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14. ABSTRACT

Purpose and scope:

Stereotactic ablative radiotherapy (SABR) has become a new standard of care for early stage lung cancer in patients who are not candidates for surgery because of excessive surgical risk, and will be an important treatment option for a growing segment of patients with lung cancer. This is particularly true as lung cancer screening efforts are expected to diagnose a greater proportion of lung cancers at earlier stages, yet the aging of the population will lead to a greater proportion of patients having comorbidities that increase surgical risk. Tumor hypoxia is a major known mechanism of radiation resistance and is especially expected to affect very short courses of radiation as in SABR. Imaging using a third generation hypoxia PET agent, ^{18}F-EF5, is a promising approach for noninvasive hypoxia measurement that needs to be validated in the clinical setting.

Our objectives are (1) to understand the prevalence of hypoxia detectable by imaging in early stage NSCLC; (2) to validate ^{18}F-EF5 PET as an indicator of tumor oxygenation status in this patient population; and (3) to evaluate ^{18}F-EF5 PET as a prognostic imaging biomarker for local primary tumor control after SABR.

Progress, results, and major findings:

All institutional and DOD human subjects approvals are complete and current. We have now accrued and completed all study procedures on 14 patients out of the planned total accrual of 43 patients. All scans have been successfully acquired with good technical quality, and follow-up is currently up-to-date for all enrolled patients.

As described in the last (Year 2) annual report, per the protocol, a planned preliminary analysis was conducted on the scan data from the first 5 patients. In order to inform the remainder of the current study, we conducted a preliminary analysis including four additional previous patients from a parallel study in our department who meet the eligibility requirements of the current study. Preliminarily, with respect to the primary endpoint, 3 of 5 patients (6 of 9 including the parallel study patients) had imageable hypoxia as defined by our plan of analysis. With respect to the endpoint of imaging response to tumor oxygenation perturbation, 2 of 3 patients (4 of 6 including the parallel study patients) with initially positive EF5 scans had the expected imaging response to carbogen. 1 of 2 patients (1 of 3 including the parallel study patients) with an initially negative EF5 scan had the expected imaging response to DCA. Follow up is ongoing for the endpoint of local primary tumor control, but is too short to assess this endpoint meaningfully.

Per the protocol, the primary endpoint is to determine the proportion of patients with stage I non-small cell lung cancer undergoing SABR who have imageable hypoxia by EF5-PET. A preliminary analysis of all 14 patients enrolled to date shows that 4 of 14 (7 of 18 including the parallel study patients) had imageable hypoxia. Per the Statement of Work, a more detailed interim analysis of the primary and second endpoints will be performed when 20 patients have been accrued, hopefully by the time of the next quarterly progress report or the subsequent one.

Significance:

In summary, our preliminary findings suggest the presence of tumor hypoxia even in relatively small, early stage lung cancer. Additional validation of this finding is pending completion and analysis of our study. Because tumor hypoxia is a strong mechanism of radioresistance, particularly for hypofractionated courses of radiation as in SABR, if validated this finding has substantial implications for the optimal application of SABR to early stage lung cancer. EF5-PET imaging could be useful as a risk stratification factor for clinical trials of lung cancer SABR, and could ultimately be used to individualize therapy for patients with early stage lung cancer.

15. SUBJECT TERMS

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INTRODUCTION:

Stereotactic ablative radiotherapy (SABR) has become a new standard of care for early stage lung cancer in patients who are not candidates for surgery because of excessive surgical risk, and will be an important treatment option for a growing segment of patients with lung cancer. This is particularly true as lung cancer screening efforts are expected to diagnose a greater proportion of lung cancers at earlier stages, yet the aging of the population will lead to a greater proportion of patients having comorbidities that increase surgical risk. Tumor hypoxia is a major known mechanism of radiation resistance and is especially expected to affect very short courses of radiation as in SABR. Imaging using a third generation hypoxia PET agent, ^{18}F-EF5, is a promising approach for noninvasive hypoxia measurement that needs to be validated in the clinical setting. Our objectives are (1) to understand the prevalence of hypoxia detectable by imaging in early stage NSCLC; (2) to validate ^{18}F-EF5 PET as an indicator of tumor oxygenation status in this patient population; and (3) to evaluate ^{18}F-EF5 PET as a prognostic imaging biomarker for local primary tumor control after SABR. If accomplished, these would lay the foundation for future prospective therapeutic clinical trials using ^{18}F-EF5 PET as a stratification factor, and ultimately to individualize therapy.

BODY:

Initiation of this project was initially delayed in response to revisions requested by the DOD human subjects review process. We received the approval memorandum from DOD to start the project on February 13, 2013. The period covered by this report is September 2014 to September 2015, corresponding to project months 19-30 in the Statement of Work. The tasks in the Statement of Work pertaining to project months 1-30 and the progress on each are described below.

A. Progress on Statement of Work by task (only tasks for months 1-30 included)

Task 0. ***Pre-award preparation (4 months prior to award)***

0a. Application for Stanford institutional review board (IRB) and scientific review committee (SRC) approval (4 months)

0b. Recruitment of clinical research coordinator (2 months prior to award)

Status: *Completed during pre-award period*.

All institutional and DOD human subjects and SRC approvals are complete and current. A clinical research coordinator is in place.

Task 1. ***Patient recruitment (months 1-24)***

We received the approval memorandum from DOD to start the project on February 13, 2013. Prior to this we obtained all the required IRB and FDA approvals and recruited a clinical research coordinator (*Task 0*). As such this report covers through Q12, corresponding to through month 30 of the project timeline. During the past four quarters covered by this report, we screened 30 patients and enrolled 5. This brings the total accrual to 14 patients to date, compared to a projected 50 patients (see Figure 1).

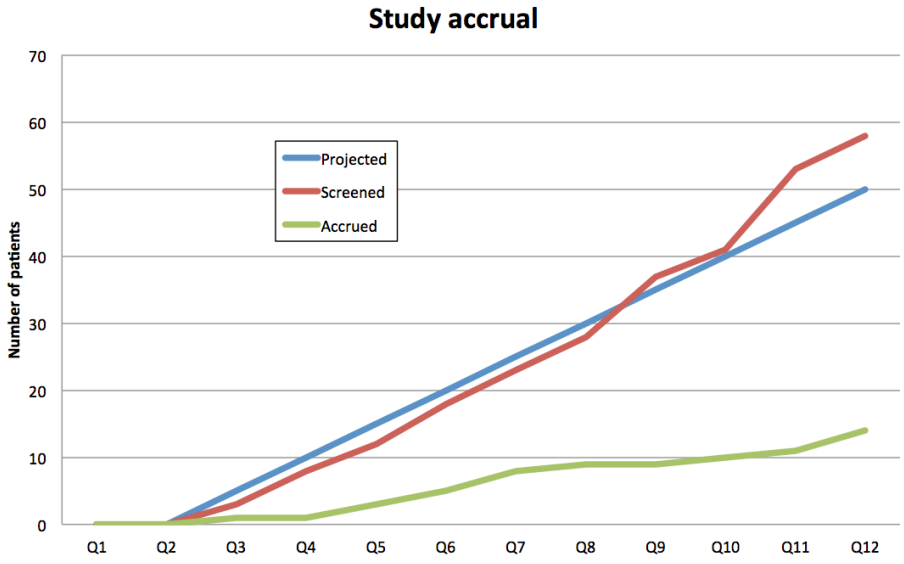

Figure 1

Of note, our patient screening rate (ie, identification of eligible patients) now exceeds the projected accrual rate. The discrepancy between screening and accrual reflects primarily patient willingness to accept the logistical challenges of completing two non-standard-of-care EF5-PET scans, mostly because of the time commitment and long distance traveled by a large proportion of our patients. Furthermore, during Q9-10 there was a period during which our radiochemistry facility that produces the EF5 tracer was offline and patients could not be accrued.

In the last two quarters there appears to be a trend toward increased accrual corresponding to more comprehensive screening efforts.

Task 2. ***Patient follow-up (months 4-34)***

Task 2a. Completion of case report forms at each follow-up visit: **Follow-ups are complete to date for the enrolled patients. Scheduled follow-up imaging is at 3-month intervals post-SABR. There has been no evidence of local recurrence in any patient at this point, though follow up remains short. One patient, unfortunately, passed away as of the time of the last annual report.**

Task 2b. Review of data from first 5 patients (months 3-5). The study team will assess any technical barriers to collecting all the required imaging data for the first 8 patients, and address deficiencies if necessary: **All of the first five patients each successfully completed two EF5 PET scans prior to SABR. Synthesis of ^{18}F-EF5 was consistently reliable with good yield, and there were no technical barriers to scan acquisition or maneuvers to modify oxygenation (carbogen breathing or DCA administration). In addition, there were no technical barriers encountered for any of the subsequent patients to date. This was completed as described in the last annual report.**

Task 2c. Semi-annual internal data review (every 6 months). The study team will internally audit all data collected on the study to ensure complete collection of study endpoints including imaging data. Missing information will be reconciled: **Collection of all imaging and clinical data has been reviewed and is current to date.**

Task 3. Data analysis (months 4-36)

Task 3a. Preliminary analysis of ^{18}F-EF5 PET imaging data from first 5 patients (months 3-5). We will evaluate the image quality and technical adequacy to perform all the quantitative analysis specified by the protocol. We will also assess whether modifications to the software are needed to streamline and automate data analysis, and implement the improvements: **We have preliminarily analyzed the EF5-PET imaging data from the first 5 patients. The results were described in the last annual report.**

Task 3b & 3d. Preliminary analysis of ^{18}F-EF5 PET imaging data from first 20 patients (months 13-15); Scoring of clinical outcomes endpoints in first 20 patients (months 19-24): **We have not yet accrued 20 patients. This analysis will be done when sufficient patients have been accrued, hopefully by the time of the next quarterly report or the subsequent one**.

Tasks 3c, 3e-g (analyses to be completed when all 43 patients have been accrued)

B. Preliminary analysis of data to date

The preliminary results for the first 5 accrued patients are provided in Table 1.

Pt	Histology	Stage – Location	TMR1	Hypoxic	Intervention	TMR2	Hypoxic	Change	Expected
1	Adeno	IA – LLL	1.19	Yes	Carbogen	1.31	Yes	↑	↓
2	SCC	IA – LLL	1.95	Yes	Carbogen	1.39	Yes	↓	↓
3	SCC	IA – RUL	0.65	No	DCA	0.63	No	↓	↑
4	Adeno	IA – RUL	0.70	No	DCA	0.86	No	↑	↑
5	NSCLC	IA – LUL	1.28	Yes	Carbogen	1.11	Yes	↓	↓

Table 1. Abbreviations: Adeno = adenocarcinoma; SCC = squamous cell carcinoma; NSCLC = non-small cell lung cancer, not otherwise specified; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; TMR = tumor:muscle EF5 uptake ratio; Yes = TMR significantly > 1; DCA = dichloroacetate

Of note, we have been conducting a parallel study of EF5-PET imaging with a very similar design, but for a much broader population of patients with different tumor primary sites, histologies, and stages. Prior to the initiation of the current project, four patients enrolled on our parallel study met the inclusion criteria of the current study and had the same study procedures (ie, early stage NSCLC treated with SABR, with two pre-treatment EF5 scans and tumor oxygenation perturbation intervention as per the current study). As such, a preliminary analysis including these patients is presented here in Table 2 as it is relevant to the current study.

Histology	Stage – Location	TMR1	Hypoxic	Intervention	TMR2	Hypoxic	Change	Expected
Adeno	IA – LUL	1.53	Yes	Carbogen	1.07	Yes	↓	↓
SCC	IB – RLL	0.66	No	DCA	0.54	No	↓	↑
Adeno	IA – RLL	1.16	Yes	Carbogen	1.05	Yes	↓	↓
Adeno	IB – RML	1.45	Yes	Carbogen	1.66	Yes	↑	↓

Table 2. Data from previous patients in parallel study meeting eligibility criteria for current study

Preliminarily, with respect to the primary endpoint, 3 of 5 patients (6 of 9 including the parallel study patients) had imageable hypoxia as defined by our plan of analysis. With respect to the endpoint of imaging response to tumor oxygenation perturbation, 2 of 3 patients (4 of 6 including the parallel study patients) with initially positive EF5 scans had the expected imaging response to carbogen. 1 of 2 patients (1 of 3 including the parallel study patients) with an initially negative EF5 scan had the expected imaging response to DCA. These preliminary results were included in the last annual report.

With 14 patients now accrued, with respect to the primary endpoint (proportion of patients with imageable hypoxia), 4 of 14 patients had higher than background uptake of EF5 on PET imaging suggesting hypoxia, and were administered carbogen prior to the second EF5 PET scan. A more detailed analysis of the images and secondary endpoints awaits accrual of 20 patients, which will hopefully be completed by the next quarterly report or the subsequent one.

Follow up is ongoing for the endpoint of local primary tumor control, but is too short to assess this endpoint meaningfully.

KEY RESEARCH ACCOMPLISHMENTS:

- All human subjects approvals obtained
- Scans of good technical quality
- 58 patients screened, 14 enrolled; follow up current to date
- Preliminarily, analysis of the first 5 patients as well as 4 similar patients from a parallel study in our department suggest promise. To date, 4 of 14 patients appeared to demonstrate imageable hypoxia on EF5-PET.

REPORTABLE OUTCOMES:

None to date.

Publication of results (Task 4 of Statement of Work) is scheduled for project months 30-36.

CONCLUSIONS: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

The preliminary analysis to date supports the hypothesis that a substantial proportion of patients with early stage non-small cell lung cancer have tumor hypoxia that can be detected by EF5-PET imaging. A more detailed image analysis is ongoing to optimize the quantitation of tumor EF5 uptake. This includes evaluating the stability of uptake in the background regions between the serial scans and whether the background in muscle or the mediastinal blood pool may be a more appropriate reference; evaluating the sensitivity of region of interest delineation to lesion size and partial volume effects and if so, approaches for mitigating these effects.

With respect to the endpoint of being able to detect a change in tumor oxygenation status after interventions expected to perturb tumor oxygenation, additional patients will need to be studied to assess whether there is a statistically significant effect. Similarly, longer clinical follow up will be required to assess correlation of EF5 uptake with local primary tumor control.

Based on the number of eligible patients screened, we anticipate that our patient volume will be sufficient to complete this study. However, clearly a substantial barrier to patient enrollment is the logistical challenge of coming for two extra appointments to receive the two EF5-PET scans. Particularly because SABR offers a much shorter treatment course than conventional radiation therapy, similar to surgery that involves a short course of treatment, patients are coming for treatment from a large geographic region. Extra trips present a significant burden to these patients.

Action plan: To address this issue, we will modify our workflow to combine the EF5-PET scan dates with existing appointments, such as pre-treatment appointments for radiation therapy simulation or pulmonary function testing. We anticipate that this should be possible for the majority of patients and would eliminate this consistent barrier to enrollment. This would require no modification to the clinical trial protocol. We will also expand our efforts to screen patients from other thoracic oncology clinics outside of Radiation Oncology. Since we have encountered no other barriers, and have been able to complete all scans with good technical quality and have had complete patient follow-up to date, we expect this action plan to help bring us back into alignment with the originally planned study timeline.

Furthermore, we will perform an interim analysis of the data after 20 patients have been accrued to determine if a discernable trend is emerging in the secondary endpoints. If appropriate based on this analysis, we will consider whether the study design should be modified so that one of the two investigational EF5-PET scans may be omitted without compromising the overall study goals while making the study much more logistically feasible.

In summary, our preliminary findings suggest the presence of tumor hypoxia even in relatively small, early stage lung cancer. Additional validation of this finding is pending completion and analysis of our study. Because tumor hypoxia is a strong mechanism of radioresistance, particularly for hypofractionated courses of radiation as in SABR, if validated this finding has substantial implications for the optimal application of SABR to early stage lung cancer. EF5-PET imaging could be useful as a risk stratification factor for clinical trials of lung cancer SABR, and could ultimately be used to individualize therapy for patients with early stage lung cancer.

REFERENCES:

None to date.

APPENDICES:

None.