HHS Public Access

Author manuscript

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2016 September 1; 96(1): 9–17. doi:10.1016/j.ijrobp.2016.04.027.

A Strategy of Using Intra-treatment Hypoxia Imaging to Selectively and Safely Guide Radiation Dose Deescalation Concurrent with Chemotherapy for Loco-regionally Advanced Human Papillomavirus-Related Oropharyngeal Carcinoma

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Conflict of Interest for all authors: none

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Abstract

BACKGROUND—Human papilloma virus(HPV)-associated oropharyngeal cancer(OPC) treated with chemoradiation has an excellent prognosis leading to the question of whether de-escalated radiotherapy can result in a similar outcome. Hypoxia is a known negative prognostic factor for OPC. A prospective multi-arm IRB #)-070 study using functional imaging to assess pre/intra-treatment hypoxia for all head and neck cancer is currently on-going. A subset study of this large multi-arm study was designed to test functional imaging response as a selection criteria for de-escalation to gross nodal disease in HPV-associated OPC patients receiving concurrent chemoradiation.

METHODS—Patients with HPV-positive oropharyngeal carcinoma were enrolled on an IRB approved prospective study of which de-escalation based on imaging response was done for node(s) only. Pretreatment ^{18}F-FDG (Fluorodeoxyglucose) and dynamic ^{18}F-FMISO(fluoromisonidazole) positron emission PET were performed. For patients with pretreatment hypoxia on^{18}F-FMISO PET(defined >1.2 tumor to muscle standard uptake value ratio), a repeat scan was done one week after chemoradiation. Patients without pretreatment hypoxia or with resolution of hypoxia on repeat scan received a 10 Gy dose reduction to metastatic lymph node(s). The 2-year local, regional, distant metastasis(DM)-free, and overall survival(OS) rates were estimated using the Kaplan-Meier product-limit method. A subset of patients had biopsy of a hypoxic node done under image-guidance.

RESULTS—33 HPV+ OPC patients were enrolled in this pilot study. 100% showed pre-treatment hypoxia[at primary site and/or node(s)] and among these, 48% resolved[at primary site and/or node(s)] 30% met criteria and received 10Gy reduction to the lymph node(s). At the median follow-up of 32 months[21–61 months], the 2-year locoregional control was 100%. One patient

failed distantly with persistence of hypoxia on ^{18}F-FMISO PET. The 2-year DM-free rate was 97%. The 2-year OS rate was 100%. Hypoxia on imaging was confirmed pathologically.

CONCLUSIONS—Hypoxia is present in HPV+ tumors, but resolves within 1 week of treatment in 48% of cases either at the primary site and/or Lymph node(s). Our 100% locoregional control suggests that intra-treatment functional imaging used to selectively de-escalate node(s) to 60Gy was confirmed safe using our stringent imaging criteria. Intra-treatment functional imaging warrants further study to determine its ultimate role in de-escalation treatment strategies.

INTRODUCTION

Historically, tobacco/alcohol related head/neck squamous cell carcinoma(HNSCC) treated with chemoradiation had modest rates of long-term survival.[1] However, due to the rising incidence of human papillomavirus(HPV)+ oropharyngeal cancer(OPC), overall survival(OS) rates of nearly 90% are seen [2, 3] [4] The excellent prognosis of HPV-associated tumors raises the question of whether a de-intensified approach can result in similar outcomes. However, some HPV-associated tumors still recur and pre-clinical work suggests that while some HPV+ tumors are exquisitely sensitive to radiotherapy, others appear no different than their HPV− counterparts. [5] [6, 7] In addition, early *in-vitro* work suggested radio-responsiveness was not affected by HPV status, and that some HPV-positive cell line may be less sensitive to radiotherapy.[8, 9] Therefore, additional biomarkers are needed to determine which group of HPV+ OPC patients can safely undergo treatment de-intensification.

Hypoxic cells can be up to three time more resistant to radiation compared to aerobic cells. [10] [11, 12] Multiple studies have demonstrated that hypoxia is associated with worse locoregional control(LRC), distant metastases and OS in HNSCC. [12, 13] A non-invasive approach using positron emission tomography(PET) and hypoxia specific tracers can quantitatively determine the distribution of hypoxic regions for a given tumor.[14] ^{18}F-FMISO(fluoromisonidazole) PET is U.S. Food and Drug Administration(FDA) approved for use in detecting hypoxia. Rischin et al.[15] have shown that patients with detectable hypoxia on pre-treatment ^{18}F-FMISO PET receiving standard chemoradiation had an increased risk of relapse versus those treated with a hypoxic cytotoxin, tirapazamine, and chemoradiotherapy. Multiple other studies using hypoxic cell sensitizers with radiation have also shown improved LRC and disease-free survival(DFS) versus radiation alone for HNSCC.[16–18]

Studies using ^{18}F-FMISO PET have focused on its role as a prognostic marker based on a single pretreatment scan. Our earlier study found that ^{18}F-FMISO PET may also be predictive.[19] [19] We found that patients with resolution of hypoxia on their intra-treatment ^{18}F-FMISO PET had excellent outcome with LRC and OS >90%. At our institution, we have an on-going large prospective multi-arm imaging study of using ^{18}F-FMISO PET to detect hypoxia in head and neck cancer patients. The current paper is the report of a small sub-study of this on-going trial where we hypothesied that pre- and early-treatment hypoxia assessment using functional PET imaging may help select which HPV+

OPC patients can safely receive radiation de-escalation without jeopardizing treatment outcomes.

METHODS

Patient Characteristics and Treatment

Stage III-IVB HPV+ OPC patients enrolled prospectively on this trial(xxx IRB #04-070; NCT xxx on clinical trials.gov) underwent pretreatment FDG/^{18}F-FMISO PETs.[20] Patients received standard chemoradiation. Patients with pretreatment hypoxia had a repeat scan one week into chemoradiation(^{18}F-FMISO$_{1week}$ PET). In this pilot sub-study, only nodal de-escalation from 70 Gy to 60 Gy was allowed. The primary tumor site received 70Gy. The overall goal of this pilot study was to test the feasibility and safety of de-escalation based on hypoxia imaging response and we focused only on the lymph nodes. HPV+ tumors(by *in sit hybridization* or p16 status by IHC when tissue was limited) received a de-escalated dose of 10 Gy from 60 Gy from 70Gy to the involved lymph node(s) when there was no pre-treatment hypoxia or there was resolution of hypoxia on ^{18}F-FMISO PET. There were two IMRT plans for each patient. Upon enrollment to the study, the first phase of IMRT consisted of both primary and nodal gross disease receiving 60Gy in 2Gy per daily fraction. The subclinical region in the primary site and the nodal levels received 54Gy in 1.8Gy per daily fraction. If the ^{18}F-FMISO PET scan did not exhibit any evidence of hypoxia in the node(s) or that there was no evidence of hypoxia on the repeat ^{18}F-FMISO PET, the second plan will consist of the gross disease in the primary site receiving additional 10Gy boost in 2Gy per daily fraction. If however, the node(s) continued to exhibit evidence of hypoxia on ^{18}F-FMISO PET, both the primary and nodal gross disease received additional 10Gy boost in 2Gy daily fraction. Respective PTV's were given to the gross disease and the subclinical regions in both plans. Figure 1 lists the workflow of the PET scans.

PET Protocol and Method of Analysis

Patients are positioned on the PET/CT scanner in the radiotherapy position, within a custom immobilization mask. A scout and low dose CT scan are performed to localize the field the view for the dynamic PET scan. Whilst in the PET scan position, patients are injected with an 8–10 mCi (296–370 MBq) bolus of ^{18}F-FMISO simultaneous with start of a dynamic acquisition. The PET/CT scan is acquired in 3 separate image segments: (1) 0–30mins, and at the nominal post-injection times of (2) 90–100 min and (3) 150–180 mins respectively. The patient was allowed to rest between the PET scan segments. Low current (10 mA) CT acquisitions are used to guide the PET acquisition field of view and to co-register the 3 PET sets into a single PET series for use in kinetic analysis. Two methods are used to detect tumor hypoxia as published previously.[14, 23] The first method was made based upon visual inspection and accordance with the tumor/muscle contrast ratio (>1.2) of ^{18}F-FMISO uptake for the third and final PET scan. The second was based upon the results of a compartmental analysis on the dynamic image series that allows a determination of the rate of irreversible ^{18}F-FMISO trapping (*k3*). In the majority of the patients, there is good concordance between the two methods in determining the presence and location of hypoxia. On the few cases when there was discordance, the results were discussed amongst experts

(N.L., H.S., J.H., B.B.) and collectively determined whether to classify the lesion as hypoxic or non-hypoxic. For further methodologic details, please refer to the supplemental text.

Follow-up and Statistical Analysis

This is a prospective pilot imaging biomarker study (a substudy of the on-going IRB# 04-070) . Given it was a pilot study to assess feasibility and generate preliminary evidence for efficacy, no formal sample size justification was done or required for this small sub-cohort. However, to roughly assess the probability of achieving our expectation based on this small sample, we provide a table as a guideline in the supplemental text. The objective of this current sub-study was to describe clinical outcomes of the patients treated according to this pilot. Standard evaluations including a 3-months post-treatment FDG PET were performed. Neck dissection was done when there was persistence of disease. The 2-year estimates for local, regional, distant metastasis rates, as well as OS rates were calculated using the Kaplan-Meier product limit method. Acute toxicities/late complications were recorded as per the Common Toxicity Criteria for Adverse Events Version 4.0.

Imaging-guided Biopsy Methods and Analysis

Image guided biopsies were taken only on a subset of the study population. These were done directly under PET-CT-guidance in our Center for Image Guided Intervention(CIGI) by our expert radiologists(interventional radiologists/nuclear medicine physicians). After undergoing ^{18}F-FMISO hypoxia imaging, patients were escorted to the CIGI facility, where they underwent an additional ^{18}F-FMSIO PET/CT image acquisition. With the patient in position on the scanner couch, biopsy needle placement was performed. To ensure the accuracy of needle placement, an additional low dose CT and 1 minute PET acquisition was performed to verify the location accuracy and correct positioning of the needle in the hypoxia location of the tumor. Hypoxia was defined by our expert nuclear medicine physician visually at the time of biopsy as the tumor to muscle ratio of >1.2. In these biopsies, immunohistochemistry (IHC) analysis was performed for HIF-1alpha HIF-1α (5.0 ug/mL of a mouse anti-human monoclonal antibody(clone 54/HIF-1a) from BD Transduction Laboratories. The stained slides were evaluated for the percentage of the nuclear and cytoplasmic staining. IHC was also performed on KI-67 (MIB-1) mouse (MAB) form Dako, catalog# M7240; Dilution 1:100 (0.46 mg/L). The proliferative rate was evaluated as the percentage of nuclear staining in the examined immunostained cells. [21, 22]

RESULTS

Total sample size for protocol IRB# 04-070 is 150 head and neck patients. In this substudy, we set out to prove the concept that reducing the dose of radiation based on hypoxia imaging response does not compromise locoregional control. We have de-escalated 10 patients out of the 33 patients enrolled. The first patient enrolled in 12/2010 and the last patient was enrolled in 4/2014. Table 1a contains the patient/treatment characteristics. The initial distribution of ^{18}F-FMISO demonstrated the spatial heterogeneity of hypoxia in the primary tumor and/or metastatic lymph nodes. The presence of hypoxia was frequently discordant between the primary site and the nodal region, as has been previously reported.[15, 19]

All 33 HPV+ exhibited high prevalence of hypoxia. 26 patients showed pretreatment hypoxia at the primary site and 15 patients had persistence of hypoxia at the primary tumor site even after one week of chemoradiation. For this paper, we focused on de-escalation to the lymph nodes(Figure 1). Ten patients(30%) met the criteria for radiation de-escalation to their involved node(s)[Table 1b]. Figure 2a is an example of imaging for a patient who received radiation de-escalation versus Figure 2b where imaging results suggested persistent hypoxia and radiation de-escalation was not performed.

The median follow-up of surviving patients was 32 months(range, 21–61months) with 100% 2-year local and regional progression-free rates. Metastasis to the lungs developed in one patient who had pretreatment and persistent hypoxia at one week into chemoradiation. This patient did not receive de-escalated treatment.. The 2-year DM-free rate was 97%. The 2year OS rate was 100% for all patients. Patients tolerated their treatment regimens very well overall. Acute grade 3 mucositis was experienced by 11 patients.. No patients experienced acute grade 3 dysphagia. Only two patients complained of late grade 2 xerostomia. Eleven patients consented to biopsies under ^{18}F-FMISO PET guidance. The biopsy specimens all showed evidence of tumor.(Table 2) Up to 70% of the biopsy specimens stained for HIF-1α and nearly 90% stained for Ki67. The degree of HIF-1α or Ki67 IHC staining did not correlate with the degree of ^{18}F-FMISO PET uptake.

DISCUSSION

Treatment with chemotherapy and 70 Gy for HNSCC has resulted in excellent LRC, DFS and OS of nearly 90%, most likely due to the rising incidence of HPV+ tumors. However, the treatment-related toxicities can be significant. Up to 75% of the head/neck cancer patients can experience ≥acute grade 2 mucositis, pharyngitis, dysphagia, and skin toxicities. [23, 24] [2] Despite IMRT's ability to reduce xerostomia, patients still experience dental caries, swallowing difficulties, osteoradionecrosis, and strictures leading to percutaneous gastrostomy tube(PEG) dependence.[25, 26]

Improved outcomes of HPV+ OPC have led to a concerted effort to de-intensify treatment. There is a consensus that HPV status alone is insufficient to base de-escalation decision as there is still a subset of biologically aggressive HPV+ OPCs that recur after chemoradiation. Therefore, attempts to non-selectively reduce either chemotherapy or radiation therapy for HPV related tumors need to proceed with caution. [5] Many other investigators have chosen traditional clinical parameters to identify patients for de-escalation, i.e. T-stage, N-stage, and smoking status. Although these factors are prognostic, whether they are predictive of radiation sensitivity remains to be determined.[27] Smoking history may play a role in prognosis, however, the optimal cut-off regarding whether a patient is a candidate for de-escalation(10 pack years) is unclear.[4, 27]

Since not all HPV+ tumors respond favorably to treatment, we investigated whether an additional factor, i.e. hypoxia, can help guide us to decide which HPV+ patients are safe to undergo de-escalation. Hypoxia is well-established to confer radio-resistance through a reduction in free radical production and limiting radiation induced DNA damage. This is in contrast to aerobic cells where molecular oxygen acts as a potent chemical radiosensitizer

leading to radiation induced DNA damage..[28, 29] . Further pre-clinical studies have shown that HPV+ cells exhibit the same relative radio-resistance under hypoxia compared to HPV− cells.[30] Further, HPV+ cells under hypoxia had approximately the same radiosensitivity as HPV− cells under normoxia.[30] A recent paper has shown a decrease in tumor hypoxic fraction following radiation only in HPV+ tumors. [31] Lastly, although most *in vitro* data demonstrates that HPV+ cell lines to be distinctly more radiosensitive versus HPV− cell lines, there are a couple of studies that show the contrary.[8] The differences in radiosensitivity across series may be attributable to the presence of hypoxia. One paper even showed that in human and murine transformed cell lines, HPV+ cells were more resistant to radiation and cisplatin therapy versus HPV− cells.[9]

Tumor hypoxia as manifested by the overexpression of HIF-1α has been reported as an independent poor prognostic factor in HNSCC. In one series of 98 oropharynx tumors, 94% showed overexpression of HIF-1α [22] which inversely correlated with both rate of complete remission of gross disease as well as local failurefree, disease-free, and OS. Having knowledge of tumor hypoxia can help identify patients more likely to fail therapy versus good-responders. Rischin et al.[15] have demonstrated that patients demonstrated higher locoregional failure when there was evidence of hypoxia in the absence of a tirapazamine containing chemoradiation regimen(8 of 13 patients). Those who did not exhibit hypoxia on imaging rarely experienced locoregional failure(1 of 10 patients). This data along with our own data[19]suggest a rationale for using ^{18}F-FMISO at baseline and as an early response hypoxia biomarker with the goal to select the radiation responders among HPV+ patients. At the time of trial inception(2008) and given the conflicting data on HPV+ tumors and radioresponsiveness along with concerns that dose de-escalation may result in tumor recurrences not amenable to curative salvage therapy, we chose to be very careful and focused on lymph node(s) for de-escalation. We felt that neck dissection was one good salvage option should the deescalated therapy resulted in persistent nodal disease in these highly curable HPV+ tumors. We designed this trial incorporating functional imaging with ^{18}F-FMISO PET to determine whether tumors pretreatment without hypoxia or tumors with early hypoxia resolution could suggest a radiosensitive HPV+ tumor that can safely undergo de-escalated radiotherapy. Both scenarios take advantage of fundamental radiobiologic processes: radiosensitization due to oxygen(pre-treatment) and reoxygenation(early intra-treatment), respectively. There are logistic advantages with early imaging time points, since the design of this protocol will provide sufficient time for the investigators to interpret the data, inform the patient, and replan the reduced dose plan for eligible patients. With this approach, our locoregional control at 2 years is 100%.

Other strategies that focus on de-intensifying treatments include the use of an alternative systemic therapy instead of platinum-based regimens such as Cetuximab, although with accelerated radiation fractionation. [32] Several randomized trials have indicated that that the acute(grade 3–4 mucositis) and late(soft tissue fibrosis and PEG dependence) effects of accelerated radiation are higher versus standard fractionation(RTOG 90-03, GORTEC 99-02).[33, 34] O'Sullivan et al.[35] also reported that 20% of the patients who underwent CRT with an accelerated radiotherapy experienced ≥grade 3 fibrosis, dysphagia, and/or osteoradionecrosis. In addition, subsequent studies of EGFR-based radiotherapy strategies have demonstrated similar rates of Grade 3–4 toxicity as platinum-based regimens,

suggesting this approach alone may not reduce toxicity significantly.[36–38] Lastly, whether EGFR-inhibition is as effective a method of sensitizing radiotherapy versus platinum-based therapy remains controversial, with retrospective and Phase II studies suggesting caution. [39, 40] [37] The recently closed RTOG 1016 was designed to definitively determine whether cetuximab can safely replace cisplatin for HPV+ OPC and whether cetuximab will have less toxicities versus cisplatin.

Another approach to de-escalating treatment involves using induction chemotherapy to select patients with radiosensitive tumors. ECOG 1308 [41] focused on reducing the dose of radiation with concurrent cetuximab for HPV+ tumors after 3 cycles of induction chemotherapy consisting of paclitaxel, cisplatin and cetuximab. With a median follow-up of 23.3 months, 62 patients(78%) received reduced-dose IMRT at 54Gy with cetuximab after complete response to induction chemotherapy. The 23-month progression-free survival was 84%. This study suggests that induction chemotherapy can identify tumors sensitive to therapy. However, with this approach the ability to reduce toxicity remains unclear as patients receive 3 additional cycles of multi-agent therapy that they typically would not receive with standard therapy. Although we agree with the principle of response-assessment to guide treatment de-escalation decisions, we believe that intra-treatment functional imaging during definitive chemo-radiotherapy may be a better approach to guide these decisions.

One question is whether HPV+ tumors can be treated effectively with radiation alone. One series showed that HPV+ tumors with stage T1-3N0-2b at low risk for DM are potentially well suited for de-intensification strategies.[35] Although high loco-regional control was observed, distant control was not altered. Given that the predominant failure pattern for oropharyngeal cancer is distant, efforts to reduce RT dose should not omit systemic therapy as it can eradicate micrometastasis.[42] In fact, one would argue that additional systemic therapy might be needed for those with persistent hypoxia. Further, O'Sullivan et al. showed that in the most favorable low risk HPV+ oropharynx group, locoregional recurrence rate(15 failures) in the RT alone group versus 5 failures treated with chemoradiation.[35] Lastly, Riaz *et al.*[43] used recursive partitioning analysis to show that patients with T2N1-3 disease with a low lying lymph node or those with T4N2b-N3 disease are at high risk for DM. Since HPV+ tumors usually present with multiple lymph nodes, often low lying(neck levels III – IV), our group has sought to identify de-intensification strategies encompassing chemotherapy since it has been shown to improve OS.[44] These data along with the strong evidence of benefit of synergistic effects of chemotherapy with radiation in other HPV-related malignancies(anal and cervical cancer) has led our group to focus on radiotherapy dose de-escalation rather than accelerate radiation treatments without chemotherapy. Lastly, Huang et al.[27] proposed a new T and N stage grouping for HPV+ patients appeared to be very strong prognostic factor for outcome. Although the proposed stage grouping for HPV+ oropharyngeal cancer allowed for better prediction of OS, the authors cautioned the use of the new proposed TNM staging system to change current management whether it is de-intensification or intensification or even chose different treatment modalities outside of a clinical trial setting(NRG HN002).

70 Gy was chosen that achieved tumor control with an acceptable normal tissue complication probability. However, this was established not based on differing tumor control probability curves for HPV+ versus HPV− tumors. Therefore, it is conceivable that 70 Gy over treats a significant fraction of HPV+ HNSCC. We know that a lower radiation dose(≤60 Gy) in combination with chemotherapy has proven to be effective for organ preservation in anal carcinoma.[45] Since HNSCC and anal cancer have similar squamous histology and viral etiology, it is reasonable to consider that both of these cancers may exhibit similar dose response characteristics. A recent study in HNSCC revealed that a dose reduction of 10 Gy from 70 Gy to 60 Gy decreases toxicities such as mucositis, late xerostomia, ORN, dental caries.[46] There remains the question how to safely dose de-escalate in a manner that is consistent with maintaining the high level of treatment response. Consideration needs to be made in the context of the RTOG01-29 trial where even amongst the most favorable HPV+ patients(non-smokers or ≤10 pack year), undergoing a 70Gy accelerated radiation regimen with concurrent high dose cisplatin, the 3 year OS was 93% and not 100%. Therefore, a non-selective reduction of the radiation dose in all HPV related tumors may result in failures that are difficult to salvage. Chera et al. reported their de-intensified approach for 43 HPV or p16 positive oropharyngeal cancer patients with minimal/remote smoking history treated with reduced dose radiation of 60Gy and 6 weekly doses of cisplatin at 30mg/m^2. With a median follow-up of 14.6 months(4 to 31 months), the overall clinical complete response rate was 64% at 6 weeks post chemoradiation with a pathologic complete response of 86%. The long-term durable control and treatment outcome remains unknown.[47]

In this study, the hypoxic “hot” subzones on ^{18}F-FMISO PET on node(s) were biopsied. One patient who had multiple pre-treatment core biopsies under hypoxia guidance showed in one core tumor and in the other stromal, fibrous, and lymphoid tissue. Similarly, 3 patients in their repeat biopsies done under hypoxia guidance also had similar findings. Given that we had validation of needle placement after biopsy, one plausible hypothesis is that the highly inflammatory nature of HPV+ tumors results in their FDG avidity while the prevalence of lymphoid tissue and lower tumor burden might illuminate why these tumors regress rapidly during chemoradiation. A recently presented abstract stated that there is a distinct pattern of intra-tumoral immune cell infiltrates in patients with HPV+ tumors which may play a crucial role in the better therapeutic response and clinical outcomes.[48] Further work is needed to define the role of immune cells in the etiology, treatment response, and prognosis of HPV+ HNSCC.

To our knowledge, this is the first study using an approach to radiation de-escalation based using functional PET imaging to assess early hypoxia treatment response in HPV+ tumors. Our locoregional control remains 100% with minimal toxicities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was funded by NIH R01 CA157770-01A1

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Summary

A review of a large multi-center randomized study by Ang et al. published in N Engl J Med 2010; 363:24–35 July 1, 2010, showed that human papilloma virus (HPV) associated tumors have a better prognosis versus those not associated with HPV. Our work takes this new biologic understanding of Head and neck cancer and combines it with an additional biomarker of radio-sensitivity (hypoxia) to attempt to personalize the amount of radiotherapy a patient receives.

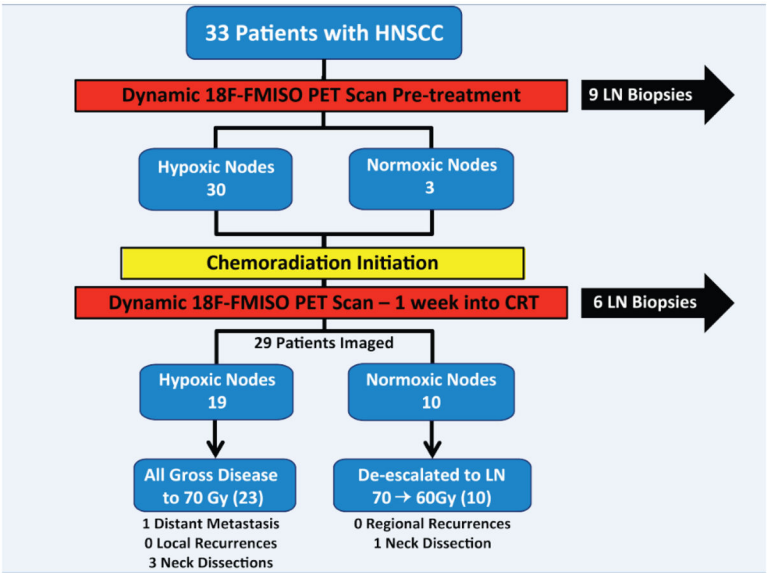

Figure 1.
PET workflow

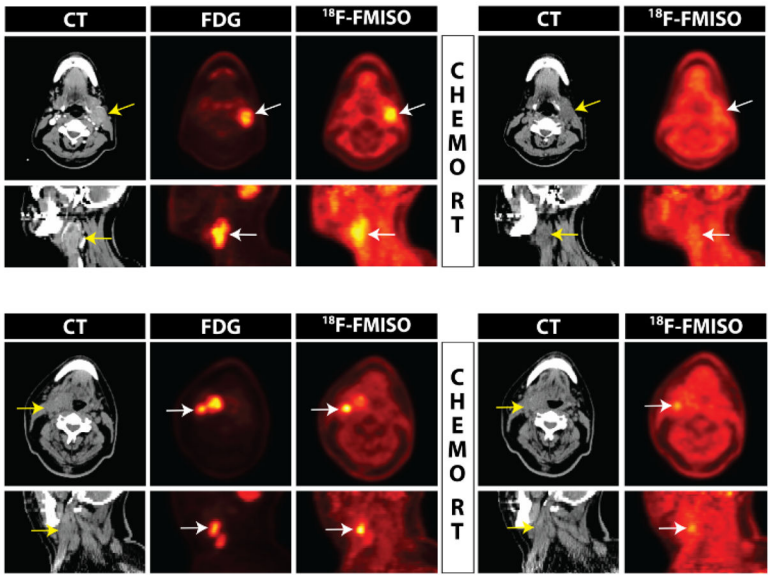

Figure 2.

Figure 2a A patient with hypoxia on pretreatment ^{18}F-FMISO PET and with resolution on ^{18}F-FMISO$_{1week}$ PET.

Figure 2b A patient with hypoxia on pretreatment ^{18}F-FMISO PET and persistent hypoxia on ^{18}F-FMISO$_{1week}$ PET.

Table 1a

Patient Characteristics (n=33)

Characteristic	Value
Age (y)	
Median	58
Range	26–79
Primary Site	
Tonsil	17
BOT	15
BOT & Tonsil	1
T stage	
1	6
2	17
3	7
4	3
N stage	
0	0
1	1
2	30
3	2
Stage Group	
III	1
IV	32
HPV Status/p16	
Positive	33
Chemotherapy regimen	
Cisplatin	27
Carboplatin/5-Fu	2
Carboplatin/Paclitaxel	2
Cetuximab/Cisplatin/Bevacizumab	1
Cetuximab	1

Table 1b

Patient Stage versus De-Escalation(n=33)

T Stage	N Stage	Overall Stage	HPV/p16 Status	Smoking History	De-escalated
T2	N2b	IVA	Positive	30 pack years	Yes
T2	N2	IVA	Positive	None	Yes
T2	N2b	IVA	Positive	Currently Smoking	Yes
T3	N2a	IVA	Positive	15 pack years	No
T1	N2b	IVA	Positive	None	Yes
T2	N2b	IVA	Positive	None	No
T2	N2b	IVA	Positive	None	No
T1	N2c	IVA	Positive	4 pack years	No
T2	N2b	IVA	Positive	None	No
T3	N2c	IVA	Positive	20 pack years	Yes
T2	N2c	IVA	Positive	None	No
T2	N2b	IVA	Positive	None	No
T2	N2b	IVA	Positive	None	No
T2	N2c	IVA	Positive	None	No
T3	N2c	IVA	Positive	None	No
T1	N2b	IVA	Positive	10 pack years	No
T2	N2a	IVA	Positive	None	No
T2	N2c	IVA	Positive	None	No
T1	N2b	IVA	Positive	None	No
T2	N2c	IVA	Positive	35 pack years	No
T2	N2a	IVA	Positive	30 pack years	Yes
T1	N2b	IVA	Positive	None	Yes
T3	N2b	IVA	Positive	40 pack years	No
T2	N2b	IVB	Positive	None	No
T1	N2b	IVA	Positive	None	No
T3	N2c	IVA	Positive	40 pack years	No
T2	N2b	IVA	Positive	None	Yes

T Stage	N Stage	Overall Stage	HPV/p16 Status	Smoking History	De-escalated
T3	N1	III	Positive	15 pack years	Yes
T2c	N2b	IVa	Positive	15 pack years	No
T4a	N2c	IVA	Positive	6 pack years	No
T3	N3	IVB	Positive	None	No
T4a	N2b	IVA	Positive	None	No
T2	N2b	IVA	Positive	5 pack years	Yes

Table 2

^{18}F-MISO PET and the corresponding ^{18}F-MISO PET directed biopsies.

Case #	HPV/p16 Status	1st FMISO scan Specific Node	1st Biopsies Results K1-67/Hif1α(% Staining)	2nd FMISO scan Specific Node	2nd Biopsies result K1-67/Hif1α(% staining)
1	positive	1	tumor/tumor * 80%/15%	1	Tumor 35%/<5%
2	positive	1	tumor/tumor * 65%/50%	1	Tumor 85%/10%
3	positive	1	Tumor 40%/50%	0	Refused
4	positive	1	Tumor 80%/70%	1	Refused
5	positive	1	Tumor 90%/10%	1	Tumor 30%/40%
6	positive	1	Tumor 40%/50%	1	Tumor 50%/10%
7	positive	1	Tumor 50%/60%	1	tumor/no tumor * (Staining not done)
8	positive	1	Tumor 80%/20%	0	Refused
9	positive	1	tumor/no tumor *(Staining not done)	1	rare atypical cells/no tumor *

Note: Positive for hypoxia on ^{18}F-MISO PET is designated as “1” and negative for hypoxia on ^{18}F-MISO PET is designated as “0”.

* The patient had multiple core biopsies from the same location.