A Phase II Study of Intensity-Modulated Radiation Therapy (IMRT) in the Treatment of Non-Anaplastic Non-Medullary Thyroid Cancer

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single-institution, non-randomized, phase II study. The primary endpoint is to determine the 2-year loco-regional progression-free interval for non-anaplastic and non-medullary thyroid cancer patients with unresectable disease or gross residual disease after surgical resection treated with definitive IMRT. Eligible patients will be enrolled and will receive standard definitive IMRT to 70Gy in once-daily fractions with concurrent weekly doxorubicin (10 mg/m^2). This is a standard of care protocol to capture acute and late toxicities prospectively.

All patients will undergo baseline history and physical exam, laboratory studies and biopsy as part of the initial assessment for protocol eligibility. Baseline imaging will include FDG PET/CT scan, according to our standard of care. Standard FDG PET/CT can be done prior to radiation simulation or can be incorporated as part of the standard FDG PET/CT radiation simulation. Recommended approximate weekly DW and multiparametric MRI will be available to both Main Campus and regional patients unless contraindicated. Research multiparametric MR scans for both Main Campus and regional patients will be performed on the same designated Philips 3T scanner located in the Main Hospital in the Department of Radiation Oncology according to the standard IVIM departmental protocol. MSKCC Physics and Radiation Oncology team utilize modern fusion soft wares that allows for the fusion of anatomy with or without the use of immobilization devices during research MRI scans. As fusion soft wares help ensure patients' are in the same position, patients are allow to undergo optional research MRI's without utilizing immobilization devices. DWI-MR images will also be acquired according to the standard IVIM departmental protocol when available. Patients will be seen weekly during radiation as per standard procedure at MSKCC.

Three months (+/- 4 weeks) after completion of radiation, radiologic response assessment will be performed as per our standard guideline. This will include a diagnostic FDG PET/CT scan. Cross-sectional imaging of the primary tumor (with CT scan and/or MRI) will be recommended as well. Imaging will be repeated at 6 months (+/- 4 weeks), and then every six months (+/- 6 weeks) until 2 years post-RT. Clinic visits will take place approximately every 3 months for 2 years, approximately every 6 months for the next 3 years, and approximately annually thereafter. The DW and multiparametric MRI will be recommended for 3 months, 6 months, and then every 6 months (all +/- 4 weeks) until 2 years post-RT for noncontraindicated patients.

27 patients will be enrolled in approximately two years.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective: To determine the two-year rates of local-regional progression-free interval

Secondary Objectives:

2.2.1 To determine the overall survival rates

2.2.2 To evaluate the rates of acute toxicities (CTCAE, v. 4) during treatment

2.2.3 To evaluate the rates of late dysphagia, dry mouth, and other toxicities (CTCAE, v. 4)

2.2.4 To assess objective measures of late dysphagia using standard Modified Barium Swallow-Imp and Penetration-Aspiration scale (pre-treatment, 6 months, 12, months, 18 months, and 24 months post-treatment.

2.2.5 To evaluate BRAF and other exploratory mutations at baseline and correlate with treatment outcome.

2.2.6 To assess changes in tumor heterogeneity over the course of external beam RT using serial multiparametric MR scans

2.2.7 To assess normal tissue response as a function of dose for parotid, submandibular glands, muscles and bones in the head and neck region during and after EBRT using serial multiparametric MR scans

3.0 BACKGROUND AND RATIONALE

Thyroid cancers have an incidence of about 18,000 per year in the US, the majority of which are differentiated (follicular or papillary) cancers.[1] While there has been an increase in incidence of these cancers, there has also been a decrease in mortality.[1] Ten-year survival for papillary cancer is 95% and 85% in follicular cancer.[2] However, with continued follow-up one-third of all patients recur of which two-thirds of these recur locally.[3]

The standard approaches to the treatment of differentiated thyroid cancer include surgical resection, radioactive iodine treatment (RAI), and thyroid-stimulating hormone suppression. Efforts to improve on surgical outcome have focused mainly on radioiodine treatment where RAI can destroy occult cancer, increase sensitivity of I^{131} scanning by eliminating uptake by normal residual tissue, and improve the value of serum thyroglobulin as a tumor marker during follow-up.[3] As a result, RAI has led to improvement in local control,[3-6] distant metastasis rate,[7, 8] and overall survival.[8-10] Consequently, for high-risk patients, radioiodine is routinely incorporated into initial treatment strategies universally. However, there is a group of patients where their tumors are refractory to RAI but can potentially benefit from external beam radiotherapy (EBRT), [10a]

The role of external beam radiotherapy (EBRT), however, remains controversial. In the absence of prospective trials, the current indications for EBRT have largely been determined from retrospective data. A randomized trial that opened in Europe failed to accrue because of the reluctance of multiple centers to adopt EBRT.[11] Multiple single institution experiences have shown EBRT to improve local control in select patients, in particular, those with unresectable and/or gross residual disease after surgical resection.[6, 12-23] Studies have supported the use of EBRT in populations that included unresectable and gross residual disease after surgical resection as well as those tumors that are refractory to RAI therapy.[6, 10a, 16-24] Chow *et al.*[12] demonstrated a significant improvement in 2-year loco-regional control (risk reduction of 0.36) in patients with either nonpalpable or palpable gross residual disease with the addition of EBRT.

Loco-regional control is an important endpoint when examining outcomes after EBRT for thyroid cancer. Progression of loco-regional recurrent disease despite the presence of metastatic disease can significantly affect morbidity and quality of life because of the proximity of critical organs, including the esophagus, larynx, and spinal cord. By adding EBRT to improve loco-regional control despite the presence of metastatic disease, there is the potential to avoid the morbidity associated with uncontrolled loco-regional cancer such as obstruction of the esophagus and/or trachea, need for a laryngectomy, neurovascular compromise, pain, hemorrhage and avoiding repeated surgical procedures. Therefore, EBRT is frequently recommended for patients with and without metastatic disease when

locoregional recurrent disease is unresponsive to RAI. Furthermore, there is no role for salvage RAI as these tumors are already refractory to RAI therapy. Systemic therapy is not the first line for this RAI refractory, unresectable non-anaplastic thyroid cancer as controlling the disease loco-regionally takes precedence. Our thyroid disease management team consisting of head and neck surgery, medical oncology, and endocrine service routinely discuss all patients undergoing EBRT in a multidisciplinary meeting prior to the initiation of radiotherapy.

A retrospective review of 66 patients with gross residual or unresectable non-anaplastic non-medullary thyroid cancer that underwent EBRT with or without low dose concurrent chemotherapy at Memorial Sloan-Kettering Cancer Center showed that the 3-year locoregional progression-free survival rate was 77.3%, with a 3-year overall survival rate of 54.4%. [51]. The median radiation dose was 6630 cGy (Interquartile range 6000-7000cGy). Concurrent low dose radiation sensitizing chemotherapy was administered to 21 of the 66 patients (31.8%) with a non-significant increase in the 3-year locoregional progression-free survival rate (90.0% versus 73.0%). Despite this improvement in local control, there was no difference in the median overall survival (43.1 versus 37.1 months) likely secondary to the fact that patients treated with concurrent chemotherapy had larger volume of disease and a greater incidence of poorly differentiated histology both of which are known negative prognostic factors. These promising results were in a heterogeneous cohort of patients with multiple poor prognostic risk factors, majority of whom had RAI refractory disease. This is the only published series focused on patients with gross residual or unresectable disease. Grade 3 acute mucositis and dysphagia occurred in 11 (16.7 %) and 13 (19.7 %) patients, respectively. The addition of concurrent chemotherapy only resulted in a 10% increase in acute grade 3 hoarseness (10% versus 0%), with no differences in acute or late toxicities for dermatitis, dysphagia, mucositis, nausea, vomiting, fatigue, or need for a reactive feeding tube. Late adverse toxicity was notable for percutaneous endoscopic gastrostomy tube use in 4 patients (6.1 %), though 2 of these patients had the percutaneous endoscopic gastrostomy tube placed prior to EBRT. There was no difference in the late toxicities between EBRT and CCRT patients including hoarseness and need for a feeding tube. Although patients with metastatic disease fared worse than patients with localized thyroid cancer, loco-regional control was still achieved in a significant number of patients (61.4% versus 88.4%). Thus, EBRT should be considered, even for patients with metastatic disease, because progression in the thyroid bed or neck can cause significant morbidity. Thus our update of the MSKCC experience demonstrated that in patients with unresectable disease or gross residual disease, the 3 year locoregional progression-free interval was 73.0% in patients treated with EBRT alone and 90.0% in patients who underwent concurrent low dose radiation sensitizing chemotherapy with only a slight increase in hoarseness that was self resolving.

The American Thyroid Association Task Force recommends EBRT for gross residual disease not amenable to surgery or RAI treatment.[25] However, in all patients, the potential benefit of EBRT should be weighed against the acute and long-term risks. Non-randomized studies have identified a potential role for adjuvant treatment of high-risk patients with external beam radiation therapy,[20, 26] documenting improved local control,[18, 21, 23, 27-30] with no survival benefit.[30] The inclusion criteria for receiving external beam radiation therapy have included advanced age (>40 years), extrathyroidal extension, high EORTC score or other scoring system for prognostic variables. Local recurrence has purportedly declined from 20-

25% to 4-7% with the addition of external beam radiation therapy in these studies. This translates to a 65-85% decrease in local recurrence. Of note, these are patients who present with gross residual disease where a second surgery is unlikely.

Given that the data to date are largely retrospective and hypothesis generating, that these retrospective studies reported a heterogenous group of non-anaplastic thyroid cancer patients who underwent EBRT, i.e., both resectable with positive margin to an unresectable cohort, a prospective study is needed to settle the controversies associated with the role of

EBRT in thyroid cancer management. Furthermore, we would like to gather both the acute and late complications associated with EBRT in a prospective manner. In order to minimize heterogeneity, we chose to focus on patients who we believe benefit the most from EBRT, i.e., those with unresectable or gross residual disease.

Although mutations such as BRAF are present in greater than 70% of all papillary thyroid cancers and are known to be associated with a poorer prognosis with increased risk of insensitivity to RAI [31-33], to our knowledge, there is no data on what effects external beam radiation has on tumors with these mutations. Hence, one of the goals of this protocol is to collect tissue in a prospective manner and perform exploratory analyses pre-radiation (at baseline) so that we may further understand this disease and these mutations.

MRI is a non-invasive technique to assess morphological and physiological changes in tumor and irradiated normal structures. The excellent soft tissue contrast will aid in improved normal tissue contouring of salivary glands and lymph nodes which will ultimately help in further sparing of normal structures during external beam planning. Similar immobilization technique employed during CT simulation and MR scan will help in co-registering MR images with CT and PET scans.

Radiation of the head and neck can irreversibly damage oral mucosa, vasculature, muscle and bone resulting in xerostomia, dental caries, trismus, soft tissue necrosis and osteoradionecrosis. A change in intensity or image texture over the course of radiation obtained from these MR scans may be an indication of radiation damage to these sensitive structures. In addition, we hypothesize that perfusion and diffusion changes observed in tumor and normal structures could be dose dependent.

DWI measures differences in tissue microstructures based on the random brownian motion of water molecules in biological tissues. It quantifies the degree of restriction of water diffusion or tissue diffusivity and has the potential to differentiate benign lesions from malignant tumors. The quantitative measure of water mobility is calculated in terms of apparent diffusion coefficient (ADC) by varying the diffusion weighting or ‘b’ values. Tumors with more densely packed tumor cells and more cell membranes have a lower ADC due to greater restriction to diffusion. Non tumoral tissue changes such as edema, inflammation, fibrosis and necrosis typically have low cellularity and result in high ADC. [Ref 28, 29]. In addition to molecular diffusion of water in biological tissue, microcirculation of blood (or “perfusion”) in the capillary network can also be captured using low ‘b’ values. DW I MRI using both low and high b values (also called intravoxel incohenerent motion sequence or IVIM) gives a quantitative measure of true diffusion (D) and perfusion fraction (f) [ref 30] without the use of an intravenous contrast agent.

DWI MRI technique has been successfully applied for various disease sites. Its clinical applications in head and neck cancer has been in differentiating malignant tumors from benign lesions [ref 31,32], characterizing and staging of lymph nodes in the head and neck region [ref 33] and monitoring tumor response [ref 34,35,36,37]. A few studies have investigated the salivary gland response based on changes in ADC value. [Ref 38, 39]. Malignant tumors usually show low ADC values compared to benign tumors. A mean cut-off value of 1.2x10-3 for adult tumors and 1.25x10-3 for pediatric head and neck tumors has

been shown to distinguish between malignant and benign tumors with 87% and 92.8% accuracy respectively [ref 5]. Dirix et al have shown superior accuracy of DW-MRI compared to conventional imaging in nodal staging where DW-MRI was shown to agree with pathology with a sensitivity of 89% and specificity of 97% per lymph node. [33]
Very few studies have looked at the utility of DWI for normal tissue response. Dirix et al and Zhang et al have looked at radiation induced changes in major salivary glands using DWI. ADC changes were inversely related to salivary flow measurements and may represent a sensitive marker of salivary gland dysfunction. Both these studies have shown potential to predict radiation-induced xerostomia. A more recent study from our group looked at the efficacy of pre-treatment multimodality imaging consisting of MRS, DCE-MRI and FDG PET [ref 40] in head and neck cancer patients to predict short-term response to treatment.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single-institution, non-randomized, phase II study. The primary endpoint is to determine the 2-year loco-regional progression-free interval for non-anaplastic non-medullary thyroid cancer patients with unresectable disease or gross residual disease after surgical resection treated with definitive IMRT and doxorubicin at 10mg/m^2 weekly.

<u>MR Scan Protocol</u>
Multi parametric MR scan will be performed on the Philips 3T scanner located in the Department of Radiation Oncology according to the standard IVIM departmental protocol and utilization of the patient's immobilization device when the immobilization device is available and the patient agrees to utilize it. MSKCC Physics and Radiation Oncology team utilize modern fusion soft wares that allows for the fusion of anatomy with or without the use of immobilization devices during research MRI scans. As fusion soft wares help ensure patients' are in the same position, patients are allow to undergo optional research MRI's without utilizing immobilization devices. DWI-MR images will also be acquired according to the standard IVIM departmental protocol when available. At the pre-treatment scan only, an additional scan will be acquired based on a research sequence provided by Philips that will allow visualization of cortical bones in the head and neck region and potentially differentiate bone from air sinus cavity. This scan will be used to evaluate the potential of using MR alone images to differentiate and segment normal tissues used in radiotherapy treatment planning. This additional sequence will add an extra 5 minutes to the total scan time.

The scan duration will be approximately 45 minutes during the first MR acquisition obtained at the time of CT simulation and approximately 30 minutes during the followup MRs Scans

which occur during chemoradiation. Information collected will not affect the standard of care. Scans will be acquired on our Philips 3T research scanner. Images will be sent to the research Pinnacle workstation for storage and evaluation. These images may be used for contouring of normal structures during the treatment planning process. DW-MRI images will be processed on the Philips research platform and corresponding diffusion and perfusion maps will be analyzed for therapy response assessment and treatment planning. Spatial changes during treatment will also be evaluated using functional diffusion maps or parametric response maps. No clinical decision will be made at this point based on MR findings.

4.3 Intervention

All patients will undergo baseline history and physical exam and laboratory studies as part of initial assessment for protocol eligibility. Baseline imaging will include a FDG PET/CT scan, according to our standard of care. All patients will provide written informed consent. A recommended DW and multiparametric MRI will also take place pre-treatment, during and post treatment for noncontraindicated patients. Patients will receive intensity-modulated radiation therapy (IMRT) in once-daily fractions (Monday through Friday, excluding holidays). A total dose of 70Gy is planned. Patients will be seen weekly during radiation as per standard procedure at MSKCC. Patients will also receive concurrent doxorubicin at 10 mg/m^2. A recommended DW and multiparametric MRI may also take place approximately weekly unless contraindicated for patients. Approximately 3 months after completion of radiation, radiologic response assessment will be performed as per our standard guideline. This will include a FDG PET/CT scan, as well as a recommended cross-sectional imaging of the primary tumor (with CT scan and/or MRI). Clinic visits will take place approximately every 3 months for 2 years, approximately every 6 months for the next 3 years, and approximately annually thereafter. The DW and multiparametric MRI will be recommended for 3 months, 6 months, and then every 6 months (all +/- 4 weeks) until 2 years post-RT unless contraindicated for main campus patients only. This schedule may be altered, as clinically indicated.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 IMRT

Definitive IMRT to 70Gy is standard as per MSKCC guidelines. IMRT is a sophisticated technique that uses a computer controlled multileaf collimator to shape the intensity of each treatment beam to optimally deliver the dose to the tumor and protect normal tissue. The radiotherapy delivery systems used is standard and FDA approved. The dose fractionation scheme has also been used routinely at MSKCC.

5.2 Chemotherapy

Low dose radiosensitizing doxorubicin at 10 mg/m^2 will be administered weekly . The chemotherapy delivered will be standard, FDA approved, and administered per institution's guidelines.

Doxorubicin is a commercially available medication with a complete description of the drug, clinical pharmacology, contraindications, warnings, precautions and adverse reactions available in the package insert.

Doxorubicin is administered intravenously, according to institutional procedures.

5.3 Modified Barium Swallow Impairment Profile (MBSImP)

The MBSImP is a standardized tool which assesses swallowing impairment as it relates to oral, pharyngeal, and esophageal impairments.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

6.2.1 Pathologically confirmed diagnosis of non-anaplastic non-medullary thyroid cancer that is either grossly recurrent after surgery or unresectable with or without metastatic disease.

6.2.2 Age ≥18 years

6.2.3 Karnofsky performance status ≥70%

6.2.4 Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least 3 months after treatment.

6.2.5 Patients must have ability to understand and the willingness to sign a written informed consent document**.**

6.3 Subject Exclusion Criteria

6.3.1 Women who are pregnant or lactating

6.3.2 Inability to comply with study and/or follow-up procedures

7.0 RECRUITMENT PLAN with limited waiver of authorization

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team in the Head and Neck Cancer Clinics at Memorial Sloan-Kettering Cancer Center (MSKCC) Main Campus and/or Network Sites. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of

the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of maintaining information in a screening log of patients approached (if applicable).

8.1 PRETREATMENT EVALUATION

- Pretreatment biopsy must confirm diagnosis of non-anaplastic non-medullary thyroid cancer prior to treatment. A core biopsy may be obtained from the primary tumor or regional lymph node metastases. If the diagnostic biopsy was performed outside of MSKCC, and tissue cannot be obtained, a repeat core biopsy may be required.

Within 8 weeks prior to start of treatment

- Electrocardiogram as per institution standard
- Standard pretreatment dental evaluation and initiation of dental prophylaxis (unless patient is edentulous)
- FDG PET/CT with calculation of metabolic tumor volume
- Recommended research MRI

Within 30 days prior to start of treatment:

- Complete medical history including current medications, and physical examination including evaluation of Karnofsky Performance Status
- The following laboratory studies: Complete blood count with white blood cell differential and platelet counts; Comprehensive Metabolic Panel.
- Baseline TSH, T3, T4, thyroglobulin
- Mandatory pre-treatment evaluation in the Speech and Swallowing Center with Standard objective measures of pre-treatment swallow evaluation using Modified Barium Swallow Impairment Profile (MBSImP) and Penetration-Aspiration scale

Within 14 days prior to the start of treatment

- Serum pregnancy test for women of childbearing potential within 14 days prior to therapy.
- Complete blood count with white blood cell differential and platelet counts; Comprehensive profile (including electrolytes, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, albumin, and glucose); magnesium level; prothrombin time with INR, and activated partial thromboplastin time.

9.1 TREATMENT/INTERVENTION PLAN

All patients will undergo radiation treatments using IMRT with concurrent low-dose radiosensitizing doxorubicin at 10 mg/m^2 will be administered as per standard MSKCC guidelines.

Exploratory analyses will be performed on the standard care pre-treatment biopsy.

9.2 Radiation Therapy Treatment Plan

9.2.1 External beam equipment and techniques

6 MV photon beams produced will be used to deliver computer controlled multi-segmental therapy with multi-leaf collimators (MLCs) in dynamic mode. The number of fields will be determined by the treatment planning system. All fields will be treated each day. Portal images will be taken of each field. The accuracy of patient position and MLC aperture will be monitored weekly by portal images for selected fields.

9.2.2 Standard treatment planning

Treatment will be directed to the primary tumor and bilateral cervical lymph nodes, if applicable. The target volumes and normal tissue structures will be defined using CT (or MRI) and PET images. Patients will be simulated in the treatment position with individualized Aquaplast immobilization masks. All patients will undergo standard of care positron emission and computed tomography (PET/CT) simulation for treatment planning. If a FDG PET/CT was already performed as part of the pretreatment workup, the investigator can fuse the FDG PET/CT with the CT portion of the radiation simulation as per standard of care guidelines in the department of radiation oncology. Standard uptake value, metabolic tumor volume, and total lesion glycolysis from PET/CT scans will be reported. A CT scan with slices of 3mm thickness or less will be acquired through the target region. A margin of 5-10 cm superior and inferior to the target will be scanned with slices of 5mm thickness or less. All patients will be treated with standard IMRT plans. The volumes of interest will be identified on each axial CT slice. GTV will consist of the gross primary tumor and involved lymph nodes. A high risk subclinical clinical target volume (CTV high risk) as well as a lower risk subclinical volume (CTV low risk) will be defined according to the risk associated with the disease site. A planning target volume (PTV) will also be defined to account for biologic and technical uncertainties. Normal structures of interest including the spinal cord, parotid glands, submandibular glands, oral cavity, and larynx will be outlined in 3 dimensions.

The CT data will be transferred to the 3D treatment planning system. A plan using multiple beams will be tailored to the patient‘s anatomy and disease distribution. The method of inverse-planning will be utilized to determine the intensity profiles of the treatment beams. All dose constraints, maximum, mean, and minimum are standard as per our MSKCC treatment planning guidelines for patients undergoing IMRT for their thyroid cancer.

9.2.3 Treatment schedule

Treatment will be delivered as one fraction per day on a standard 5 day per week schedule (excluding weekends and holidays), to a total dose of 7000 cGy. Each radiation treatment will last approximately 15 to 30 minutes. If the patient misses a scheduled treatment, this treatment will be added on the end of the treatment plan.

9.2.4 Treatment delivery

Photon beams with an energy of 6 MV will be used to deliver computer controlled multi-segmental therapy, and multileaf collimators in a dynamic mode will be used to produce the intensity modulated treatments. Electron beams may also be used if clinically indicated.

9.2.5 PEG tube

PEG placement is optional, if the investigator determined that PEG tube placement is appropriate either prior to or during IMRT.

9.2 Chemotherapy

9.2.1 Radiosensitizing low dose doxorubicin at 10 mg/m^2 will be administered weekly. Dose reduction or missed scheduled chemotherapy session will be dealt with at the treating physician's discretion.

Every attempt will be made to administer treatment on schedule. Doxorubicin may be given up to 3 days before or after the scheduled dates, if necessary for medical or personal reasons.

Guidelines regarding dose delays and/or reductions are provided in Section 11. Reasons for such changes will be outlined in the medical record.

9.2.2 Complete blood cell count should be obtained within 48 hours prior to each scheduled chemotherapy treatment date.

Dose recalculation by weight is only required if the weight has change by > 10% from the BSA being used.

Day 1 refers to the first day of IMRT.

9.2.3 Day 1 : During week 1 of IMRT, patients will receive doxorubicin 10 mg/m^2 intravenously. The weekly start day of doxorubicin 10 mg/m^2 will be at the discretion of the treating physician. Recommended anti-emetic administration will be given per MSKCC Guidelines but may be given as per the treating physician's discretion.

Note in clarification regarding MD clinic visits: Patients should be seen by an MD in clinic weekly during chemoradiation. Missed visits for reasons such as inpatient admission, logistical difficulties, or other medical reasons will be addressed on a case by case basis by the Principal Investigator and/or Treating Physician.

9.3 Specimen Collection and Tissue Banking and Translational Research

<u>Mutational profile of the tumors:</u>

As part of the main consent patients will consent to required pre-treatment tissue analysis. This analysis will only be required for those patients who have sufficient tissue available.

General sequence of events after tissue is obtained: Dr. Ghossein will mark the regions of the slides enriched for tumor cells. Dr. Fagin's lab will then dissect the tissue from the slide and send the samples to Beene Core for DNA isolation and mass spectroscopy. Dr. Fagin's lab will analyze the traces and perform confirmatory sequencing if needed to clarify ambiguous cases. Tissue will be stored at Dr. Fagin's laboratory.

In detail, to evaluate the molecular profile in these patients, 6 sections of 10 microns from formalin-fixed paraffin embedded primary or recurrent tumor tissue will be subjected to DNA extraction and mutation detection as previously described [34]. Briefly, a Mass spectrometry Sequenom–based genotyping assay (Sequenom Mass array; Sequenom, San Diego CA) platform for thyroid carcinomas developed at MSKCC by Dr Fagin's laboratory will be used

for mutation analysis. The latter consists of 116 assays, to interrogate mutations in 16 genes, including the most common thyroid oncogenes such as *BRAF, NRAS, HRAS, KRAS, PIK3CA, and AKT1*. As the mass spectrometry genotyping assays for codons 12 and 13 of *HRAS* are not informative in this platform, all the tumors that are wild type for *BRAF or RAS* mutations will be sequenced using primers designed for this regions (codon 12 and 13 of *HRAS*) [34]. All these mutation analysis will be performed at MSKCC in Dr Fagin's laboratory and MSKCC core facilities.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Evaluation during IMRT

Patients will be assessed at weekly status check as per institutional standard practice. At the weekly assessments patients will have a limited physical exam, KPS evaluation, and toxicity assessments. CBC will also be completed weekly during treatment. A recommended DW and multiparametric MRI should also take place approximately weekly unless contraindicated for patients.

10.2 Follow-up after IMRT

10.2.1 Clinic visits will take place approximately every 3 months for 2 years, approximately every 6 months for the next 3 years, and approximately annually thereafter with Radiation Oncology and/or Medical Oncology. This schedule may be altered, as clinically indicated.

Patients who are removed from study for toxicity (but who maintain active follow-up) will be followed according to the same post-treatment surveillance plan as patients who complete study treatment. The following will be completed at these visits: physical exam, KPS assessment, toxicity assessment (according to NCI CTCAE v 4.0)

10.2.2 Three months (+/- 4 weeks) after completion of IMRT, radiologic assessment will be performed. This will include a diagnostic FDG PET/CT scan, along with a recommended CT and/or MRI scan of the primary tumor/neck, mean and maximum standardized uptake value, metabolic tumor volume, and total lesion glycolysis will be recorded prospectively for all FDG PET/CT scans. The MRI scan may be performed in addition to the CT scan, or instead of the CT scan, as clinically indicated. Imaging will then be repeated at 6 months (+/- 4 weeks) post-RT and then every 6 months (+/- 6 weeks) until 2 years post-RT. The DW and multiparametric MRI will be recommended for 3 months, 6 months, and then every 6 months (all +/- 4 weeks) until 2 years post-RT unless contraindicated for main campus patients only.

10.2.3 Patients will be advised to undergo routine surveillance dental exams approximately 4 to 8 months after completion of definitive locoregional therapy. The dental visit dates may vary due to logistical considerations, but all patients will be advised to maintain dental follow up. Assessments of salivary flow may be performed at dental visits, but are not mandatory. Additional dental evaluations may be performed, as clinically indicated.

10.2.4 Mandatory post-treatment evaluation in the Speech and Swallowing Center with Standard objective measures of pre-treatment swallow evaluation using Modified Barium Swallow Imp and Penetration-Aspiration scale**. (See Appendix 1).**
Speech and Swallowing assessment should be performed at baseline, and after radiation at approximately 6 months, 12 months, 18 months, and 24 months post treatment.

	Pre-Rx (within 30 days prior to RT unless otherwise indicated)	Weekly during RT	Follow up (Q3 mos until 2yrs, Q 6 mos until 5yrs; annually thereafter)
Confirmation of Non-Anaplastic Non-Medullary Thyroid Cancer[a]	X		
Collection of tumor tissue for translational research if available[a]	X		
H & P by MD	X	X[b]	X
KPS	X	X	X
CBC	X	X	
Comprehensive Metabolic Panel	X		
TSH, Thyroglobulin, T3, T4	X		
EKG	X[c]		
Recommended CT and/or MRI of the neck with contrast	X[j]		X[d]
Recommended DW and multiparametric MRI unless contraindicated for patients	X[c]	X	X[d]
FDG PET/CT	X[c]		
Pregnancy Test (for women of child bearing potential)	X[e]		
Speech and Swallowing Evaluation	X		X[f]
Dental Evaluation (unless patient is edentulous)	X[c]		X[g]
Low dose radiosensitizing doxorubicin (10 mg/m^2)		X	

IMRT		X[h]	
AE monitoring[i]		X	X
Co-morbidities	X		

a) Any time prior to RT start
b) Weekly status check
c) Within 8 weeks of RT start
d) At 3 months (+/- 4 weeks) and 6 months (+/- 4 weeks), and then every 6 months (+/- 8 weeks) until 2 years
e) Within 14 days of RT start
f) Performed after radiation at approximately 6 months, 12 months, 18 months, and 24 months post-treatment.
g) At approximately 4-8 months post-RT only
h) Daily except for weekends and holidays
i) AEs will be assessed according to CTCAE v 4.0 throughout the treatment course and in follow up.
j) Pre-treatment MRI to be completed within 8 weeks prior to treatment start, if recommended

11.0 TOXICITIES/SIDE EFFECTS

During radiation, adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events—Version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

Treatment modifications are based on CTCAE version 4.0. Once a patient has had a doxorubicin dose reduction for toxicity, the dose will not be re-escalated.

Reproductive risks: There is a risk of birth defects associated with this study. Patients must use birth control while on this study. Women should not breastfeed while on this study.

11.1 Radiation Therapy-Associated Adverse Events

Reversible radioepithelitis of pharyngeal mucosa is expected and its timing with dose and severity will be noted and graded according to NCI CTCAE v4.0. Epilation of treated areas and various degrees of skin reaction are expected. Other expected acute reactions include hypogeusia, dysphagia, thick saliva, hoarseness, radiation dermatitis, nausea, vomiting, anemia, fatigue, and weight loss.

Late toxicities are those that occur at least 3 to 4 months post radiation. Late effects may include permanent xerostomia, hypogeusia, dysphagia, ototoxicity, nasal dryness, serous otitis media, dental decay, hypothyroidism, dysphagia, and trismus. Osteoradionecrosis may occur in 5% or less of patients, but can be reduced by dental evaluation before radiation.

11.2 Chemoradiation Therapy-Associated Adverse Events

The following may be experienced with doxorubicin: myelosuppression, decreased albumin, decreased calcium, abnormal liver function tests, kidney problems, digestive, or pancreas problems, high blood sugar, nausea, vomiting, loss of appetite, heartburn, hair loss, fatigue, skin rash, diarrhea, belly pain, weight loss. In rare instances, heart damage manifested as congestive heart failure may occur.

Previous data have noted that the additional of concurrent chemotherapy only resulted in a 10% increase in acute grade 3 hoarseness, but with no difference in late toxicity with a

median follow up of 35 months. There were no differences in acute or late toxicities for dermatitis, dysphagia, mucositis, nausea, vomiting, fatigue, or need for a feeding tube. Chemotherapy will be held for ANC < 1, platelets < 75,000. Dose adjustments for intolerable Grade 2 or Grade 3-4 toxicities associated with the chemotherapy will be up to the treating physician.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary endpoint of this study is to assess the 2-year loco-regional progression-free interval using standard post-radiation imaging studies. Scans will be performed at 3 months (+/- 4 weeks) and 6 months (+/- 4 weeks) post-RT and then every 6 months (+/- 6 weeks) until 2 years post-RT. Patients will be followed for life with standard screening for disease recurrence, according to the schedule in Sections 9 and 10.Patients will be classified as loco-regional progression free as long as there is no evidence of loco-regional progression of disease. Loco-regional failure will be defined as infield progression if included in the RT field and meets one of the following criteria: 25% increase in tumor volume, new lesions, and/or 25% increase in metabolic tumor volume or total lesion glycolysis.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease he/she will be taken off study and referred for alternative therapy. Patients who develop distant metastases will not be removed from protocol therapy.

If at any time the patient develops unacceptable toxicity he/she will be removed from study and considered a treatment failure.

If the patient is unable to receive doxorubicin due to doxorubicin -related toxicities, he/she **may remain on study to continue IMRT.**

Patients may be removed from the study for protocol non-compliance.

Patients who exhibit continual non-compliance with the follow-up schedule may be removed from the protocol at the discretion of the Principal Investigator.

All patients enrolled on the study will be included in an intent-to-treat analysis.

14.0 BIOSTATISTICS

The primary objective of this study is to determine the 2-year loco-regional progression-free rate. Current literature showed that the 2-year loco-regional progression-free rate is about 40% [16-24]. We expect to improve this rate substantially to 90% by applying the proposed chemoradiation treatment strategy. It should be mentioned that according to previous versions of the protocol 8 patients had been treated with IMRT alone. But prospectively we will treat patients with the current standard which is chemoradiation. To this end we will still employ a single-stage binomial design. We will recruit 19 patients, and we will claim the proposed treatment promising when at least 14 patients are without progression of disease at 2 years from the end of the treatment. This decision rule gives a power (that is, probability of declaring success when the true 2-year progression rate is 90% or higher) of 0.99 with the

type 1 error rate (that is, probability of declaring success when the true 2-year progression rate is 40% or lower) less than 0.01. Patients who died due to any reason, or were lost to F/U within 2 years will be regarded as having loco-regional progression. Patients who do not complete treatment due to excessive toxicity will be excluded from the primary endpoint analysis and replaced by new eligible patients. We expect to accrue the total of 19 analyzable patients in 2 years. The 8 patients who had received IMRT alone will not be counted towards this endpoint and will be summarized separately.

To better understand the loco-regional progression we will also use the cumulative incidence function for summaring the endpoint of time to loco-regional failure, which will be carried out by a competing risks anlaysis. Overall survival rates will be assessed by Kaplan-Meier method. Rates of (acute or late) toxicities will be computed by sample proportions and confidence intervals will also be provided. Summary statistics and/or longitudinal plots for the Modified Barium Swallow-Imp and Penetration-Aspiration scales will be supplied for assessing objective measures of late dysphagia. BRAF and other mutation measurements at baseline will be correlated with clinical outcomes such as overall survival and local-regional control using survival analysis tools. All secondary endpoints will be analyzed for the 19 patients under chemoradiation. The 8 patients who had received IMRT alone will be summarized separately.

Multiparametric and DW scans will also be obtained. Due to the small pilot size of this exploratory aim, we may not produce significant results. In that case, we will present summary statistics and suggest directions for future study.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

16.1 DATA MANAGEMENT ISSUES

A Clinical Research Associate (CRA) and Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRA and CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled —Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center‘s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research: This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.2 Privacy

MSKCC’s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
  - An explanation of how the AE was handled
  - A description of the participant's condition
  - Indication if the participant remains on the study

- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

17.4 Financial Costs/Burdens

Pathology DNA studies will not be charged to the patient or insurance. The patient will be responsible for all other costs related to treatment and complications of treatment. Costs to

the patient (third party insurer) will include the cost of radiation therapy, chemotherapy, hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, and doctor's fees.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

20.1 Modified Barium Swallow Impairment Profile and Penetration-Aspiration scale