Study Title: Prospective Randomized Pilot Clinical Trial of Margin-Based Vs. Robust Photon Radiotherapy Planning in Intensity-Modulated Radiation Therapy of Squamous-Cell Carcinoma of the Head and Neck

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BACKGROUND AND RATIONALE

Xerostomia following radiotherapy cancer treatment is mainly caused by permanent damage to the salivary glands that are in the radiotherapy field [1]. Changes in salivary functionality and symptomatology show deterioration in the short term (< 6 months) with some subsequent improvement [2]. This decrease in functionality is associated with a decrease in quality of life, especially involving the faculties of eating, speaking and swallowing [3-4]. Radiation therapy-induced chronic xerostomia is a challenge for both patient and treating physician. Although, there are remedies available to mitigate the symptoms, the best approach would involve prevention or minimizing its incidence. This may be done by utilizing radiotherapy planning strategies that reduce normal tissue complication probabilities (NTCP) [5].

There are numerous studies that describe NTCP of different organs [6-10]. Regarding the parotid glands, the most commonly used model is the Lyman-Kutcher-Burman (LKB) model using the mean dose to the parotid gland as predictive of xerostomia [11-12]. Although, dose-volume techniques are a mainstay of current treatment planning, the use of biological objectives in IMRT planning has shown potential for reducing radiation-induced toxicity [13-15].

Traditionally, uncertainties in radiation therapy have been handled by the introduction of margins to the target(s). For example, a margin applied to the clinical target volume (CTV) defines the planning target volume (PTV). These margins ensure that there is adequate target dose coverage and at the same time that sufficient normal tissue is spared. A feasible approach to reducing toxicity while at the same time maintaining similar cure rates is to reduce the margins used in radiation treatment planning [5], specifically reduce the CTV to PTV margin. This can be achieved by the use of cone-beam CT (CBCT) imaging which has shown improved patient set-up to approximately 1 mm [16]. Advances in computation and technology in radiation therapy have allowed the possibility of integrating set-up uncertainties in the optimization process of the dose calculation [17-21]. This probabilistic approach for achieving robust radiation treatment plans take into

account set-up uncertainties explicitly in the optimization process by considering the probability distributions of the uncertain parameters during optimization. As such, as an alternative to the use of biological objectives in the dose optimization process, robustness can be used as a tool to minimize dose to normal tissue and reduced toxicity leading to better quality of life [5].

Based on the above, we hypothesize that robust radiotherapy planning can improve the toxicity profile of xerostomia in patients with squamous cell carcinoma of the head and neck (HN-SQCC) compared to margin-based radiotherapy planning. However, the amount of improvement to expect remains unknown.

Therefore, we propose to perform a prospective randomized pilot clinical trial, stratified by primary tumor site, to evaluate the degree of xerostomia and quality of life (QOL) in subjects with HN-SQCC treated with radiation therapy under margin-based and robust radiotherapy treatment plans. Margin-based plans will use both biological (biological optimization) and physical objectives whereas robust planning will use physical objectives for sparing of the parotid glands. Intensity-modulated radiation therapy (IMRT) and standard chemotherapy will be used. QOL (quality of life) will be measured using the EORTC QLQ-C30 questionnaire and EORTC QLQ-H&N35 (head and neck) module before radiotherapy (baseline) and then 3, 6, 9 and 12 months after radiotherapy. Xerostomia will be measured in study subjects using two patient-reported scoring systems completed by each subject before radiotherapy and then 3, 6, 9, and 12 months after radiotherapy: the LENT/SOMA grading system and the University of Michigan's Xerostomia Questionnaire (XQ; see Eisbruch *et al.* 2001). The data collected by this randomized pilot clinical trial will be used to inform the design of, and decision-making for, future larger studies that seek to compare different methods of radiotherapy planning in the treatment of HN-SQCC.

STUDY OBJECTIVES

Primary Objective

To evaluate descriptively over time the prevalence and grade of xerostomia in subjects treated for HN-SQCC with IMRT under either biologically optimized margin-based or robust photon radiotherapy.

Secondary Objectives

1) To compare descriptively the arm treated with IMRT under the margin-based radiotherapy plan to the arm treated with IMRT under the robust radiotherapy plan for possible differences in derived outcomes of interest, including but not limited to: (1) occurrence rate of grade≥2 xerostomia as determined using the LENT/SOMA scale; and (2) occurrence rate of overall score ≥30 on the XQ.
2) To obtain NTCP values of the parotid glands from both margin-based and robust radiotherapy treatment plans using validated parameter values of the NTCP mean dose model. Each subject will have their parotid NTCP values computed under both plans, even though they will receive IMRT delivered under only the plan they are randomized to.
3) To obtain dose statistics for dose delivered to the parotid glands of each subject via either margin-based or robust treatment plans.
4) To determine quality of life (QoL) at baseline and at 3, 6, 9 and 12 months following treatment using the EORTC QLQ-C30 instrument combined with the EORTC QLQ-H&N35 module. The main scores of interest at each time point will be the global QoL scale and the individual scales for dry mouth, oral pain, swallowing, opening mouth, sticky saliva, and social eating.
5) To correlate NTCP values with change in QoL results.

STUDY POPULATION

Research subjects will be recruited from the Radiation Oncology clinic on the UAMS campus. The potential research subject will be identified by the physician during their routine clinic visit. Prior to any research activities, the subject will be approached for participation in the study by their physician or staff member, who will discuss the protocol along with the risks and potential benefits of participating in it. Subjects currently taking saliva stimulating drugs will be asked if they are willing to discontinue such drugs in order to participate. A clear statement will be made concerning the voluntary nature of participation and that the decision will have no effect on their remaining care.

We plan to consent up to 75 subjects in order to reach our maximum accrual of 50 subjects, randomized to the two study arms. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be enrolled in the study. Study procedures may not begin until a subject is consented.

Inclusion criteria

1. Histological documentation of HN-SQCC
2. Older than 21 years of age
3. Subject is eligible for routine chemo-radiotherapy for treatment of HN-SQCC
4. Informed consent is obtained
5. Karnofsky performance status of at least 70 points

Exclusion criteria

1. Women with a positive urine pregnancy test are excluded from this study; women of childbearing potential (defined as those who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months) must agree to refrain from breast feeding and practice adequate contraception
2. Unable to comply with study procedures

3. Use of saliva stimulating prescription drugs such as Evoxac or Salagen
   The use of saliva stimulating drug shave the potential of confounding the degree of xerostomia experience by the subject due to radiotherapy. Because of this, these type of drugs are not allowed during the duration of the subject's participation in the clinical trial. Symptomatic relief of xerostomia will be approached using medications that do not stimulate the production of saliva. Such drugs include artificial salivas and Biotene oral spray. Potential subjects who are currently using saliva stimulating drugs must discontinue the drugs to qualify for the study. A washout period of 3-5 days is required.
4. Unable to receive standard chemotherapy

INVESTIGATIONAL PLAN

Upon consenting to the study, the subject will complete a series of questionnaires, including the subjective LENT/SOMA xerostomia form, the University of Michigan's XQ, and the EORTC QLQ-C30 and H&N35 modules. Then the subject will attend their scheduled routine chemotherapy as prescribed by the treating medical oncologist. This will be given concurrently with radiation therapy as discussed with the Radiation Oncologist.

Following the completion of the scheduled chemo-radiotherapy, the subject will be seen in Radiation Oncology every 3 months for routine follow-up visits related to their radiation treatment. During those visits, the subjects will once again complete the packet of questionnaires. The EORTC questionnaires and the xerostomia assessments (the LENT/SOMA form and the XQ) will also be filled out at 3 months (+/- 30 days), 6 months (+/- 30 days), 9 months (+/- 30 days) and 12 months (+/- 30 days) after chemo-radiotherapy. The packet will be completed in the clinic, but if necessary can be sent home with the subject with a return envelope, emailed to the subject, or the subject may be called to respond to the questions over the phone. The subject is also to be seen at the discretion of the medical oncologist and surgeon as part of routine oncologic follow-up.

Duration of follow-up

The subject will not be followed after the completion of the questionnaires at the 12 month visit.

Removal of subject from study

Subjects will be removed from the study when any of the criteria listed below apply:

- Subject withdraws consent from study;
- Subject is unable to comply with protocol requirements;
- Subject experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the subject's best interest;
- Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event).

The Principal Investigator will be notified, and treating physician will document the reason for study removal and the date the subject was removed in the subject's medical record. The study coordinator will record the reason for removal and date in the Case Report Form (CRF).

STUDY PROCEDURES

Investigator will use one of the two strategies (i.e. Margin based or Robust) to plan for radio-therapy. Both of the strategies are standardly used at UAMS. Generally, it is just a physician's preference that determines which is used.

Margin-based and robust radiotherapy are both standard ways of delivering radiotherapy; therefore, no protocol-specific procedures are required with the chemo-radiotherapy.

The EORTC questionnaires and the xerostomia assessments will be filled out at 3, 6, 9 and 12 months after chemo-radiotherapy.

Radiotherapy

Subject will receive either routine margin-based or robust radiotherapy. The selection of which type of planning will be assigned to a subject will be determined in a 1:1 randomized fashion with stratification by primary tumor site.

Follow-up visits

Subjects will be seen in Radiation Oncology every 3 months for one year. Adverse events will be assessed during routine physical exams at each visit. In addition, at the time of each visit the subject will complete the EORTC quality of life-30 questionnaire and associated module HN-35 module, and subjective LENT/SOMA xerostomia scoring form.

MEASURES

Xerostomia: The Late Effects of Normal Tissues Subjective-Objective Management Analytic (LENT-SOMA) system includes subjective (patient-rated) and objective (clinician-rated) indices of radiotherapy toxicities [23]. The patient-rated xerostomia item is used in the current study. The item is rated on a 4-point Likert scale with 1 being the minimum and 4 being the maximum grades shown on the form. Evidence supports the convergent and construct validity of this measure [22, 23]. The University of Michigan's Xerostomia Questionnaire (XQ) is a brief, 8-item measure of patient-reported xerostomia. Individual items are rated on a 10-point scale with 0 being the minimum and 10 being the maximum on each item. The instrument has demonstrated evidence of internal consistency, test-retest reliability, construct validity, and sensitivity to change [24-26].

Quality of Life: The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [27] is a widely used core module, designed to capture multidimensional aspects of health-related quality-of-life across a wide spectrum of different malignancies. It generates a global score, 5 functional scores, and 9 symptom scores. The H&N35 module [28] assesses concerns specific to head-and-neck cancer patients; it yields 18 symptom scores. Scores on both modules are transformed to a 0-100 scale, with higher scores representing more favorable outcomes on the functioning scales but poorer outcomes on the symptom and head-and-neck-specific scales. In the current study, scales of special interest include dry mouth, oral pain, swallowing, opening mouth, sticky saliva, social eating, and global QOL. Evidence supports the reliability and validity of the EORTC scales [27-29].

Demographic and Clinical Characteristics: Demographic information will be collected at the baseline assessment to record basic background information (e.g., age, race, gender, education, comorbidities, etc.). Clinical variables will be obtained from the treatment team or medical record (e.g., stage, site, recurrence status, prior treatments, time since diagnosis, etc.).

ADVERSE EVENTS

Adverse events associated to study participants

The potential risk to study participants is the potential for loss of confidentiality. Measures to protect the confidentiality of study participants will be implemented as described in the Data Handling and Recordkeeping section.

There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefits patients in the future.

Adverse event monitoring

Adverse event data collection and reporting, which is required as part of every clinical trial, is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event will be monitored until the completion of the subject's post-radiotherapy visit:

- the adverse event resolves or the symptoms or signs that constitute the adverse event's return to baseline;
- there is a satisfactory explanation other than the study agent for the changes observed; or
- death.

Definitions of adverse effects

An adverse event is any untoward medical occurrence in a subject undergoing study assessments and which does not necessarily have a causal relationship with the assessments. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study assessments, whether or not related to the assessments.

Severity of adverse effects

Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html.

Serious adverse effects

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

• Results in death.

  o If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

• Is life-threatening.

  o The subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

• Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

• Results in persistent or significant disability or incapacity.

• Is a congenital anomaly/birth defect.

• Is an important medical event.

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the subject, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

Reporting requirements for adverse events

Expedited reporting

• The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study.

• The UAMS IRB must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR/UPIRTSO; See UAMS IRB Policy 10.2).

Routine reporting

All other adverse events, such as those that are expected, or are unlikely or definitely not related to the study participation, are to be reported annually as part of regular IRB continuing review.

STATISTICAL CONSIDERATIONS

This is a randomized, two-arm, open-label pilot clinical trial conducted in subjects with squamous-cell carcinoma of the head and neck. Its primary objective is to evaluate descriptively over time the prevalence and grade of xerostomia in subjects treated with IMRT under either biologically optimized margin-based or robust photon radiotherapy of HN-SQCC. Xerostomia will be measured in study subject using two patient-reported scoring systems completed by each subject before radiotherapy and 3, 6, 9, and 12 months after radiotherapy: the LENT/SOMA grading system and the University of Michigan's Xerostomia Questionnaire (XQ; see Eisbruch *et al.* 2001).

To accomplish this study's primary objective, the analysis will proceed as follows: To analyze the XQ, scores on its 8 items will be summed for each subject at each time point to produce an overall XQ score whose values theoretically can range from 0 to 80; it will be treated as a continuous variable. LENT/SOMA grades as written on the form will simply be recorded electronically, and non-integer grades will be allowed if that's what the subject wrote on the form. Longitudinal LENT/SOMA grades will be summarized by treatment arm and time point as the number and proportion of subjects achieving each grade, and also as the mean and SD of grade. Longitudinal overall XQ scores will be summarized by treatment arm and time point as the mean, SD, median, quartiles, and range. Both the correlation between xerostomia measures within each time point and the correlation within each xerostomia measure across time points will be studied using Spearman correlation analysis. Estimated means, SDs, medians, and quartiles will be accompanied by 90% confidence intervals. In exploratory analysis,

we will employ mixed-models analysis to investigate more deeply the interrelationships among the xerostomia measures between treatment arms and time points. Also in exploratory analysis to accomplish the primary objective, we will use means, SD, and ranges to summarize each of the 8 individual items from the XQ by treatment arm and timepoint, and investigate using mixed-models approaches to compare the XQ items descriptively for treatment-arm differences over time.

This study also has the following secondary objectives:

1) To compare descriptively the arm treated with IMRT under the margin-based radiotherapy plan to the arm treated with IMRT under the robust radiotherapy plan for possible differences in derived outcomes of interest, including but not limited to: (1) occurrence rate of grade≥2 xerostomia as determined using the LENT/SOMA scale; and (2) occurrence rate of overall score ≥30 on the XQ.
2) To obtain NTCP values of the parotid glands from both margin-based and robust radiotherapy treatment plans using validated parameter values of the NTCP mean dose model. Each subject will have their parotid NTCP values computed under both plans, even though they will receive IMRT delivered under only the plan they are randomized to.
3) To obtain dose statistics for dose delivered to the parotid glands from both margin-based and robust treatment plans.
4) To determine quality of life (QoL) at baseline and at 3, 6, 9 and 12 months after treatment using the EORTC QLQ-C30 instrument combined with the EORTC QLQ-H&N35 module. The main scores of interest at each time point will be the global QoL scale and the individual scales for dry mouth, oral pain, swallowing, opening mouth, sticky saliva, and social eating.
5) To correlate NTCP values with change in QoL results.

To accomplish this study's secondary objectives, the analysis will proceed as follows:

1) Xerostomia grades from the LENT/SOMA scale will be dichotomized as grade≥2 versus grade<2, then summarized by treatment arm and time point as the number and proportion achieving grade≥2. The dichotomization is placed at grade </≥2 because that was the cutpoint used in the PARSPORT study [22], but we will also consider an alternative dichotomization at grade </≥3. As for the overall XQ score (a continuous variable), we will dichotomize it at different cutpoints chosen for their potential clinical relevance, beginning with a cutpoint of </≥30, then summarize the result by treatment arm and time point as the number and proportion of subjects who surpass the cutpoint. For all dichotomized versions of both xerostomia measures, the proportions on each arm and proportion differences between treatment arms will be estimated at each time point. Estimated proportions and their differences will be accompanied by two-sided 90% confidence intervals. Exploratory mixed-models analysis may be used in follow-up mode, as time permits, to explore more deeply the differences between treatment arms and how they change over time.
2) NTCP values from both plans will be summarized by plan and treatment arm as the mean, SD, median, quartiles, and range. Data will be graphed using box plots versus treatment arm. Plans will be compared descriptively by calculating the paired difference between them, and summarizing the result as means, SDs, and ranges. Means will be accompanied by 90% confidence limits.
3) Dose statistics on each subject (i.e., the mean, SD, median, 1st and 3rd quartiles, 5th percentile, and 95th percentile of dose received by the subject) will be summarized by statistic and treatment arm as the mean, SD, median, quartiles, and range. Data for each statistics will be graphed using box plots versus treatment arm.
4) The global EORTC QOL scale and individual scales for dry mouth, oral pain, swallowing, opening mouth, sticky saliva, and social eating will be summarized by treatment arm and time point as the mean, SD, and range, and also (for individual Likert-scaled items that have 5 or fewer ordered categories) as the

number and proportion of subjects whose answer falls into each ordered category. Data will be graphed using box plots or scatter plots versus treatment arm and profile plots versus time point. In general, the mean differences between treatment arms will be estimated at each time point, and such estimates will be accompanied by two-sided 90% confidence intervals. Exploratory mixed-models analysis may be used in follow-up mode, as time permits, to explore more deeply the differences between treatment arms and how they change over time.

5) Changes in QoL results after treatment (compared to baseline) will be calculated at each post-treatment time point, then assessed for correlation with NTCP values by Spearman correlation analysis.

For analyses in support of the secondary objectives, the outcomes at all time points will be of interest, but outcomes at the 12-month time point will be of special interest because of this time point's prominence in previous studies such as PARSPORT [22].

Sample-size considerations. We plan to consent up to 75 subjects in order to reach our maximum accrual of 50 subjects. Twenty-five subjects will be assigned randomly to IMRT under the margin-based radiotherapy plan, and 25 subjects will be assigned randomly to IMRT under the robust radiotherapy plan.

The IMRT arm of the PARSPORT study [22] lost 17% of its enrolled subjects to death and dropout before they could be evaluated at 12 months for that study's primary endpoint, grade≥2 xerostomia. If similar results hold in our study, and if we enroll 25 subjects per treatment arm, then we can expect the number of subjects who remain on each treatment arm for 12 months to be binomially distributed with expected value of 20.75 and 95% probability of being 18 or higher.

In each analysis, the precision of the estimates can be quantified through their standard errors, with smaller standard errors denoting greater precision. At 3 months, when each treatment arm should still contain 25 subjects, the standard

errors on estimated means will be ±0.200 times the group SDs, while the standard errors on proportion estimates of 10%, 30%, and 50% will be ±6.0%, ±9.2%, and 10.0%, respectively. At 12 months, when the number remaining on each treatment arm could be as few as 18 subjects, the standard errors on estimated means will be ±0.236 times the group SDs, while the standard errors on proportion estimates of 10%, 30%, and 50% will be ±7.1%, ±10.8%, and ±11.8%, respectively. These standard errors are considered small enough to assure that the estimates obtained from this pilot clinical trial will have the level of precision needed to be informative in the design of future larger studies that seek to compare different methods of radiotherapy planning in the treatment of HN-SQCC.

STUDY MANAGEMENT

Registration procedures

All subjects must be registered with the Cancer Clinical Trials Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Research Staff. To register a subject, call CCTO Monday through Friday, 8:00AM-4:30PM.

Randomization

Twenty-five subjects will be assigned randomly to IMRT under the margin-based radiotherapy plan, and 25 subjects will be assigned randomly to IMRT under the robust radiotherapy plan.

The study coordinator will use RPRS, a cancer Biomedical Informatics Grid (caBIG®, NCI) application, to randomize the subject to either the Margin-Based Arm or the Robust Arm. Once a subject is registered in RPRS, the computer system will generate a randomly assigned arm.

Data Handling and Record Keeping

Data must be submitted according to protocol requirements for ALL subjects registered, whether or not study procedures are performed. For screen failures, only the eligibility criteria case report form will be completed. Data obtained during the study will be collected at each subject visit and entered into the protocol database. Subjects will be registered in RPRS, a cancer Biomedical Informatics Grid (*caBIG®,* NCI) application. Data will be entered into OpenClinica through electronic web-based case report forms (CRFs). OpenClinica is a secure open source system for electronic data capture and clinical data management. All information in OpenClinica will be coded with a unique identifier and will be stored in the database indefinitely. In the event that a subject fails screening, only the eligibility criteria case report form will be completed.

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and integrity of the study. All study subject material will be assigned a unique identifying code. Only the research staff will have access to the information that identifies the subject in this study.

Ethical considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent

process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject or legally authorized representative (only if applicable), and the individual obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject's research record.

Dissemination of data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant.

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