups and overall, respectively. Histology had no effect on ablation rate ***(16).***

Another study of ***Caglar, et al.***(2012), suggested that remnant thyroid tissue in patients with low-risk, well-differentiated thyroid cancer after total thyroidectomy can be ablated with 21mCi of I-131. The success rate is not different from that obtained with 100mCi I-131. It was conducted on a total of 108 non metastatic low-risk patients with DTC had I-131 ablation for the postoperative thyroid remnant. 53 patients received a low dose 21mCi (800 MBq) and 55 patients received a high dose 100 mCi (3700 MBq) of I-131 after total thyroidectomy. In low dose RAI group, 32 out of 53 (60%) and 43 out of 53 (81%) patients were successfully treated versus 35 out of 55 (64%) and 42 out of 55 (76%) for high dose RAI group, respectively (P=NS). The differences were not statistically significant between the two groups ***(17).***

High Dose Ablation:

On the other hand ***Prpic, et al.***(2012), evaluated 259 DTC patients confined to the thyroid has reported that 100 mCi of RAI was significantly more effective in thyroid ablation

than 30–50 mCi and also superior to 75 mCi. However, ablation rates were nearly similar after a second RAI dose. This second dose ranged from 30–100 mCi. Unfortunately, the authors did not explain their rationale for the second ablation dosage, plus the results of the first ablative dose activity outcome was contradictory to that of the second dose***(26).***

Also a meta-analysis of 19 studies by ***Doi& Woodhouse*** on 2000 compared 518 patients ablated with 30 mCi against 449 ablated with 100 mCi, they found that 100 mCi of RAI was significantly more effective and concluded that one in seven recurrences would have been prevented by high-dose ablation***(27).***

Furthermore ***Pacini, et al.*** stated that 'when using stimulation with rhTSH, a 30 mCi standard dose of RAI is not sufficient for satisfactory thyroid ablation' ***(28).***

No RAI ablation in low- or intermediate-risk DTC patients:

Rosario et al. (2012) in their study of 136 Patients who had initial stimulated TG values of <1.0 ng/ml, and their follow-up consisted of monitoring non-stimulated serum TG levels and neck ultrasound. None of these patients had the further assurance of 'absent disease' with a negative post-RxWBS. Lymph node metastases were 'excluded' by ultrasound and the lack of suspicious nodes at surgery. Prophylactic cervical node dissection was not performed. Patient follow-up ranged from 12 to 72 months (mean, 44). They concluded that a larger number of patients with longer follow-up were needed to confirm this approach in the post-operative follow-up of 'low-risk' non-RAI-ablated DTC patients ***(29).***

Also***Ibrahimpasic, et al,***(2012), recommended no post-operative RAI ablation in low and intermediate-risk patients with un-stimulated TG<1.0 ng/ml, claiming equivalent outcome when comparing non-RAI-treated patients with RAI-treated patients. The authors support using un-stimulated TG, '.because recurrence rates are so low with un-stimulated TG measurements, one can argue that the routine use of stimulated TG in these patients. The limitations of this follow up methodology using stimulated TGfor detecting DTC recurrence have been described earlier. The mean patient follow up was a relatively short duration of 59 months. Careful scrutiny also reveals that this article's cohorts were not equivalent, and there were two major differences; out of 75 patients, 69 (92%) with known nodal metastasis received RAI ablation, while 6 (8%) were not ablated and among the intermediate-risk patients, based on the authors' classification system, more than 90% (73/81) of patients were treated with RAI ablation while <10% (8/81) were not. This indicates that the results are skewed against RAI ablation as the RAI-ablated cohort was at a higher risk than the cohort without ablation. ***(30, 31).***

Another publication in 2013 has reported that the number of metastatic DTC nodes should be determined before post-operative RAI ablation is performed (***Tuttle & Sabra***)(32). they recommended no RAI with nodal metastasis unless there are more than ten metastatic nodes that are <5 mm in size, or more than five metastatic nodes of which the majority are 5–15 mm in size, or any single node more than 15 mm in size. The authors state, '.these are clearly arbitrary criteria for indications of RAI treatment. Accordingly, the validity of this approach is unestablished, stressing the need for prospective trials that would confirm or refute these criteria and in order to firmly establish the clinical management that would minimize the risk of recurrent DTC***(32).***

Follow up and Risk of Recurrence Following RAI Ablation:

An obvious concern before adopting low-dose iodine ablation is its effect on disease recurrence on follow up.***Kukulska et al.*** in 2010 concluded that no significant differences in the 5 years efficacy of thyroid remnant radioiodine ablation using 30, 60 and 100 mCi were observed in low-risk DTC patients operated by total thyroidectomy and neck lymph node dissection. The study involved 309 DTC patients with no clinical, histopathologic, sonographic or biochemical signs of persistent disease after total thyroidectomy and appropriate extent of neck lymph node dissection. For radioiodine thyroid remnant ablation, 30 mCi of ^{131}I was applied in 86 patients, whereas 60 mCi in 128 and 100 mCi in 95 patients. The median follow-up was 10 years for subjects treated with 30 mCi and 60 mCi and 6 years for patients treated with 100 mCi of ^{131}I. After first dose ablation, a second ^{131}I treatment was necessary in 10% patients, without difference between groups treated with 60 and 100 mCi and in 22% patients treated with 30 mCi. All patients entered full remission. To evaluate the long-term outcome of the adjuvant ^{131}I treatment, the course of the follow-up and the most recent disease status were assessed by sonography, radiological examinations and serum TG estimation (on LT4- suppressive treatment). Within the whole observation period local relapse was stated in 2 (2.4%), 4 (3%) and 3 (3%) patients treated with ^{131}I activities of 30 mCi, 60 mCi and 100 mCi respectively and serum TG concentration on LT4-suppressive treatment was low, without differences between groups***(21).***

Another study of ***Kuruijff, et al***., (2013) reported that decreasing the dose of RAI at initial ablation for patients with pT1–pT3 PTC does not seem to be associated with an increased risk of structural cancer recurrence. They conducted a retrospective study of 1,171 patients with PTC from 1990 to 2012 who underwent thyroidectomy and RAI. They divided the cases into those who had < or =3

GBq (75 mCi) RAI (group A) and those who had >3 GBq (75 mCi) RAI (group B). The primary outcome measure was the rate of structural recurrence. Patients were followed for a mean of 60 months. The overall rate of recurrence was 8%. When corrected for TG stage, the recurrence rates were not different for T1 tumors (2% group A versus 4% group B; P = .54) nor for T2 and T3 tumors (P = .36 and .55, respectively) ***(33).***

In Elrasad, et al., (2014). study follow up 6-18 months after the ablative RAI-131 dose was available for 12 patients of the low-dose group all of them didn't have recurrence, and 17 cases of the high-dose group, 16 of them had no recurrence an one patient had local recurrent disease that was detected on US and WBS with RAI with re-elevation of Tg level. Obviously they could not draw a conclusion from this small number of patients, over that short duration of follow up ***(25).***

On the other hand, ***Doi& Woodhouse*** in 2007 published a meta-analysis of risk of recurrence following high- vs low-dose ablation in 2584 patients (1094 low dose and 1490 high dose) extracted from the 22 datasets, six of them were randomized controlled trials with mixed surgical status (group 2), four were cohorts with near-total thyroidectomy (group 1), and 12 were cohorts with mixed surgical status (group 3). Most studies used a high dose of (75-100 mCi). The result of high-dose to low-dose group relative risk (RR) of non-ablation after the first dose was 0.58 (95% CI, 0.46-0.74) for the cohort studies in group 1 and 0.88 (95% CI, 0.78-1) for group 3. RR was 0.68 (95% CI, 0.43-1.07) for the randomized controlled trials (group 2). The subgroup summary and individual study RRs and 95%. Finding further support for high-dose ablation in reduction of recurrent disease ***(34).***

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