

Phase II Randomised
Controlled Trial of
Postoperative Intensity
Modulated
Radiotherapy(IMRT) in
Locally Advanced
Thyroid Cancers

Head Neck Oncology

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Background

Locally advanced thyroid cancers (AJCC - T4a, N1), are known to have high rates of loco-regional recurrences after conventional treatment with surgery and radioactive iodine therapy. Most patients with recurrences are amenable to salvage surgeries; however these surgeries have very high morbidity. This is because of the close proximity of the thyroid gland to important structures of the aero-digestive tract, like the larynx, trachea, esophagus and the recurrent laryngeal nerve. In a disease where life expectancy is good despite recurrences, quality of life is greatly compromised by repeated salvage surgeries with resection of parts of the aero-digestive tract.

A few retrospective studies have shown that the addition of radiotherapy (RT) after surgery and radioiodine treatment has decreased the loco-regional recurrence rate in locally advanced thyroid cancers (LATC). However, all these studies are retrospective and heterogenous with no clear indications or protocols for radiotherapy.¹⁻⁴

The revised ATA (American Thyroid Association) guidelines (2009) recommend use of radiotherapy in patients with gross extrathyroidal disease. Recommendation 41 of ATA guidelines states that, "The use of external beam irradiation to treat the primary tumor should be considered in patients over age 45 with grossly visible extrathyroidal extension at the time of surgery and a high likelihood of microscopic residual disease, and for those patients with gross residual tumor in whom further surgery or RAI would likely be ineffective."⁵ Thus the use of adjuvant RT in advanced differentiated thyroid cancer may be considered as standard of care.

However there are certain caveats to this:

1. The level of recommendation is B ('the strength of the evidence is limited by the number, quality, or consistency of the individual studies').
2. All the previous studies have been retrospective, with heterogenous patient population, no clearly defined inclusion criteria and end points.

3. There is no data regarding toxicity of adjuvant RT in any of these studies in any of these studies as most have been retrospective in nature.

As a result, the use of radiotherapy has not become a common clinical practice and standard of care, reflecting a lack of prospective data on toxicity and loco-regional control in locally advanced thyroid cancers.

We therefore plan to perform a Phase II randomized controlled trial looking at loco-regional control and toxicity of adjuvant radiation in locally advanced high risk thyroid cancer after surgery with or without radio-iodine ablation.

This study will help to define the role of this modality in management of thyroid cancer and provide prospective data on loco-regional recurrence and toxicity in this group of patients.

Aims/Objectives

Primary aim:

- To assess the impact of adjuvant RT on loco-regional control in patients with locally advanced thyroid cancers who have undergone surgery with or without radioiodine therapy

Secondary aim:

- To assess toxicity (early and late at 2 years) of adjuvant RT in these patients

Design

Phase II randomized study

Setting

Tertiary level comprehensive cancer care centre in Western India.

Patients and methods

All patients undergoing total thyroidectomy for locally advanced differentiated thyroid cancer presenting to our hospital will be considered for the study.

Inclusion criteria

A) All patients of thyroid cancer (papillary/follicular/poorly differentiated) who have undergone total/completion thyroidectomy at our institute and having at least two of the following features (listed below) intra-operatively and/or on histopathology

1. Gross extrathyroidal spread into soft tissues of the neck, trachea, esophagus, recurrent laryngeal nerve (constituting stage T4a)
2. R1/ shave resections (minimal residual disease)
3. R2 resections (gross residual disease)
4. Multiple lymph nodes positive(>2) with perinodal extension at level VI

B) Normal baseline haematological and biochemical parameters

Exclusion criteria

1. Anaplastic or medullary thyroid cancer
2. Previous history of radiation
3. Pregnancy
4. < 18 years
5. Patient unwilling to participate in the study

Prescreening

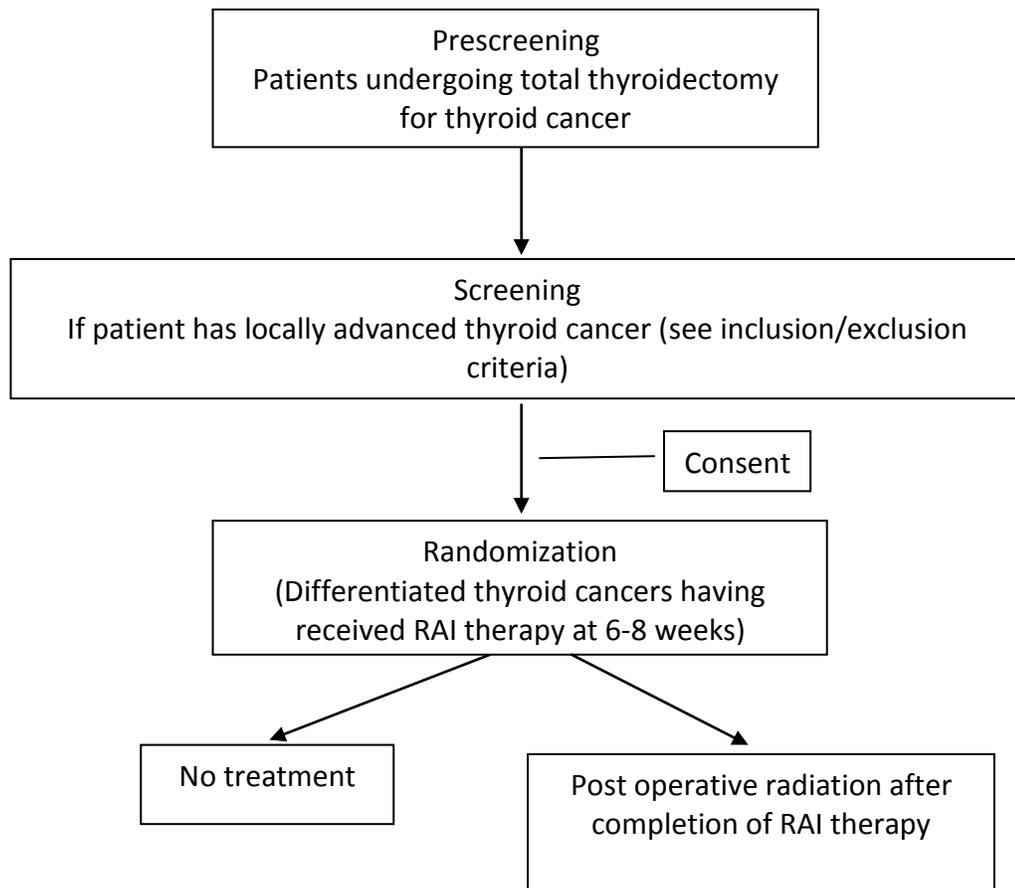
A detailed history including comorbid conditions and performance status of the patient will be recorded on presentation. A diagnosis of thyroid carcinoma (excluding anaplastic thyroid cancer) will be confirmed in our hospital and documented.

Patients will have undergone routine surgery in the form of total thyroidectomy/ completion thyroidectomy with or without neck dissection, as is standard practice for thyroid cancer. If the histopathology report along with the intra-operative findings is suggestive of locally advanced thyroid cancer (as defined above), patients will be screened for the study (Eligibility checklist, annexure 3). Patients will be explained about the trial and written informed consent will be obtained (Informed Consent, annexure 2).

Study Methodology

All patients who are willing to participate on the trial and have signed the informed consent form will be randomized to either receive adjuvant external beam RT or no treatment. All patients (irrespective of randomization), will proceed to receive radioactive iodine scanning and therapy as is standard for patients with locally advanced differentiated thyroid cancers. This will be performed between 4-6 weeks after thyroidectomy providing adequate period for thyroid hormone withdrawal, to allow TSH to rise beyond 30microIU/ml. Adjuvant radiotherapy will be administered after radioiodine therapy, within 8-10 weeks of the surgery. Patients in both arms of the trial will be followed up for 5 years.

Trial schema



Follow up assessment:

Patients will be followed up three monthly for the first two years, and 6 monthly thereafter.

Assessments for patients in RT arm:At completion of radiotherapy

Clinical examination

Acute toxicity reporting using toxicity criteria (CTC version 3)

3 monthly

Clinical examination only

6 monthly

Clinical examination

USG neck

Serum thyroglobulin

Serum TSH

Annually

QOL EORTC questionnaire will be administered **at baseline prior to start of RT and annually thereafter.**

At 2 years

LENT SOMA late toxicity reporting

Barium swallow

Assessments of patients in observation arm:3 monthly

Clinical examination only

6 monthly

Clinical examination

USG neck

Serum Thyroglobulin

Serum TSH

Annually

QOL EORTC questionnaire

Details of treatment

Total thyroidectomy:

Total thyroidectomy will involve removal of both lobes of the thyroid gland along with central compartment clearance. Neck dissection can be added as merited by the stage of the thyroid cancer and as per tumor board decision. In recurrent cases, surgery as warranted by the disease extent (completion thyroidectomy, thyroid bed recurrence excision etc) will be done.

Radio-Iodine treatment: I-131 ablation of residual tissue will be undertaken using the standard approach that exists in our institute. All necessary standard precautions and measures for radiation will be adopted. The dosage of I-131 will be based on the sites and extent of uptake on the RAI scan, as is the practice in the institute. Locally advanced thyroid cancers are administered higher dose of I-131 based upon the extent of disease noted at surgery, residual disease after surgery and the histology.

Radiotherapy details:

Pre-treatment work-up:

- Dental Care:

Adequate and appropriate dental care will be given including extraction of carious teeth, application of fluoride gel etc.

- Nutritional Support

Pre-treatment nutritional counseling will be done.

Weight reduction > 8%, feeding tube support is recommended

Patient positioning and immobilization:

Patients will be immobilized in the supine position, using a thermoplastic mask.

Planning scan: Contrast enhanced planning CT scan of the area of interest with 3mm slices on a CT scanner that is networked to the treatment planning system

Treatment volumes and doses:

1. *Definition of target volumes:* Planning target volumes (GTV and CTV) and organ at risk volumes will be contoured on each slice.

CTV: Pre-op thyroid Bed

Involved (+) lymph node areas as defined clinically, radiologically and pathologically

Potential for subclinical or microscopic involvement

Further divided into low risk and high risk levels according to dose levels

High risk: (CTV1/ 56-60):

Pre-op thyroid bed

Involved neck nodes

Low risk: (CTV2/ 50):

Elective radiation of uninvolved bilateral lymph node regions, encompassing the central compartment and level VI nodes, if not already encompassed in CTV1

2. *Delineation of nodal CTV:* Various nodal levels will be delineated as per established guidelines for contouring. (RTOG, EORTC, DAHANCA guidelines)
3. *PTV:*

A minimum of .5 cm margin will be added to CTV to generate the corresponding PTV

4. *OAR:*

Spinal cord, larynx, brainstem, salivary glands, constrictor muscles, uninvolved oral mucosa, base of tongue, uninvolved upper airway

PRV will be generated appropriately for spinal cord, with 3mm margin.

Target delineation: An isometric margin of 5 mm to be provided to the CTV for final PTV and 3mm to organs at risk for planning organ at risk volume (PORV). The GTV will include only the primary and involved neck nodes. The delineation of the various volumes will be as per consensus guidelines. The priorities and constraints for IMRT plan will also be decided on a case to case basis

Prescription: The goal of the treatment plan would be to encompass the PTV subclinical disease with a dose of 54-60 Gy and the PTV of the gross disease with 70-74 Gy while sparing as much of the aforesaid critical structures as possible.

The maximum permissible point doses to the spinal cord will be limited to 46 Gy. IMRT planning and delivery will be carried out on the Tomotherapy Hi Art System.

Dose Specification for IMRT

The prescription dose is the isodose which encompasses at least 95% of the planning target volume (PTV). No more than 5% of any planning target volume (PTV) will receive >107% of its prescribed dose. No more than 1% of any planning target volume (PTV) will receive <95% of its prescribed dose.

Treatment will be delivered once daily, 5 fractions per week, over 7 weeks. All targets will be treated simultaneously. Breaks in treatment should be minimized. The reported doses for each PTV shall include the prescription dose as well as the maximum point dose, % target volume receiving > 103% and >105% of its prescribed dose and the % target volume receiving < 95% of the prescribed dose, and the mean dose to the PTV.

Critical Normal Structures

DVHs must be generated for all critical normal structures and the unspecified tissues.

Dose constraints to normal tissues should be as follows:

Brainstem 50 Gy

Spinal cord 46 Gy

Mandible 70 Gy

Unspecified tissue outside the targets: < 110% of the prescribed dose to PTV70

Planning Goals for IMRT: Salivary Glands

Parotid glands:

- 1) Mean dose to either parotid < 26 Gy or
- 2) At least 50% of the either parotid gland will receive < 30 Gy or

3) At least 20 cc of the combined volume of both parotid glands will receive < 20Gy.

Plan evaluation: Cumulative dose volume histograms (DVHs) will be computed for PTV and each PORV to assist in plan evaluation. Plans will be evaluated with respect to conformal avoidance of organs at risk, conformity index, homogeneity index and DVHs.

Toxicity

Acute toxicity will be assessed by physical examination, interim history and laboratory assessments.

Radiotherapy related early toxicity will be recorded as per the National Cancer Institute Common Terminology Criteria (NCI CTC), version 3. These will be documented in the radiotherapy form of the CRF. Any Grade 3/4 toxicity will be considered an event.

Late toxicity will be collected at the end of two years using the LENT SOMA scale for late toxicity. (Annexure 4)

Details of adjuvant radiation treatment will be collected in the radiotherapy form of the CRF (Annexure 1)

Statistical analysis and sample size calculation

Sample size for the study has been calculated considering a 23% decrease in loco-regional recurrence with addition of adjuvant RT, as obtained from a previous study.⁶

Eight patients (5%) have been added to account for lost to follow up. The total sample size is 72 with 36 in each arm

Alpha- 80%

Beta- 0.05

Delta- 23% decrease in loco-regional recurrence with the addition of adjuvant RT

A two-sided log rank test with an overall sample size of 64 subjects (of which 32 are in group 1 and 32 are in group 2) achieves 80% power at a 0.05 significance level to detect a difference of 0.23 between 0.70 and 0.93--the proportions surviving in groups 1 and 2 respectively. Patients will enter the study during an accrual period of 3 years. A follow-

up period of 5 years is assumed to have 5% loss from group 1 and a 5% loss from group two.

Stratification: Patients will be stratified as
R2 vs. R1/R0

Main research variables

Primary end point

Loco-regional recurrence

Secondary endpoints

1. Acute toxicity
2. Late toxicity
3. Quality of life

Assessment of Endpoints

Primary Endpoint

Loco-regional control: Recurrence will be defined as presence of histologically proven (FNAC/Biopsy) thyroid cancer recurrence in

- a. Thyroid bed
- b. Lymph nodes at levels II-VI

Tools used for this diagnosis: clinical examination, USG and FNAC

Secondary endpoints

1. Acute toxicity will be assessed using the CTC version 3 on a weekly basis till conclusion of RT. Patient will also be assessed at 3 months for acute toxicity
2. Late toxicity: Using the LENT SOMA scale for late toxicity of radiotherapy
Barium swallow will be done to assess strictures, swallowing dysfunction and penetration-aspiration score (PAS) at the end of two years

3. Quality of Life: This will be assessed using the QOL- HN35, QLQC 30 questionnaires. These will be administered at baseline (before starting RT) and at 1 and 2 years of completion of RT.

Investigation time table for patients on RT arm

Investigations	Pre-Rx	Week1	Week2	Week3	Week4	Week5	Week6	Week7	At conclusion of RT	3mths	6mths	1yr	2yr
Clinical exam	x	-	-	-	-	-	-	-	x	x	x	x	x
Toxicity scoring	-	x	x	x	x	x	x	x	x	x	-	-	-
Hemoglobin	x	-	-	-	-	-	-	-	-	-	-	-	-
WBC	x	-	-	-	-	-	-	-	-	-	-	-	-
S creatinine	x	-	-	-	-	-	-	-	-	-	-	-	-
S electrolytes	x	-	-	-	-	-	-	-	-	-	-	-	-
S TSH	-	-	-	-	-	-	-	-	-	-	x	x	x
S Tg	-	-	-	-	-	-	-	-	-	-	x	x	x
USG neck	-	-	-	-	-	-	-	-	-	-	x	x	x
QOL questionnaire	x	-	-	-	-	-	-	-	-	x	-	x	x
Ba swallow	-	-	-	-	-	-	-	-	-	-	-	-	x
LENT SOMA	-	-	-	-	-	-	-	-	-	-	x	-	x

Ethical Considerations: This study will be conducted in accordance with applicable laws and regulations including, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. Patients will be consented using the HSRC/HEC approved ICF before any procedures specified in the protocol are performed.

Discussion

Thyroid cancer accounts for about 2% of all newly diagnosed cancers every year. An overwhelming majority of these (>90%) are differentiated cancers, consisting of papillary, follicular, or mixed papillary-follicular histologies. Moreover a large number of these are low to intermediate risk thyroid cancers, which in general have excellent outcome. The mainstay of treatment is surgery, complemented by radioactive remnant ablation as mandated by histology and clinical risk factors.

A fraction of all thyroid cancers are high risk group, which are associated with a graver outlook, and are therefore presumably helped by intensification of adjuvant therapy. Management of the approximately 10% of patients presenting with locally advanced disease remains controversial. It is in these cancers, that the role of adjuvant radiotherapy (RT) may come into picture.

Indications for adjuvant radiotherapy generally include high risk presentations involving local invasion or encasement of surrounding structures (e.g. trachea, esophagus, larynx, mediastinum, and/or great vessels) with evidence of residual microscopic or gross disease, especially if it is iodine non-avid. Support for the use of adjuvant RT in these scenarios comes from several studies which have shown that that curative dose of radiotherapy can reduce the 25–50% loco-regional recurrence rates reported for surgery alone. However, this data comes from retrospective studies, with variable inclusion criteria.^{1-4,6}

Furthermore, some older evidence suggests that adjuvant radiotherapy may not necessarily improve treatment outcomes especially in R2 resections. This has led to continuing controversy regarding the utility of adjuvant RT, especially for patients following their first surgical procedure and/or with microscopic residual disease.

Radiotherapy is associated with certain acute as well as long term toxicities, a fact that should be borne in mind, while incorporating this modality in treatment. Most of the literature reporting on adjuvant RT in thyroid cancers has not detailed the associated toxicity.

We therefore endeavor to conduct a phase II randomised controlled trial to analyse the loco-regional control and toxicity in a well-defined group of advanced thyroid cancers. We believe that the results of our prospective study will help delineate our clinical policy towards these high risk thyroid cancers.

Summary

Adjuvant RT in advanced thyroid cancers has been investigated in numerous studies, all of which have unfortunately been retrospective. Some retrospective studies have had several matching inclusion criteria and have shown a benefit in loco-regional control with the addition of adjuvant radiotherapy. However a few older reports have reported no benefit with adjuvant RT. Any benefit obtained from the addition of adjuvant RT will have to be counterbalanced against the toxicity associated thereof. There is a need to conduct a prospective randomised trial evaluating the toxicity and the disease free survival advantage obtained from adjuvant RT in advanced thyroid cancers.

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