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ORIGINAL REPORT

Prognostic Significance of [^{18}F]-Misonidazole Positron Emission Tomography–Detected Tumor Hypoxia in Patients With Advanced Head and Neck Cancer Randomly Assigned to Chemoradiation With or Without Tirapazamine: A Substudy of Trans-Tasman Radiation Oncology Group Study 98.02

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ABSTRACT

Purpose
To determine the association between tumor hypoxia, treatment regimen, and locoregional failure (LRF) in patients with stage III or IV squamous cell carcinoma of the head and neck randomly assigned to radiotherapy (70 Gy in 35 fractions over 7 weeks) plus either tirapazamine and cisplatin in weeks 1, 4, and 7 and tirapazamine alone in weeks 2 and 3 (TPZ/CIS) or cisplatin and infusional fluorouracil during weeks 6 and 7 (chemoboost).

Patients and Methods
Forty-five patients were enrolled onto a hypoxic imaging substudy of a larger randomized trial. Pretreatment and midtreatment [^{18}F]-fluoromisonidazole positron emission tomography scans (FMISO-PET) were performed 2 hours after tracer administration, with qualitative scoring of uptake in both primary tumors and nodes.

Results
Thirty-two patients (71%) had detectable hypoxia in either or both primary and nodal disease. In patients who received chemoboost, one of 10 patients without hypoxia had LRF compared with eight of 13 patients with hypoxia; the risk of LRF was significantly higher in hypoxic patients (exact log-rank, $P = .038$; hazard ratio [HR] = 7.1). By contrast, in patients who received the TPZ/CIS regimen, only one of 19 patients with hypoxic tumors had LRF; risk of LRF was significantly higher in chemoboost patients ($P = .001$; HR = 15). Similarly, looking at the primary site alone, in patients with hypoxic primaries, zero of eight patients treated with TPZ/CIS experienced failure locally compared with six of nine patients treated with chemoboost ($P = .011$; HR = 0).

Conclusion
Hypoxia on FMISO-PET imaging, in patients receiving a nontirapazamine-containing chemoradiotherapy regimen, is associated with a high risk of LRF. Our data provide the first clinical evidence to support the experimental observation that tirapazamine acts by specifically targeting hypoxic tumor cells.

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INTRODUCTION

The potential importance of tumor hypoxia as a cause of treatment failure in patients treated with radiation has been recognized for a long time.[1] In particular, studies using oxygen-sensitive needle electrodes in patients with head and neck cancer treated with primary radiation therapy have shown a correlation between the presence of hypoxia and decreased locoregional control.[2,3] However, progress has been hampered by the significant limitations of previously available methods of hypoxia detection and by the limited benefit seen with treatment strategies tested to overcome hypoxia (eg, hypoxic cell sensitizers and hyperbaric oxygen).[4]

Hypoxia-activated prodrugs represent a new strategy to exploit the presence of hypoxia in human tumors. One such compound is tirapazamine, a benzotriazine compound, which acts as a hypoxic cytotoxin and potentiates both radiation and cisplatin cytotoxicity.[5-7] Because the addition of concurrent platinum-based chemotherapy to radiation has

been demonstrated to improve locoregional control and overall survival in patients with locoregionally advanced head and neck cancer,[8-10] we developed a regimen in which tirapazamine was added to a standard radiation and cisplatin regimen (TPZ/CIS). Promising results were seen in the initial trial,[11] which led to testing of this regimen in a cooperative group randomized phase II trial (Trans-Tasman Radiation Oncology Group [TROG] 98.02) conducted under the auspices of TROG.[12] The other regimen tested was the chemoboost regimen, which seems to have similar efficacy to other platinum-based concurrent chemoradiotherapy regimens.[13-15] We have previously reported the overall results of this trial; 122 patients were enrolled, and both regimens were found to be feasible, with acceptable toxicity profiles in the cooperative group setting.[12] Three-year failure-free survival rates were 55% (95% CI, 39% to 70%) with TPZ/CIS and 44% (95% CI, 30% to 60%) with chemoboost (log-rank test, $P = .16$). Three-year locoregional failure (LRF) –free rates were 84% (95% CI, 71% to 92%) in the TPZ/CIS arm and 66% (95% CI, 51% to 79%) in the chemoboost arm ($P = .069$). Given the promising efficacy seen in this trial, TPZ/CIS is being evaluated in two large international phase III trials.

As part of the TROG 98.02 trial, patients treated at one center, the Peter MacCallum Cancer Centre (PMCC), were also enrolled onto a hypoxic imaging substudy with serial [^{18}F]-fluoromisonidazole (FMISO) positron emission tomography (PET) scans. We now report the results of this hypoxic imaging study.

PATIENTS AND METHODS

Study Design and Eligibility

This was a substudy of an open-label, randomized, phase II trial studying two concurrent chemoradiotherapy regimens that was conducted under the auspices of the TROG. All patients enrolled onto the randomized trial at a single institution, PMCC, were eligible and provided written informed consent to participate in this FMISO-PET substudy.

Eligibility criteria for the TROG 98.02 trial included previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; stage III or IV disease (excluding T1N1 and distant metastases); and no concurrent active cancer in the last 5 years. The PMCC ethics committee approved the protocol, which included this imaging substudy.

Pretreatment Evaluations

Before enrollment, all patients underwent a full history, physical examination, blood tests, computed tomography (CT) or magnetic resonance imaging scan of the head and neck, chest x-ray (CT of the chest if involved low neck nodes), and PET scan with [^{18}F]-fluorodeoxyglucose (FDG-PET) and FMISO-PET.

PET

Scans for tumor hypoxia (FMISO-PET) were performed at baseline and at weeks 4 to 5 during treatment. If there was residual hypoxia present on the week 4 to 5 scan, then it was to be repeated at the end of treatment. Static high-resolution mode images of the neck were acquired at 2 hours after radiotracer administration. All PET imaging was performed on a dedicated PET scanner (PENN-PET 300H; UGM Medical System Inc, Philadelphia, PA). On each occasion, PET images of the neck were acquired and processed using measured attenuation correction and iterative reconstruction in treatment position.[16] After coregistration with a baseline FDG-PET study, tumoral regions of interest were applied for analyses of FMISO uptake in the primary and nodal sites. FMISO-PET lesions were scored qualitatively by consensus of two readers blinded to CT results, according to the following scheme as previously published[17]: 0, uptake less than background; 1, no regions of focal uptake greater than background; 2, focal uptake mildly greater than background; 3, focal uptake moderately greater than background; and 4, focal uptake markedly greater than background.

However, unless FMISO uptake was as intense as FDG uptake qualitatively, a score of 4 could not be given. The FMISO scan was interpreted to be positive if there was greater activity (score of 2 or 3) within the sites of tumoral uptake of FDG than the activity present in adjacent or mirrored soft tissue sites on the 2-hour images when reviewed using a linear rainbow color scale.

Treatment Plan

Arm 1. Tirapazamine was supplied by Sanofi-Aventis Pharmaceuticals (Sydney, Australia). On day 2 of weeks 1, 4, and 7, tirapazamine (290 mg/m^2) was administered over 2 hours, followed 1 hour later by cisplatin (75 mg/m^2) over 1 hour, followed immediately by radiotherapy. In addition, tirapazamine (160 mg/m^2) was administered before radiation three times a week in weeks 2 and 3.

Arm 2. Cisplatin (50 mg/m^2) was administered before radiotherapy on day 1 of weeks 6 and 7 of radiotherapy. Fluorouracil (360 mg/m^2/d) was administered by continuous infusion from days 1 to 5 (120-hour infusion) in weeks 6 and 7 of radiotherapy.

Radiation Therapy

Planned radiation therapy was 70 Gy in 35 fractions over 7 weeks in both arms. The radiation was administered via a shrinking-field technique. The initial 50 Gy encompassed the gross clinical disease and sites suspected of harboring subclinical disease. The maximal spinal cord dose was 45 Gy. The fields were then reduced in size to treat the areas of gross macroscopic disease to 70 Gy, with a buffer zone of 60 Gy around larger nodal masses.

Random Assignment and Stratification

Patients were randomly assigned 1:1 to the two arms and stratified by institution, as previously described. For patients in the imaging substudy, the result of the baseline FMISO-PET was not a stratification factor.

End Points

Failure was defined as persistent disease in the primary site, progression of disease in the neck (in patients not undergoing planned neck dissection), residual disease left behind after neck dissection (if performed), locoregional relapse after complete response, or distant metastasis. Time to LRF was measured from random assignment to the date of LRF, and failure-free survival was measured from random assignment to the date of first failure or death. Both times were censored by the close-out date; time to LRF was also censored by distant metastasis and death without preceding failure.

Statistical Methods

Analyses of time to LRF and failure-free survival are based on the intent-to-treat policy. A close-out date of May 20, 2004 was used for this analysis. The Kaplan-Meier method was used to estimate time to event curves. Log-rank (exact) test and Cox proportional hazards regression were used to analyze time to event data. Two-sided tests were used throughout. No formal adjustment for multiple comparisons was made.

Role of the Funding Source

Sanofi-Aventis partially supported the study but was not the sponsor of this trial, which was conducted by TROG. Sanofi-Aventis was involved in monitoring the source data but was not involved in the study design, database entry, analysis, interpretation of data, writing of the report, or decision to submit the paper for publication.

RESULTS

Patient Characteristics

Fifty-three of 122 patients enrolled onto the TROG 98.02 randomized trial were treated at PMCC. Forty-five of these 53 patients participated in the hypoxic imaging substudy. In the remaining eight patients, FMISO-PET could not be performed before they commenced treatment because of unavailability of the tracer or the PET scanner. The median potential follow-up time for the 45 patients from

commencing treatment to the close-out date was 3.6 years (range, 1.8 to 5.7 years). Baseline patient characteristics were reasonably balanced between patients on the two arms, although there was a higher incidence of node-positive and N3 disease in the TPZ/CIS arm (Table 1).

Hypoxia in the Primary Tumor and/or Nodes

Thirty-two (71%) of 45 patients had detectable hypoxia in the primary tumor and/or a lymph nodal metastasis (Table 2). In only six patients was hypoxia detected in both the primary tumor and a node. Of the seven patients with node-negative disease, only one had hypoxia evident in the primary tumor.

For the purposes of assessing the correlation between hypoxia, treatment arm, and outcome, patients were divided into four groups based on treatment arm and the presence or absence of hypoxia in the primary tumor and/or nodes (Table 2). Because random assignment was not stratified by hypoxia status, it is not surprising that the distribution between the four groups turned out to be unbalanced.

Table 1. Baseline Characteristics by Treatment Arm

Characteristic	Total No. of Patients	Treatment Arm: TPZ/CIS No. of Patients	TPZ/CIS %	Chemoboost No. of Patients	Chemoboost %
All patients	45	22	100	23	100
Median age, years		57		56	
Sex					
Male	36	17	77	19	83
Female	9	5	23	4	17
Primary site of disease					
Oral cavity	3	1	5	2	9
Oropharynx	27	14	64	13	57
Hypopharynx	8	4	18	4	17
Larynx	7	3	14	4	17
Tumor stage					
T1	7	5	23	2	9
T2	7	3	14	4	17
T3	21	10	45	11	48
T4	10	4	18	6	26
Node stage					
N0	7	2	9	5	22
N1	7	2	9	5	22
N2a	3	3	14	0	0
N2b	13	6	27	7	30
N2c	6	3	14	3	13
N3	9	6	27	3	13
Node involvement					
Negative	7	2	9	5	22
Positive	38	20	91	17	74
Disease stage					
III	12	4	18	8	35
IV	33	18	82	15	65
ECOG performance status					
0	15	12	55	13	57
1	18	9	41	9	39
2	2	1	5	1	4
Hemoglobin group					
Low	9	6	27	3	13
High	36	16	73	20	87
Baseline hypoxia					
None	13	3	14	10	43
Primary tumor only	11	4	18	7	30
Node only	15	11	50	4	17
Primary tumor and node	6	4	18	2	9

Abbreviations: TPZ/CIS, tirapazamine and cisplatin; ECOG, Eastern Cooperative Oncology Group.

Table 2. Primary Tumor Versus Node Hypoxia

Primary Hypoxia	Node Negative (No. of patients)	Node Hypoxia (No. of patients): No Hypoxia	Node Hypoxia (No. of patients): Hypoxia	Total (No. of patients)
No hypoxia	6	7	15	28
Hypoxia	1	10	6	17
Total	7	17	21	45

The complete response rates were 70% (seven of 10 patients) for chemoboost without hypoxia, 31% (four of 13 patients) for chemoboost with hypoxia, 100% (three of three patients) for TPZ/CIS without hypoxia, and 74% (14 of 19 patients) for TPZ/CIS with hypoxia.

In patients who received the chemoboost regimen, LRF was uncommon in patients without hypoxia but common in patients with hypoxia (Table 3). The risk of LRF in patients who received chemoboost was significantly higher in hypoxic patients (exact log-rank, $P = .038$; hazard ratio [HR] = 7.1). By contrast, in patients with hypoxic tumors, only one of 19 patients who received TPZ/CIS experienced LRF compared with eight of 13 patients who received chemoboost. In patients with hypoxic tumors, risk of LRF was significantly higher in chemoboost patients compared with patients who received TPZ/CIS ($P = .001$; HR = 15). Figure 1 demonstrates a differential response in an individual patient treated with chemoboost who achieved a complete response in the nonhypoxic primary tumor and a poor response in the hypoxic node.

Similar trends were seen for failure-free survival. In patients who received chemoboost, failure-free survival time was shorter in hypoxic patients (exact log-rank, $P = .095$; HR = 3.2). In patients with hypoxic tumors, risk of failure or death was significantly higher in chemoboost patients compared with TPZ/CIS patients (exact log-rank, $P = .004$; HR = 4.7). In patients with hypoxic tumors, overall survival time was shorter in chemoboost patients compared with TPZ/CIS patients (exact log-rank, $P = .11$; HR = 2.45).

Surprisingly, two of three patients without hypoxia who received TPZ/CIS experienced LRF. It is difficult to draw any conclusions about this group with such small numbers. Both cases of LRF were

Table 3. Locoregional Failure by Treatment Arm and Hypoxia

Hypoxia Status	Treatment: Chemoboost No. of Locoregional Failures	Chemoboost No. of Patients	TPZ/CIS No. of Locoregional Failures	TPZ/CIS No. of Patients
Nonhypoxic	1	10	2	3
Hypoxia in primary tumor and/or nodes	8	13	1	19

Abbreviation: TPZ/CIS, tirapazamine and cisplatin.

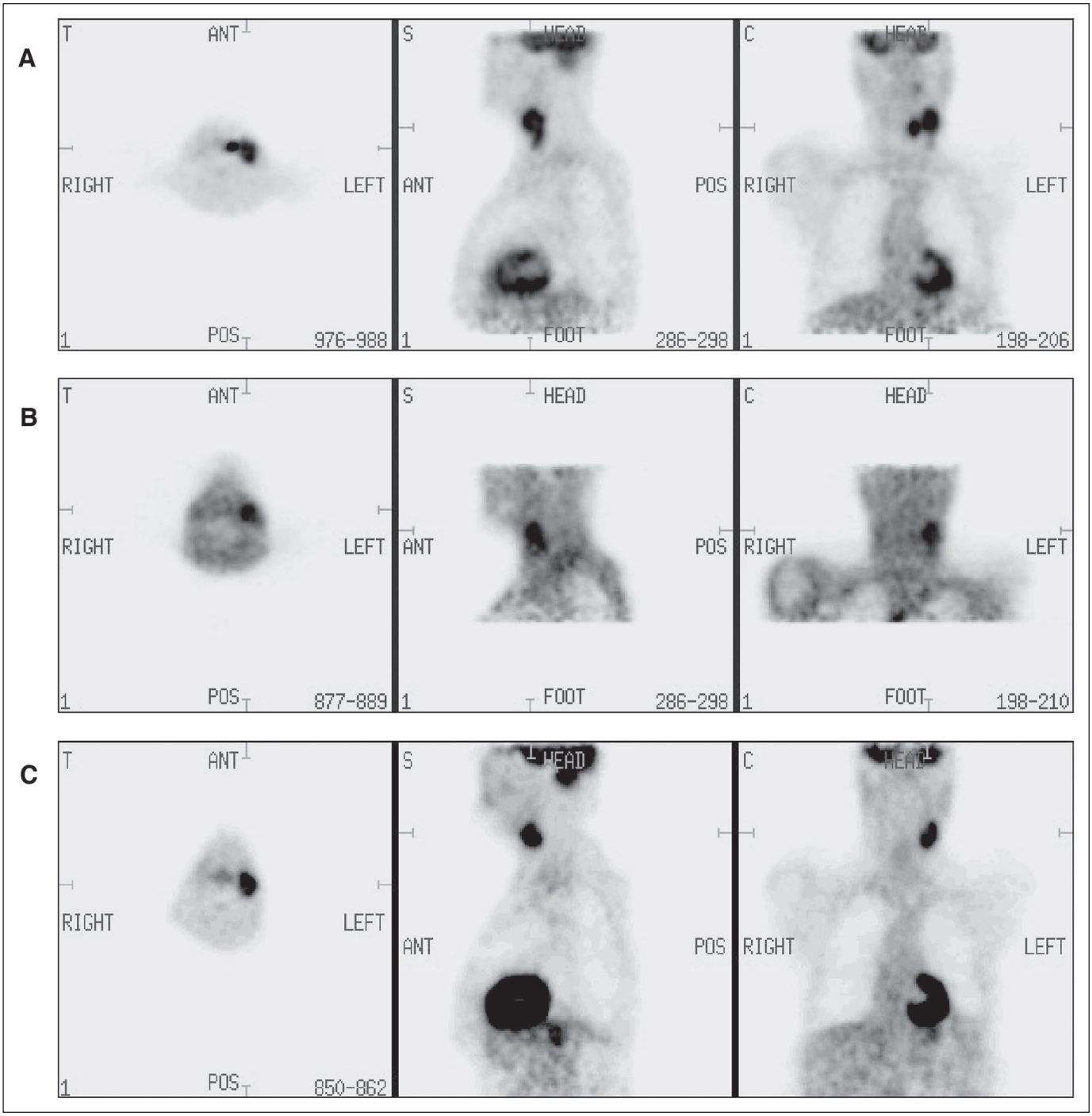

Fig 1. (A) Baseline [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) of patient with T2N2b squamous cell carcinoma of the pyriform fossa with left nodal mass. (B) [^{18}F]-fluoromisonidazole (FMISO) -PET at baseline, nonhypoxic primary tumor, and hypoxic node. (C) FDG-PET 12 weeks after chemoboost, complete response in nonhypoxic primary tumor, and poor response in hypoxic node. Residual tumor in nodal mass was confirmed pathologically after neck dissection.

unusual. In one case, a patient with a T3N0 soft palate tumor had a marginal relapse with infraorbital nerve infiltration. In the other case, a patient with a T4N2b tonsillar fossa tumor died of unrelated causes 17 months after completing treatment. At autopsy, there was microscopic evidence of residual cancer at the primary site that had not been detected antemortem.

Hypoxia in the Primary Tumor

We also examined the impact of hypoxia in the primary tumor on local control (Fig 2). In patients treated with chemoboost, one of 14 patients without hypoxia experienced failure locally compared with six of nine patients with a hypoxic primary tumor. Risk of primary failure was significantly higher for hypoxic patients (exact log-rank,

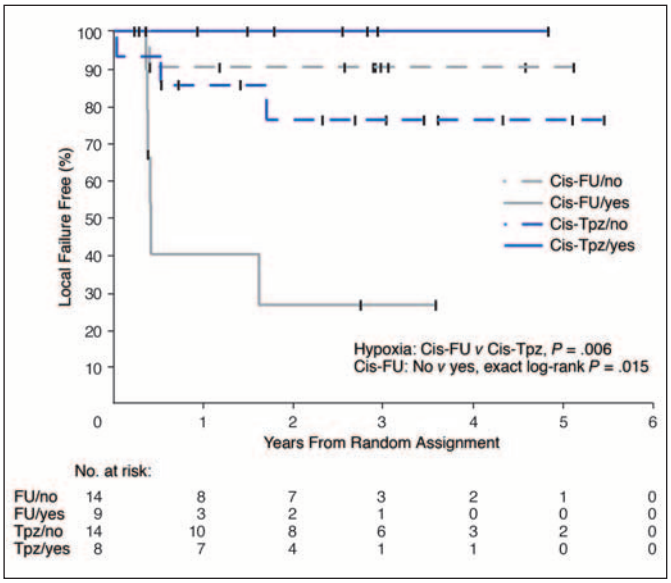

Fig 2. Time to local failure (Kaplan-Meier method) by treatment arm and hypoxia in the primary tumor (censored times are indicated as tick marks on the curves). Cis, cisplatin; FU, fluorouracil; TPZ, tirapazamine.

$P = .015$; HR = 8.9). For patients with hypoxic primary tumors treated with TPZ/CIS, zero of eight patients experienced failure locally compared with six of nine patients treated with chemoboost ($P = .011$; HR = 0.0).

Three patients with recurrent/persistent disease at the primary site underwent salvage surgery. All three patients were on the chemoboost arm, with two of the three patients having baseline hypoxia in the primary tumor.

Hypoxia in the Nodes

Four of 38 node-positive patients have experienced failure in the nodes; three of these patients were treated with chemoboost, and one was treated with TPZ/CIS (one of 12 patients on chemoboost without hypoxia in nodes, two of six patients on chemoboost with hypoxic nodes, zero of five patients without hypoxia on TPZ/CIS, and one of 15 patients with hypoxia on TPZ/CIS).

Residual Hypoxia

Twenty-nine of 32 patients with baseline hypoxia in the primary tumor and/or in a node had a repeat FMISO-PET in weeks 4 to 5. Six patients had residual hypoxia detected. Four (two primary and two nodal) of 13 patients with baseline hypoxia treated with chemoboost had residual hypoxia, and all experienced LRF (Table 4). Two (both nodal) of 16 patients with baseline hypoxia treated with TPZ/CIS had residual hypoxia, with neither experiencing LRF but both developing distant metastases.

Distant Failure

Nine of 45 patients (six treated with chemoboost, and three treated with TPZ/CIS) experienced failure at distant sites as a component of first failure. It is of interest that eight of 32 patients with baseline hypoxia experienced distant metastasis as first failure compared with only one of 13 patients without baseline hypoxia (HR = 3.42; $P = .29$).

Table 4. Locoregional Failure by Treatment Arm and Resolution of Hypoxia

	Treatment			
	Chemoboost		TPZ/CIS	
Hypoxia Status	No. of Locoregional Failures	No. of Patients	No. of Locoregional Failures	No. of Patients
No residual hypoxia	4	9	0	14
Residual hypoxia in primary tumor and/or nodes	4	4	0	2

Abbreviation: TPZ/CIS, tirapazamine and cisplatin.

DISCUSSION

In this study, we have demonstrated that baseline hypoxia, as detected by FMISO-PET imaging, is associated with a high risk of LRF in patients treated with a platinum/fluorouracil-based chemoradiotherapy regimen. Conversely, there is a striking improvement in locoregional control in patients with hypoxic tumors treated with the tirapazamine-containing regimen compared with the chemoboost regimen. Furthermore, the absence of hypoxia on FMISO was associated with a low risk of LRF when treated with chemoboost, suggesting that this group of patients does not require more intensive therapy.

In preclinical studies, tirapazamine exhibits differential cytotoxicity under hypoxic compared with aerobic conditions in the range of 15- to 200-fold.[18] However, it has been difficult to confirm that tirapazamine does indeed elicit specific hypoxic cytotoxicity in human tumors. No single-agent activity was observed in phase I clinical trials,[19] and all subsequent phase II and III trials used tirapazamine in combination with chemotherapy[20] or radiation.[12] As part of a trial conducted at Stanford University (Palo Alto, CA), patients with head and neck cancer had oxygen levels in a lymph node measured by a needle electrode and then had a fine-needle aspirate taken from the node before and after a dose of tirapazamine.[21] Single-strand DNA breaks in the aspirated cells were measured by the comet assay. It was demonstrated that tirapazamine does cause DNA damage in human tumor cells, but there was no correlation between oxygen measurements and comet tail moment. Therefore, our data provide the first clinical evidence to confirm the experimental observation that tirapazamine acts by specifically targeting hypoxic tumor cells.

Previous studies demonstrating an adverse prognosis in hypoxic head and neck cancers treated with radiation have been performed mainly with oxygen-sensitive electrodes.[2,3,22-25] This technology has a number of limitations, including its invasive nature (which makes it difficult to access primary head and neck tumors), the inability to distinguish readings from necrotic tissue versus viable hypoxic cells, interoperator variability, and the limited number of centers with the necessary equipment and technical expertise.[4,26,27] In most of the studies with oxygen-sensitive electrodes, the measurements of hypoxia were predominantly taken from the more accessible lymph nodes rather than from the primary tumors.[3,22-25] However, in one study involving 15 patients, a good correlation was found between oxygen measurements in the primary tumor and in a node.[28] In contrast, we found that the presence of hypoxia in node-positive patients may frequently be discordant between the primary tumor and the nodes. In only 13 of 38 node-positive patients was the hypoxia status concordant

between the primary tumor and nodes (seven nonhypoxic patients and six hypoxic patients). Hypoxia in the primary tumor is likely to have far greater implications for locoregional control based on our findings, possibly because of the fact that residual tumor in nodes can be removed at neck dissection.

Advantages of hypoxic PET imaging are that it is noninvasive, permits visualization of both the primary tumor and nodes, and can detect heterogeneous distribution of hypoxia.[27] Fortuitously, the volume of hypoxic tumor required to permit qualitative detection by FMISO-PET correlated with the risk of LRF with a standard chemoradiotherapy regimen such as chemoboost. Although tumor hypoxia undoubtedly exists at the microenvironmental level (which cannot be detected by PET), it seems that imageable hypoxia is a marker for failure of reoxygenation. Larger multicenter studies of hypoxic PET imaging will be required to confirm our findings and to determine the reproducibility of qualitative methods of assessing tracer uptake or whether quantitative measures are required. Such studies are currently under development. The increasing use and availability of PET in oncology will make it feasible to incorporate a PET hypoxic imaging test into clinical practice if subsequent studies confirm its utility.

Other noninvasive methods that have been used to detect hypoxic tumors include the assessment of proteins that may be upregulated under hypoxic conditions. Variable correlations between expression of endogenous markers, such as hypoxia-inducible factor-1 alpha and carbonic anhydrase 9, and adverse outcome with radiotherapy have been reported.[29-33] More recently, Le et al[34] have demonstrated that plasma osteopontin levels may correlate with hypoxia and adverse outcome. Subsequently, Overgaard et al[35] have found that high levels of plasma osteopontin correlated with adverse outcome that was improved in patients who received the hypoxic radiosensitizer, nimorazole. In the HeadSTART trial, the first phase III trial testing TPZ/CIS, plasma and tumor samples have been collected with a view to assaying markers of hypoxia, such as plasma osteopontin, and tissue markers, such as hypoxia-inducible factor-1 alpha and carbonic anhydrase 9. These ancillary studies will help determine whether these tests can predict patients most likely to benefit from the addition of tirapazamine. In addition, a smaller cohort on this study has also undergone hypoxic PET imaging. This will permit comparison of PET with plasma and tissue markers of hypoxia as a predictor of outcome.

In head and neck squamous cell carcinoma, hypoxia is common in patients with locoregionally advanced disease, as shown by our finding of detectable hypoxia in 71% of patients. However, in other tumor types or stages with a lower prevalence of hypoxia, testing of hypoxia-targeted interventions in unselected populations risks missing a true benefit in patients with hypoxic tumors as well as exposing patients with nonhypoxic tumors to a potentially more toxic treatment. Therefore, it would be advantageous to enrich the study population for patients with hypoxic tumors that would most benefit from such treatment. PET imaging for hypoxia may provide this ability.

In conclusion, both baseline hypoxia and persistent hypoxia on FMISO scans in patients receiving a nontirapazamine-containing regimen were associated with a high risk of LRF. Hypoxic PET imaging with FMISO has considerable promise as a means of identifying patients who are most likely to benefit from treatment with this tirapazamine-containing chemoradiotherapy regimen while sparing patients without hypoxic tumors, who are likely to do well with standard treatment, any unnecessary additional toxicity.

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(continued on following page)

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(continued on following page)

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