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# REVIEW OF PAPILLARY CARCINOMA THYROID MANAGEMENT IN A GOVERNMENT HOSPITAL. A CORRELATION WITH MACIS SCORING- A CROSS SECTIONAL STUDY

Oncology

**Dr. Syed Afroze Hussain*** M.S., MCh, Department of Surgical Oncology, Centre for Oncology, Government Royapettah Hospital, Kilpauk Medical College, Chennai, Tamilnadu, India *Corresponding Author

**Prof Dr. S Subbiah Shanmugam** M.S., MCh, Department of Surgical Oncology, Centre for Oncology, Government Royapettah Hospital, Kilpauk Medical College, Chennai, Tamilnadu, India

**Dr. Prinith Siga Fells** Mch Resident, Department of Surgical Oncology, Centre for Oncology, Government Royapettah Hospital, Kilpauk Medical College, Chennai, Tamilnadu, India

## ABSTRACT

**Background:** Papillary carcinoma thyroid is the commonest malignancy affecting the thyroid gland. The recommended treatment is total thyroidectomy followed by radioactive iodine therapy depending on various factors. Radioactive iodine facilities are not present in most of the hospitals. The patients are followed up with suppressive dose of thyroxine alone. As the disease process itself is quite slow most of the patients are long time survivors. Thus adequate evaluation of radio iodine therapy becomes a time consuming process and patients may be lost in follow up. This is further compounded by the fact radio iodine requirement is debated in intermediate risk group with further on-going studies. The database from these hospitals would be eye opener in this situation.

In the year 2016, 123 patients visited the hospital on follow up with at least 5 years after treatment of papillary carcinoma thyroid. As per the prevailing ATA guidelines 61 patients should have received radio iodine. Seven of these patients had taken radio iodine in private centres. The remaining 116 patients did not receive radio iodine. As per the MACIS score 42 patients should have received radioactive iodine. The MACIS score of the patients who received radio iodine showed 3 had a score of less than 6 and 4 had a score of more than 6. All the 4 patients had metastatic disease at presentation. Seven patients with a MACIS score more than 6 had developed recurrent disease in follow up, among these 2 of them had received radio iodine therapy. None of the 81 patients with MACIS score of less than 6 developed recurrences.

**Conclusion:** Recurrent disease can be predicted with MACIS scoring. This score is an excellent tool in analysis of patients who might have aggressive diseases. Patients with a score of less than 6 can be confidently reassured of cure. This score should be applied in all patients with regard to further treatment and aggressive follow-up. Further studies have to be taken up with other parameters like histological grade along with this score to delineate necessary modifications in therapy.

## KEYWORDS

Papillary Carcinoma Thyroid, Total Thyroidectomy, MACIS score, Radio Iodine Ablation, Thyroxine

### Introduction

Papillary thyroid cancer is the most common type of thyroid cancer making up to 70-80% of all thyroid cancer cases. The incidence is on the rise over the last few decades. Thyroid cancer affects women more often than men and usually occurs between the age group 25 and 65 years. Surgery remains the standard treatment followed by Radio Active Iodine (RAI) ablation based on clinico pathologic factors. It's an ironical situation where radiation is known established etiological factor in papillary carcinoma thyroid is to be used in the treatment of the same. Though there is no role for RAI in low risk patients, RAI in other patients continues to be debated due to lack of prospective randomized control trials supporting its role in reducing recurrence rates and impact on survival. Due to limited resources in developing countries most patients are not able to receive RAI.

### Patients and Methods

In the year 2016, 123 patients had come on follow-up after 5 years of completion of treatment for papillary carcinoma thyroid. The patient's data from the hospital records and files from master case sheets were taken for retrospective analysis. The data required for the calculation of the MACIS score was tabulated for grouping them. Each group was defined and the patients who received radio iodine as per the prevailing ATA guidelines on their own were noted. In the follow-up the patients who developed recurrent disease was also tabulated.

Details of the treatment protocol - Total thyroidectomy with central compartment neck dissection was done in nearly all the patients. The recurrent laryngeal nerve was identified and was traced up to its point of entry into the larynx and meticulously all thyroid tissue was removed. Patient who required a neck dissection, a functional neck dissection was done removing level II, III, IV and V nodes preserving the Spinal accessory nerve, Internal jugular vein and Sternocleidomastoid muscle. Because of the non-availability of radio iodine the patients were given the option of getting further treatment in hospitals where it is available. Due to financial and domiciliary issues most of the patients were unable to go to centres with these facilities. These patients were given suppressive dose of thyroxine as further treatment. The TSH level was maintained <0.5 U for low risk and < 0.1U in high risk patients. Calcium with vitamin D was given regularly to all patients.

### Results

One hundred and twenty three papillary carcinoma thyroid patients were seen in the follow up in the year 2016. These patients had completed 5 years of follow up after treatment of papillary carcinoma thyroid. The age at presentations ranged from 15-80 years with a median age of 35 years. There were 81 patients with age less than 45 years and 42 with age more than 45 years at the time of initial presentation. There were 91 females and 32 males in the study group. Solitary nodule was the commonest presentation with 76 patients and multi nodular presentation were 40 and there was a occult primary in 7 other patients. There were 80 patients with disease limited to the thyroid and 29 patients had unilateral nodes and 14 had bilateral nodes in the neck.

MACIS scoring- There were 81 patients with a MACIS score of 6 or less. Forty two patients had a score of more than 6. These patients were sub-divided to 6-6.9, 7-7.9 and 8 or more and there were 37, 3 and 2 patients respectively.

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Metastasis- Four patients presented with metastasis in the initial work up and they had a score of more than 6 and on subgrouping 3 were in the subgroup of 7-7.9 and 1 had a score of more than 8.

Age- A total of 76 patients were diagnosed with papillary carcinoma thyroid with age less than 40. Sixty five patients with age less than 40 had a score of less than 6, while 11 patients with age less than 40 had a score of more than 6 and all of them were in the subgroup of 6-6.9. In comparison only 14 patients in the age group of more than 40 had a score of less than 6 while 33 patients in the age group of more than 40

had a score of more than 6. Of them 28 were in the sub group of 6-6.9, 3 were in the subgroup of 7-7.9, and the remaining 2 had a score of more than 8.

Completeness of surgery- A total of 116 patients were found to have a complete resection done as per operative and pathological HPE analysis. All the 81 patients with score less than 6 had a complete resection. Complete resection was done in 35 patients with score more than 6. Incomplete resection was found in 7 patients. In the subgroup of 6-6.9 there were 4 patients, 7-7.9 there were 2 patients and more than 8 there was one patient who had incomplete resection

Invasion –beyond thyroid capsule- A total of 20 patients were found to have invasive disease beyond the thyroid capsule. Only 3 of the 81 patients with score less than 6 had invasive disease. While 17 of the 42 patients with score more than 6 had locally invasive disease. On sub grouping 13 of the 37 patients with score 6-6.9, 2 of the 3 with score 7-7.9 and 2 of the 2 with score more than 8 had locally invasive disease.

Size- In the follow up 123 patients there were 7 patients who had a size of less than 1cm, 22 patients with a size of 1-2cms, 62 patients had a size of 2-4cms and the remaining 32 had a size of more than 4cms. There were 81 patients with MACIS score of less than 6 in which 4 patients had a size of less than 1, 12 had a size of between 1-2cms, 48 had a size of 2-4cmsand 17 of them had a size of more than 4cms. In the group of 37 patients with MACIS between 6-6.9 there 3 patients with a size less than 1cm, 10 with a size between 1-2cms, 14 with a size between 2-4cms and 10 had a size more than 4cms. In the MACIS group of 7-7.9 all the 3 patients had a size between 4-5cms. In the MACIS score of more than 8 both the 2 patients had a size between 4-5cms.

Radio iodine therapy and follow up: All the patients were started on suppressive doses of thyroxine after discussing their ability to receive radio iodine in private centres. The prevailing ATA guidelines were used in the department previously and accordingly 61 of the 123 patients should have received radio iodine. Seven of these patients took radio iodine therapy. As per the MACIS protocol patients with a score of more than 6 should have received radio iodine. In all 42 patients should have received radio iodine in accordance. But the data shows that 7 patients had received radio iodine in which there were 3 with a score of less than 6 and 4 with a score of more than 6. None of the 81 patient with a score of less than 6 had recurrent disease. While 7 of the 42 patients with a score of more than 6 developed recurrent disease in the cervical nodes. Nodal dissection was done for these patients during follow up admission. Among these 7 patients 2 of them had previously received radio iodine therapy.

## Discussion

Around two thirds of the patients seen in the study were less than 45 years. There were 91 females to 32 males in the study group. The disease is twice common among females according to GLOBOCAN data base reports [1] and in our group there were females at ratio of 3:1. Some authors report a slightly higher incidence of about 2.9 times among females [2] The group had patients as early as 15 years most of the patients are in the group of 20-60 years, which is almost similar to global data of 25-65 years[3].

At presentation 43(35%) of the 123 patients had nodal disease. Unilateral nodal disease was present in 29 and bilateral nodal disease was present in 14 other patients. According to Nobuyuki Wada MD et al in his study an overall 64% had nodal involvement and 44.5% had ipsilateral lateral compartment nodal involvement[8]. Most studies show distant metastasis from PTC with frequency ranging from 1.73 to 8.4 % [5,6]. There were 4 patients in our 123 patients who had distant metastasis at presentation. As with other studies the most common site of metastasis from PTC is lung[7] .

The 5 year survival rates for thyroid carcinoma published by American cancer society based on November 2014 SEER data for all stages is > 99% for local disease and survival drops to 54% with the distant disease[9].

MACIS score developed in 1994 by Mayo Clinic is an accurate prognostic scoring system. It is used to delineate likely postoperative outcome and to determine the postoperative treatment and the intensity of surveillance for tumor recurrence. MACIS Score less than 6 is low risk and the cause specific 20 year mortality is 1%. Of the patients under follow up (123 Patients) 81 patients were low risk the reason being early presentation with small sized lesion and completeness of surgical procedure. Metastasis developed during the follow up were in the score 7-7.9 and score more than 8, which confirms the role of aggressive surveillance among score above 6. All the recurrences had a score more than 6. Again RAI was not given to majority of the high risk as RAI treatment involved patient preference and cost factors.

Following inferences can be arrived at from MACIS score, first with no recurrences or metastasis during the follow up period among the 81 patients with score less than 6 indicates RAI is not indicated for this group of patients. Secondly, RAI is indicated for patients with score more than 6 but even with RAI in this group recurrences and metastatic disease were high questioning the impact of RAI.

Of the 123 patients under regular follow up, review of histopathology showed 61 patients with high risk features according to ATA 2015 guidelines were candidates for RAI therapy. But only 7 patient received RAI therapy. Also two patients had nodal recurrence even after RAI ablation. Inspite very less number of patients treated with RAI there were no mortality reported among the follow up patients. This raises the question of significant impact of RAI therapy in improving the survival rates.

## Discussion and Controversies

The cornerstone in the management of differentiated thyroid carcinoma is surgery in the form of Total thyroidectomy. Usually surgery is followed by Radio Active Iodine (RAI) ablation[10] and suppressive dose of thyroxine. Various guidelines are in use and further studies are ongoing for clear definition of post-operative radio iodine in intermediate risk category of papillary thyroid cancer.
The primary goal of post operative RAI administration includes

1. RAI remnant thyroid ablation - to facilitate detection of recurrent disease
2. RAI adjuvant therapy- to improve DFS by theoretically destroying suspected but unproven residual disease in patients at increased risk of disease recurrence.
3. RAI therapy - improve disease specific and DFS by treating persisting disease in higher risk patients [22]

Based on the risk stratification by American Thyroid Association RAI remnant ablation is not recommended for ATA Low risk, recommendation is weak for ATA intermediate risk [24]. But there is strong recommendation for use of RAI in ATA High risk. [23,25] RAI is associated with improved survival in patients with papillary carcinoma thyroid with distant metastasis as per SEER cancer registry. There are mounting evidence to question and debate the usefulness of RAI even in high risk patients [33,34,35] with tumors ≥ 1.5 cm, multifocality, extra thyroidal disease and lymph nodal disease. Recurrence following RAI are reduced according to Mazzaferi et al [27,34]. It is doubted that the reduced recurrence following RAI ablation in Mazzaferi series may be due to surgery less than a complete Total Thyroidectomy. This is substantiated by Mayo clinic report[36] of comparable recurrence rates with or without RAI where complete thyroidectomy is routinely performed. Also to add, according to Simpson et al only patients with residual disease benefit from radioactive ablation [28]. Also in patients without obvious residual disease RAI does not significantly increase survival[37].

This raises the doubt that the role of RAI ablation in reducing recurrence may be over projected when used following a less aggressive surgery. Clear guidelines may evolve when RAI is used subsequent to complete surgery leaving behind no thyroid tissue, recurrence and survival rates are studied. According to EANM 2008 guidelines thyroid surgery when performed in highly expert hands and selected referral centres the positive influence of RAI may not be apparent[29].

The point in ablating the residual thyroid is that any tumour recurrence can be easily identified if all normal thyroid tissue is destroyed. The feared complication of a thyroid surgery like recurrent laryngeal nerve palsy and hypothyroidism is the reason behind surgeons doing a less than a complete thyroidectomy. Hence the addition of radio iodine ablation has been a part of the treatment protocol. Ablating normal thyroid tissue does not reduce recurrence but helps in early detection of recurrence with increasing Thyroglobulin (Tg) levels. But there are reports of very little elevation of Thyroglobulin even in the presence of

pulmonary metastasis[30], 20% of patients with lymph node metastasis may be undetectable in metastatic setting when patients are on Thyroxine[31]. Thyroglobulin level is undetectable in 93% during Thyroxine treatment[38].

All evidence available about the effects of RRA (Radio active iodine remanant abalation) on cancer recurrence and survival is retrospective. Current evidence suggest that some patients with DTC will benefit from RRA, while others will not[10]. For a significant group of patients evidence is inadequate or conflicting so that clear recommendation cannot be made[11,12].

The optimal $^{131}$I therapeutic activity for persistent neck disease or metastatic disease is uncertain, most of the evidence for a benefit of $^{131}$I therapy derives from studies where emprical activities of $^{131}$I were used[11,15,16]. The role of dosimetry and its impact on clinical outcome compared to emprical use of $^{131}$I is unclear[17,18]. There are three approaches to $^{131}$I first emprical fixed amounts, second therapy determined by upper limit of blood and body dosimetry and third quantitative tumor or lesional dosimetry. But comparison of these is difficult and till date there are no trials to address this issue.

In the management of loco regional recurrence the role of RAI is only in low volume disease or in combination with surgery. But surgery is the main stay of salvage in case of bulky disease or disease amenable to surgery. According to one study persistent Thyroglobulin elevation after surgery in loco regional recurrence , adjuvant RAI demonstrated no benefit[23].

$^{131}$I in pulmonary metastasis, micronodular or miliary metastases responds favourably unlike macronodular disease which rarely achieve complete response. For symptomatic solitary bone metastasis first option is surgical resection or high dose radiotherapy then comes the role of $^{131}$I but this rarely achieves complete response[19,20,21]. The survival drops to 54% in metastatic disease[9] shows even with RAI in metastatic setting the survival is poor.

Differentiated thyroid cancers frequently show reduced or no $^{131}$I avidity, measures to increase avidity have yielded disappointing results. Finally the recommendation to follow up the patients with suppressive doses of thyroxine keeping TSH < 0.1mU/L in high risk patients[22] also indicates the lack of complete reliability on RAI as an adjuvant. Suppressive doses of thyroxine may overestimate the benefit of RAI. The real benefit and effectiveness of RAI will be evident only when recurrence rates and survival rates are compared between patients undergoing RAI ablation and being followed up without suppressive dose of thyroxine and those with RAI and suppressive doses of thyroxine.

Long term side effects, uncertain effectiveness, cost and inconvenience certainly outweigh the potential benefits of RAI if any[39-45]. Among the various disadvantages risk of second malignancy is higher than previously thought[13].

The Genetic damage caused by therapeutic doses of $^{131}$ I has been studied using alkaline COMET length assay, grade of DNA damage and micronucleus assay of B lymphocytes. Observation shows that treatment with $^{131}$I for papillary thyroid cancer can cause DNA damage in circulating lymphocytes and causes significant increase in cytogenetic damage[46]. Though this has been found insignificant statistically as most of the Radioiodine induced damages are repaired in a week time[47].

Analysing the data the high risk category requiring RAI were 42 and 61 according to MACIS and NCCN/ATA guidelines respectively. This mismatch may be explained by the fact that majority of the patients aged less than 40 and a meticulously performed surgery may lower the MACIS score obviating the need for RAI. This shows a better surgery can avoid RAI therapy but this has to be validated through future RCT.
With lots of evidence for and against RAI in the management of Papillary Carcinoma thyroid current recommendation is RAI can be safely avoided in low risk and considered in intermediate risk. But a strong evidence exists for RAI role in high risk cases. Nevertheless following queries need to be answered "Does ablation of normal thyroid tissue by RAI improve survival?" "Role of RAI in case of decreased avidity to $^{131}$I?" " Do suppressive dose of thyroxine mask the pitfalls of RAI?" "Is there a de differentiation of tumor after RAI ablation?" "Why RAI has failed to improve survival in metastatic setting?" and finally "Why a comparable survival with less use of RAI as in our case."

## CONCLUSION

From our experience in treating papillary carcinoma thyroid, a meticulously performed surgery to remove entire thyroid tissue and nodal tissue in the form of neck dissection and suppressive doses of thyroxine, with fewer patients treated with RAI and survival rates comparable to current existing global trends question the real impact of RAI in improving survival rates in high risk differentiated papillary thyroid carcinoma. This has to be addressed by randomised control trials in the future. At present MACIS score should be regularly used to categorise patients for radio iodine therapy.

**TABLE 1 Classification based on pathology, patients requiring RAI, *T staging according to AJCC 7th edition for DTC.***

| Patients Low risk for RAI | Inter media te Risk | Patients High Risk For RAI | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | T1a | T2/N0 /N1<3 cm 55 | T3 | T4 a | T4b | Node s>3c m | Aggre ssive Histol ogy | Metastasis Disease during follow up | |
| Follow Up | 7 | T1b 10 | T2 45 | 17 | 20 | - | 16 | 4 | 4 |
| | | | | | 1-2c-2 2-4c-7 >4c-11 | | | | |

***TABLE 3(a) MACIS SCORE FOR PATIENTS UNDER FOLLOW UP***

| MACIS SCORE | Less Than 6 | 6-6.9 | 7-7.9 | More than 8 |
|---|---|---|---|---|
| No Patients | 81 | 37 | 3 | 2 |
| Patients received RAI | 3 | 2 | 1 | 1 |
| Patients who had Metastasis | 0 | 0 | 3 | 1 |
| Patients developing local or distant disease on follow up | 0 | 4 1 received RAI | 2 1 received RAI | 1 |

***TABLE 3(b)***

| | | No of |
|---|---|---|
| Size | Less than 1 cm | 7 |
| | 1-2cms | 22 |
| | 2-4 cm | 55 |
| | 4-5 cm | 17 |
| Invasion | Beyond thyroid capsule | 20 |
| Metastasis | | 4 |
| Age | Less than 39 | 76 |
| | More than 40 | 47 |
| Completeness of Surgery | Complete Incomplete | 116 |

***TABLE 4 MACIS SCORE***

| MACIS SCORE | Less than 6 | 6-6.9 | 7-7.9 | More than 8 | |
|---|---|---|---|---|---|
| | | No of patient s=81 | No of Patients =37 | No of Patients =3 | No of Patient s=2 |
| Tumor Size | Less than 1 cm=7-T1a | 4 | 3 | 0 | 0 |
| | 1-2cms=22-T1b | 12 | 10 | 0 | |
| | 2-4 cm=62-T2 | 48 | 14 | 0 | 0 |
| | 4-5 cm=32-T3 | 17 | 10 | 3 | 2 |
| | >5cms=0 | 0 | 0 | 0 | 0 |
| Invasion | Infiltration beyond the thyroid capsule-T4a | 3 | 13 | 2 | 2 |

| | | | | | |
|---|---|---|---|---|---|
| Metastasis | | 0 | 0 | 3 | 1 |
| Age | Less than 40 | 65 | 11 | 0 | 0 |
| | 40 years or more | 14 | 28 | 3 | 2 |
| Completeness of Surgery | Complete Incomplete | 81 | 33 | 1 | 1 |
| | | 0 | 4 | 2 | 1 |

***TABLE 5 MACIS SCORE FOR PATIENTS UNDER FOLLOW UP***

| MACIS SCORE | Less Than 6 | 6-6.9 | 7-7.9 | More than 8 |
|---|---|---|---|---|
| No Patients | 81 | 37 | 3 | 2 |
| Patients received RAI | 3 | 2 | 1 | 1 |
| Patients who had Metastasis | 0 | 0 | 3 | 1 |
| Patients developing local or distant disease on follow up | 0 | 4 1 received RAI | 2 1 received RAI | 1 |

***TABLE 6 showing Details of patients on Follow up***

| SL NO | | Clinical Presentation | No of Patients |
|---|---|---|---|
| 1 | Age | Age< 45 | 81 |
| | | Age> 45 | 42 |
| 2 | Gender | Males | 32 |
| | | Females | 91 |
| 3 | Clinical Presentation | Solitary Nodule | 76 |
| | | Multi Nodular Goitre | 40 |
| | | Occult Primary | 7 |
| 4 | Neck Nodes | Unilateral Nodes | 29 |
| | | Bilateral Nodes | 14 |
| | | No Neck Nodes | 80 |
| 5 | Surgery | Completion Thyroidectomy with Central neck dissection | 0 |
| | | Total Thyroidectomy With Central neck dissection | 80 |
| | | Thyroidectomy with U/L Neck Dissection | 29 |
| | | Thyroidectomy with B/L Neck dissection | 14 |
| 6 | Post Operative follow up | RAI Ablation | 7 |
| | | Re Operation for recurrence | 7 |
| | | Metastasis During follow up | 4 |
| | | Follow up with Suppressive Thyroxin | 123 |
| | | Presently in Follow up | 123 |
| | | Recurrence following RAI | 2 |

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