SURGERY WITH OR WITHOUT STEROTACTIC BODY RADIOTHERAPY

A Prospective Randomized Phase II Study of Surgery with or without Adjuvant Stereotactc Body Radiotherapy (SBRT) in Patients with Previously-Irradiated Head and Neck Cancer
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PROTOCOL SUMMARY

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A Prospective Randomized Phase II Study of Surgery with or without Adjuvant Stereotactc Body Radiotherapy (SBRT) in Patients with Previously-Irradiated Head and Neck Cancer

Objectives

The *primary* objective of this study is to compare the 1-year local control in patients with operable, recurrent previously-irradiated squamous cell head-and-neck cancers with or without adjuvant SBRT.

The *secondary* objectives of this study are:

1. To determine the locoregional progression-free survival (PFS) distant PFS, overall PFS (local + regional + distant), and overall survival (OS).
2. To evaluate the acute and late toxicities of adjuvant SBRT in the re-irradiation setting following salvage surgery.
3. To determine prognostic factors that may predict the likelihood of local failure, regional failure, or OS in this cohort to guide future management.
4. To compare the impact of adjuvant SBRT versus a wait-and-see approach on patient reported quality of life (PR-QoL).
5. To compare surgical versus SBRT-induced immunological serum markers in relation to local control.

Patient population

In order to be eligible for this study, patients must have a pathologically proven recurrent or second-primary head-and-neck cancer with no evidence of distant matastases. Patients mut be at least 18 years of age and able to give informed consent. They must have a Karnofsky Performance Status ≥ 60.

Number of patients

42

Study design and methodology

This is a prospective, double-arm phase II study. The treatment schema detail is in Section 6.3.

Treatment administered

Patients will or will not receive adjuvant Stereotactic Body Radiotherapy (SBRT) at various levels depending upon tumor volume. Subsequent evaluations will measure the efficacy of the adjuvant SBRT.

Efficacy data collected

The following evaluations will be performed to assess the efficacy of preoperative stereotactic radiation therapy:

- Objective local control rate measuring tumor volume
- Health Related Quality of Life assessment using the University of Washington Quality-of-Life-Revised (UW-Qol-R)

Safety data collected

The following evaluations will be conducted to assess the safety of radiosurgery:

- Recording of all toxicity data per NCI CTCAE version 4.0

1.0 BACKGROUND

1.1 Salvage Surgery for Recurrent Head-and-Neck Cancers

Recurrent and second-primary head-and-neck cancers (rHNC) in a previously-irradiated field represent a therapeutic challenge (1). Even with adjuvant therapy, rHNC occurs in ≥20-30% of high-risk postoperative patients and ≥30% of patients treated with definitive chemoradiotherapy (2-3). While there are no randomized data to test the benefits of salvage surgery after prior irradiation, for patients who can have surgical resection, based on available data, surgical resection represents the currently accepted standard of care (4-5). However, even patients with resectable rHNC are at high-risk for subsequent failure (67% overall failure rates). In patients with close or positive surgical margins following salvage surgery, recurrence rates of nearly 100% have been reported (6). To improve tumor control in this setting adjuvant re-irradiation techniques along with chemotherapy has been used with mixed but limited success (7-10).

1.2 Adjuvant Re-Irradiation

The only phase III experience evaluating adjuvant therapy after surgical salvage is from the Institute Gustave-Roussy (7). In this phase III study, 130 previously-irradiated rHNC patients were randomized following salvage surgery to chemotherapy + re-irradiation (CT/Re-RT) versus observation. Chemotherapy consisted of six cycles of hydroxyurea and continuous infusion 5-FU, while adjuvant re-irradiation was delivered to a total dose of 60 Gy in a split-course fashion (the contemporaneous RTOG standard). Disease-free survival (DFS), but not overall survival (OS), was improved with the addition of adjuvant CT/Re-RT (the study was not powered for OS). However, this treatment was not without toxicity. Grade 3 or 4 mucositis was seen in 28% of patients and 39% of patients had grade 3 or 4 late toxicity versus only 10% of patients in the observation arm. This is the only level I evidence for adjuvant therapy in re-irradiation setting. Thus the data supports the role of re-irradiation in improving local control albeit with the expense of significant toxicity.

1.3 Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT), is a treatment technique that incorporates advances in radiation planning and delivery to provide highly conformal doses of radiation with a steep-dose gradient to surrounding critical organs-at-risk. Since 2001, researchers at the University of Pittsburgh Cancer Institute have been pioneers in the use of frameless extracranial SBRT for a variety of benign and malignant lesions. The advantages of SBRT in the setting of re-treatment of high-risk patients with head and neck carcinomas are a highly conformal treatment volume that affords a small number of fractions, decreased overall treatment time, and radiobiological advantages (where acute responding tissue is better spared with higher doses per fraction/lower overall dose to) minimizing acute toxicity.

1.4 Experiences with SBRT at the University of Pittsburgh

Stereotactic body radiotherapy (SBRT) has emerged as a promising treatment option in patients with unresectable rHNC. Initial phase I dose-escalation study from the University of Pittsburgh Cancer Institute established the safety of SBRT up to 44 Gy in 5 fractions (11). Numerous subsequent international single-institution studies have confirmed the primary benefits of SBRT relative to conventional re-irradiation ± chemotherapy for unresectable rHNC: decreased toxicity with comparable tumor control/survival (12-17).

Further studies from the University of Pittsburgh Cancer Institute have established a dose volume response model and shown similar outcomes for non-squamous versus squamous histologies (18-19). Moreover, longitudinal prospective evaluations of patient-reported quality of life (PR-QoL) have shown that improved tumor control associated with SBRT reirradiation ameliorates decreased PR-QoL resulting from rSCCHN which transcended all measured domains in a validated PR-QoL assessment tool. This improvement was independent of age, use of cetuximab, tumor volume, and interval since prior irradiation (20). Finally, recent prospective data has suggested that the addition of cetuximab to SBRT may improve tumor control without significant increases in re-irradiation toxicity for unresectable rHNC (21-22). While there is growing evidence for SBRT in unresectable rHNC, there is limited data in the adjuvant setting (23). We recently reported our experience using SBRT following salvage surgery for patients with compromised/positive surgical margins and extra-nodal extension at high-risk for recurrence (24). Based on these results, SBRT may improve tumor control relative to salvage surgery alone and reduce toxicity relative to conventional adjuvant radiotherapy ± chemotherapy in rHNC (see Table 1). We seek to confirm these retrospective observations with the prospective trial evaluating SBRT to observation post-surgery.

2.0 OBJECTIVES

Primary

2.1 To compare the 1-year local control in patients with operable, recurrent previously-irradiated squamous cell head-and-neck cancers with or without adjuvant SBRT.

Secondary

2.2 To determine the locoregional progression-free survival (PFS) distant PFS, overall PFS (local + regional + distant), and overall survival (OS).

2.3 To evaluate the acute and late toxicities of adjuvant SBRT in the re-irradiation setting following salvage surgery.

2.4 To determine prognostic factors that may predict the likelihood of local failure, regional failure, or OS in this cohort to guide future management.

2.5 To compare the impact of adjuvant SBRT versus a wait-and-see approach on patient reported quality of life (PR-QoL).

3.0 INVESTIGATIONAL PLAN

3.1 Overall design and plan of the study
Detailed visit-by-visit study procedures and a study flow chart are provided in Section 6.3. Prior to enrollment, all subjects will be evaluated with medical records to confirm patient received diagnosis of recurrent or second-primary head-and-neck squamous cell carcinomas. Additionally, these records will confirm the patient had had macroscopic complete (R0/R1) salvage surgery and previous radiation. Patients will receive a Stereotactic Body Radiotherapy and then followed periodically for up until 2 years.

3.2 Screening procedures
- Medical history (including review of pathology and laboratory values) and physical examination
- Pathologic confirmation of diagnosis and disease status/staging with biopsy to rule out metastatic disease (if necessary)
- Baseline laboratory assessment, including CBC and blood chemistry
- Urine or blood β-HCG within 14 days prior to study start for females who are not at least one year post-menopausal or who have not undergone a surgical sterilization procedure
- CT or PET-CT of the neck and chest
- Baseline Quality of Life Assessment

3.3 Personnel performing the procedures
All procedures will be performed by appropriate certified medical personnel, including, but not limited to physicians, nurses, technologists and research staff.

3.4 Location and duration of procedures
All study visits will take place on an outpatient basis in the UPMC Shadyside Radiation Oncology Department. However, it is possible that a subject may be an inpatient at the time of diagnosis. All procedures will be performed by appropriate certified medical personnel.

3.5 Timeline of study procedures
Once eligible by screening and enrolled in study, patients will be randomized into one of two arms. One arm will receive SBRT treatment for 1 – 2 weeks. The second arm will receive no SBRT and will continue with standard of care treatment. Patients will be followed for 8-12 weeks after treatment and every 3-6 months for up to 24 additional months. Extended long-term follow-up will occur as clinically indicated until death.

3.6 Research Activities

3.6.1 Pretreatment Evaluation
The following tests/procedures will be performed within 3 months prior to registration unless otherwise specified:
- Medical history and physical examination
- Pathologic confirmation of diagnosis and disease status/staging with biopsy to rule out metastatic disease if necessary
- Baseline laboratory assessment, including CBC and blood chemistry

- Urine or blood β-HCG within 14 days prior to study start for females who are not at least one year post-menopausal or who have not undergone a surgical sterilization procedure
- CT (computed tomography) scan or FDG-PET-CT (^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography) of the neck and chest
- Baseline Quality of Life Assessment (University of Washington – Quality of Life – Revised (UW-QoL-R)

3.6.2 Randomization
Once the participant is deemed eligible for the study based upon the screening procedures, the patient will be randomized. The randomization of subjects to one of the two treatment arms will be in a 1:1 ratio, between the presence or absence of SBRT treatment. The Hillman Cancer Center biostatics facility has a randomizer, an intranet application for randomly assigning patients to different thresholds, which will be used for the randomization in the trial.

3.6.3 Treatment
Steriotactic Body Radiotherapy (SBRT) will be performed on 1 of the treatment arms. Group 1 will receive SBRT for 1-2 weeks.

3.6.3.1 Tumor Volume
Tumor volumes <25cc will receive 40Gy (5 fractions of 8Gy per fraction). Tumor volumes ≥25cc will receive 44-50Gy (5 fractions of 8.8 – 10 Gy per fraction). Ideally, all tumor volumes ≥25cc will receive 50Gy over 5 fractions; however, at the discretion of the treating radiation oncologist based on tumor bed volume, prior radiation dose, and proximity to critical organs, the dose can be reduced to 44 Gy over 5 fractions.

3.6.3.2 Randomized Arm
Patients randomized to the adjuvant SBRT arm will receive 40-50Gy in 5 fractions on non-consecutive days in 1-2 weeks on an outpatient basis. SBRT should be completed at a minimum of 4-weeks following salvage surgery, with a maximum of 12-weeks. CTV (clinical target volume) will represent the tumor bed/high-risk region as defined by head and neck surgeon and radiation oncologist. A maximum of 5mm expansion from CTV to PTV (planning target volume) shall be applied

Treatment Volumes < 25cc will receive 40Gy (5 fractions of 8 Gy per fraction)
Treatment Volumes ≥ 25cc will receive 44-50Gy over 5 fractions (5 fractions of 8.8Gy per fraction). Ideally, all tumors volumes ≥ 25cc will receive 50Gy over 5 fractions; however, at the discretion of the treating radiation oncologist based on tumor volume, prior radiation dose and proximity to critical organs, the dose can be reduced to 44Gy over 5 fractions as outlined in prior SBRT protocols.

3.6.3.3 Specifications
SBRT treatments are to be delineated using CT-based planning with custom thermoplastic mask for immobilization. SBRT is to be delivered using linear accelerators commissioned to deliver SBRT such as Cyberknife™ M6 (Accuracy, Inc., Sunnyvale, CA) Trilogy™ or TrueBeam™ STx (Varian Medical Systems Inc., Palo Alto, CA), with daily image guidance to

set-up verification and assessment of intra- and inter-fraction motion.

3.6.4 Follow-up/Long-term follow-up/Extended long-term follow-up procedures
Follow-up evaluations will be completed in patients in both arms (SBRT and wait-and see). They will be carefully followed every 3-6 months for 24 months or until death. Evaluations will consist of the following:

- Interim medical history and physical examination
- Careful documentation of Toxicity According to National Cancer Institute Common Toxicity Criteria Events Scale version 4.0
- Follow-up Patient-Reported Quality of Life Assessment (PR-QoL)
- FDG PET-CT at 8-12 weeks post-treatment then every 12 weeks

TABLE 1: Treatment Schema

Clinical Visit

Assessment

	Pre-Study	During 8-12 weeks	Q 12-24 weeks	SBRT Post for 2-years
History + Physical	X	X	X	X
Imaging	X	X	X	
QoL Assessment	X	X	X	

3.6.5 Methods of Measurement
The methods of measurement are as follows:

CT, PET/CT, or MRI are the best currently available methods for measuring disease status. Lesions that can be accurately measured in at least one dimension ≥ 10mm (1.0 cm). If measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Clinically detected lesion will only be considered measurable when superficial (vis-à-vis skin nodules and palpable lymph nodes). Documentation should include color photography and ruler estimation of size.

3.6.6 Evaluation of Disease Status and Survival
Survival and time to progression will be measured from the date of salvage surgery to date of death, appearance of new metastatic lesion, or objective tumor progression.

4.0 SUBJECT SELECTION AND ELIGIBILITY

4.1 Selection of subjects
Forty-two (42) patients with recurrent or second-primary head-and-neck squamous cell carcinomas within a previously-irradiated field with high-risk features (compromised/positive surgical margins or extra-nodal extension) following macroscopic complete (R0/R1) salvage surgery will be recruited for this randomized phase II study.

4.2 Identification and initiation of contact with study participants
Potential research subjects are first identified by their primary doctor/clinical team. The research project will be discussed by the caregiver with the patient. If interested, the patient will be informed at this time either to contact the research team to express his/her interest in participating. Other subjects are referred in specifically for possible participation in a study which they or their physicians are aware of based on publications which list clinical trials at UPCI. "Cold-calling" will not be used to recruit subjects. Potential subjects will be approached by clinicians who are directly involved in their care. "Finder's fees" for referring a potential subject for participation in a research study are prohibited.

Physicians and other health care professionals in the area are aware of active studies at UPMC Radiation Oncology Department by means of various publications including the World Wide Web. Such publication and Web listings are not advertisements for specific studies. Rather, they are public listings of trials available.

Once a subject is identified as a potential participant in a research study as indicated above, he/she is screened for eligibility. No identifiable information (e.g. name, diagnosis, treatment, etc.) will be released until the subject has given written authorization. No research-related procedures (including review of the subject's medical records) will be performed until the subject has provided written informed consent. The consent process will be carried out as a joint effort among the subject's physicians, the study coordinators, and a physician who is listed as an investigator on the study.

4.3 Inclusion criteria
Each patient must meet all of the following inclusion criteria for study enrollment:

- Age ≥18 with ability to provide written informed consent
- Pathologically proven recurrent or second-primary head-and-neck cancer receiving prior radiotherapy with or without chemotherapy
- Prior radiotherapy to a dose of ≥50Gy
- No evidence of distant metastases
- Macroscopic complete salvage surgery with curative intent (surgery was not performed only for biopsy or palliation). Final pathology and imaging must indicate a R0 or R1 resection (no gross disease remaining).
- High-risk pathologic features must be present: compromised/positive surgical margins (≤ 2mm) or extra-nodal extension (patient with other high-risk features gross perinueral invasion, bone invasion, angiolyphatic invasion, or a constellation of these factors may be eligible based on case-by-case basis at discretion of principal investigator).
- Karnofsky Performance Status ≥60 (ECOG 0-2)

- Any number or type of prior chemotherapy is allowed (patient may receive concurrent or adjuvant systemic therapy such as cetuximab at the discretion of the treating oncologic team).

4.4 Exclusion criteria

Patients meeting any of the following exclusion criteria are not eligible for enrollment:

- Evidence of distant metastases on any staging or imaging modality
- Women who are breast feeding, or have a positive pregnancy test (reproductive age should use effective birth control during study if randomized to SBRT treatment arm)
- Any patient with gross residual disease following salvage surgery
- Any co-morbidity or condition of sufficient severity to limit full compliance with the protocol per assessment by the principal investigator.

4.4.1 Specific criteria to exclude pregnant females and feta/neonatal exposure

For all females who are not at least one year post-menopausal or who have not undergone a surgical sterilization procedure, a urine pregnancy test will be done. If this is positive or questionable a serum pregnancy test will be done. The results of the pregnancy test must be negative in order for the patient to participate in this study.

Women who are pregnant or breastfeeding are excluded from participation in this study. All females of childbearing potential must have a serum pregnancy test within 14 days of the radiation. The results of the pregnancy test must be negative for the patient to participate in this study.

Subjects will be informed by the study staff that is extremely important that they not become pregnant or father a baby while participating in this study, and that avoiding sexual activity is the only certain method of preventing pregnancy. However, if a subject chooses to be sexually active, he or she must agree to use an appropriate "double barrier" method of birth control starting from the subject's participation in the screening process to include a negative pregnancy test to continue as a study participant and continuing until two weeks following the subject's participation in the study. The methods of birth control should include intrauterine device (IUD), contraceptive sponge and spermicide, in addition to male use of a condom, or the female should be using prescribed birth control implant. Subjects will be instructed to notify the study doctor of their birth control method prior to the start of the study, and also if they plan to change their birth control method.

Subjects that choose to be sexually active must be made aware that even with the use of birth control measures, pregnancy could still result. Subjects will be informed that if they become pregnant or impregnate a woman while taking part in this study, they must immediately notify one of the doctors listed on the consent form.

The information listed above will be relayed to applicable subjects by the study staff. It will also be listed in the consent form, a copy of which will be provided to the patients for them to take home.

5.0 TREATMENT EVALUATION, ADMINISTRATION, AND MODIFICATION

5.1 Primary outcome variables to be evaluated

(1) Primary endpoint - local progression-free survival (LPFS), defined as the time from the date of randomization to the date of local progression or the date of death from any cause. Subjects who are alive and have not progressed will be censored at their last follow-up date.
(2) Regional PFS, distant PFS, PFS (local + regional + distant): The definition of these endpoints is similar to LPFS.
(3) Overall Survival: time from the date of randomization to the date of death due to any cause.
(4) Acute and late toxicities of adjuvant SBRT. Acute toxicity is defined as toxicity occurring within 3 months of completion of SBRT. Late toxicity is defined as toxicity occurring later than 3 months after SBRT treatment.

6.0 STATISTICAL CONSIDERATIONS

6.1 Study objectives and design
The primary objective is to compare the 1-year local control in patients with operable, recurrent previously-irradiated squamous cell head-and-neck cancers with or without adjuvant SBRT.

Secondary objectives include to determine the locoregional progression-free survival (PFS) distant PFS, overall PFS (local + regional + distant), and overall survival (OS); to evaluate the acute and late toxicities of adjuvant SBRT in the re-irradiation setting following salvage surgery; to determine prognostic factors that may predict the likelihood of local failure, regional failure, or OS in this cohort to guide future management; and to compare the impact of adjuvant SBRT versus a wait-and-see approach on patient reported quality of life (PR-QoL),

This clinical trial is planned as a prospective, randomized, two-arm Phase II study.

6.2 Sample size and accrual rate
Forty (40) patients will be screened for each arm of the trial so that 21 subjects will be cleared to participate in research procedures in each arm of the trial.

The following assumptions are used in determining the sample size for this study:
Primary endpoint: local progression-free survival (LPFS)
One-sided type I error rate: 0.10
Statistical power: 90%
One-year LPFS for surgery alone: 20%
One-year LPFS for surgery + SBRT: 52%
Randomization: 1:1
2-year accrual period and one year follow-up following closure of accrual
5% lost to follow-up in each arm

To have 90% power to detect the above 32% difference in one-year LPFS, using a onesided log-rank test with a 0.1 level of significance, 21 patients are required in each arm.
The randomization of subjects to one of the two treatment arms will be in a 1:1 ratio. The UPCI Biostatistics Facility has a randomizer, an intranet application for randomly assigning patients to different treatments, which will be used for the randomization in this trial.

6.3 Statistical approach and analysis

(1) Efficacy Analysis Set: includes all enrolled and randomized patients. Subjects will be analyzed according to their randomized treatment group assignment.
(2) Safety Analysis Set: The safety analysis will be performed according to the actual treatment received.

6.4 Analysis of primary and secondary endpoints

Survival endpoints will be estimated by the Kaplan-Meiermethod and the corresponding median survival times (with 95% confidence interval) reported. The one-year LPFS will also be estimated along with its 95% confidence interval. Survival will be compared between the two arms with the one-sided log-rank test. Effect of treatment and other variables (e.g., baseline characteristics, biomarkers etc) on survival will be explored with Cox regression models.

For the quality of life (QoL) data analysis, each item of the UW-QoL-R will be individually assessed. The mean and standard deviation of the observed data will be summarized at each collection time and plotted against time, from baseline through the end of patient follow-up. Generalized linear models (such as cumulative logit models) for repeated measures will be used to explore if there are significant changes in PR-QOL over time.

Using NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0), the number of patients experiencing adverse events over their course of treatment will be characterized by type of adverse event and grade, by the time of onset in relation to the first day of therapy, and whether the event is clinically significant. Attribution of adverse events to treatment (unrelated, unlikely, possibly, probably, or definitely) will also be summarized for any serious adverse events (SAEs), CTCAE grade 3 or higher. The percentage of patients experiencing SAEs that are considered to be treatment-related (probable or definite) will be determined. The percentages of patients experiencing the acute/late toxicities associated with SBRT will also be estimated along with their exact 95% confidence intervals.

7.0 DATA SAFETY AND MONITORING

7.1 Data monitoring plan
All research-related procedures will be conducted by certified medical personnel. The study staff will monitor the subjects closely throughout the study for any adverse events, and subjects will be strongly encouraged to report all issues to the study staff. All supportive measures consistent with optimal patient care will be given throughout the study.

All subject data will be collected by the University of Pittsburgh Cancer Institute's Department of Radiation Oncology's Protocol Office. All data will be secured in a password protected file with observance of all applicable HIPAA regulation. A data safety monitoring board comprised of the PI, physicians, residents, fellows, physics, statistician and research manager will meet monthly to evaluate toxicity for this trial. Subjects/adverse events will be discussed at these monthly disease center meetings. Unexpected serious adverse events will be reported to the IRB and DSMC, and minutes of the monthly disease center meetings will be reviewed at the DSMC meetings.
Reports will be submitted annually at the time of the yearly renewal.

7.2 Adverse events
All serious AE shall be reported meeting criteria for reporting can be found on the University of Pittsburgh Institutional Review Board's website at http://www.irb.pitt.edu. In the event of such adverse event, the investigator must report the event(s) via phone within 24 hours and a written report filed within 24 hours to the Principal Investigator, or the University of Pittsburgh Cancer Institute's Department of Radiation Oncology's Protocol Office.
All adverse events will be reported as per the University of Pittsburgh IRB web site at www.irb.pitt.edu .

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