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Dual targeted agents and CRT in HNC

Prospective Trial of Synchronous Bevacizumab, Erlotinib, and Concurrent Chemoradiation in Locally Advanced Head and Neck Cancer

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Abstract

Purpose
We assessed the safety and efficacy of synchronous vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) blockade with concurrent chemoradiation (CRT) in locally advanced head and neck cancer (HNC).

Experimental Design
Newly diagnosed stage III/IV HNC patients received a two-week lead-in of bevacizumab and/or erlotinib, followed by both agents with concurrent cisplatin and twice-daily radiotherapy. Safety was assessed using Common Toxicity Criteria version 3.0. The primary efficacy endpoint was clinical complete response (CR) rate after CRT.

Results
Twenty-nine patients enrolled on study, with 27 completing therapy. Common grade 3 toxicities were mucositis (n=14), dysphagia (n=8), dehydration (n=7), osteoradionecrosis (n=3) and soft tissue necrosis (n=2). Feeding tube placement was required in 79%, but no patient remained dependent at 12 months post-treatment. Clinical CR after CRT was 96% (95%CI 82-100%). Median follow-up was 46 months in survivors, with 3-year locoregional control and distant metastasis-free survival of 85% and 93%. Three-year estimated progression-free survival, disease-specific survival, and overall survival were 82%, 89%, and 86%, respectively. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) analysis showed patients who failed had lower baseline pretreatment median $K_{\text{trans}}$ values, with subsequent rises after lead-in therapy and one week of CRT. Patients who did not fail had higher median $K_{\text{trans}}$ values that decreased during therapy.
Conclusion

Dual VEGF/EGFR inhibition can be integrated with CRT in locally advanced HNC, with efficacy that compares favorably to historical controls albeit with an increased risk of osteoradionecrosis. Pretreatment and early DCE-MRI may prospectively identify patients at high risk of failure.

Translational Relevance

The definitive, non-surgical management of locally advanced non-metastatic HNC has steadily evolved to the current standard of care, concurrent chemotherapy and radiation. Despite technological advances in radiation delivery and recognition of patient populations (HPV) with improved prognosis, treatment failure remains a difficult dilemma with few salvage options. Molecular agents that target the VEGF and EGFR pathways have already been incorporated into treatment regimens for recurrent/metastatic HNC with improved outcomes. This study represents the first to target both pathways in conjunction with a chemoradiation platform in treatment-naïve, non-metastatic HNC patients. Moreover, we examined the prognostic and predictive utility of DCE-MRI in this patient population.
Introduction

Nearly 30,000 cases of locally advanced, non-metastatic head and neck cancers (HNC) are diagnosed annually in the United States(1). The current non-surgical standard of care for these patients is concurrent chemoradiation (CRT). A recent meta-analysis demonstrates a 6.5% absolute survival benefit at 5 years for CRT compared to radiation therapy (RT) alone with the majority of benefit derived from improved local-regional control (LRC)(2). Locoregional control and overall survival remain suboptimal despite these improvements, however.

The anatomically based TNM staging system provides prognostic information and guides management, but patients with similar disease stages often exhibit markedly different outcomes despite undergoing identical treatments. Worse prognosis in HNC, independent of TNM stage, has been correlated with differences in tumor oxygenation status(3). Hypoxia induces secretion of pro-angiogenic cytokines including vascular endothelial growth factor (VEGF), with downstream increases in vascular permeability and elevated interstitial fluid pressure(4). Overexpression of VEGF in HNC is correlated with higher metastatic potential and worse survival(5, 6). The anti-VEGF antibody bevacizumab has demonstrated direct anti-vascular effects with enhanced radiosensitivity in both preclinical and clinical settings(7). A phase I study of recurrent/poor prognosis HNC patients integrated bevacizumab into a FHX (fluorouracil, hydroxyurea, radiation) CRT platform with favorable antitumor activity but higher than expected rates of fistula formation and tissue necrosis(8).

Poorer outcomes in HNC have also been associated with overexpression of the epidermal growth factor receptor (EGFR)(9). The addition of the anti-EGFR antibody
cetuximab to definitive RT improved locoregional control and overall survival in locally advanced HNC patients compared to RT alone(10). In the recurrent/metastatic setting, EGFR blockade with monoclonal antibody or small molecule tyrosine kinase inhibitors such as erlotinib or gefitinib showed modest response rates in the 5-15% range, either as monotherapy or combined with platinum chemotherapy(11, 12).

Resistance to anti-EGFR therapy may result from alternate upregulation of VEGF-mediated pathways and increased angiogenesis(13). Dual inhibition of both EGFR and VEGF signaling cascades showed supra-additive antitumor effects in preclinical models(14). In recurrent/metastatic HNC, the combination of erlotinib and bevacizumab was well tolerated and showed a response rate of 15%, with prolonged benefit in a small subset of patients(15).

Increasing utilization of investigational/FDA-approved agents that molecularly target the tumor microenvironment has magnified the need for robust correlative tools to identify novel physiologic and biologic factors that augment TNM staging. Dynamic contrast-enhanced MRI (DCE-MRI) can provide data on perfusion, vascular permeability, and the proportion of tumor comprised by the interstitial space(16). DCE-MRI parameters have been correlated with tumor oxygenation status, microvessel density, and VEGF expression(17-19). DCE-MRI has been employed to monitor changes in vascular permeability following treatment with bevacizumab(20). DCE-MRI parameters have also been correlated with local control, disease-free survival, and overall survival in multiple tumor sites, including HNC(21).

This prospective study examined the safety and efficacy of delivering bevacizumab and erlotinib in conjunction with CRT in locally advanced non-metastatic
HNC patients. Serial DCE-MRI scans were also performed before, during, and after treatment to characterize the effects of treatment on the tumor microcirculation and to generate preliminary data on the prognostic and predictive value of functional metabolic imaging (FMI) in this patient population.

**Patients and Methods**

**Patient selection**

Eligibility criteria included patients ≥18 years of age with newly diagnosed, previously untreated locally advanced head and neck squamous cell carcinoma with Karnofsky performance status ≥60 undergoing definitive curative-intent CRT. Postoperative patients were ineligible. Initial multidisciplinary evaluation included history and physical exam, fiberoptic endoscopy, exam under anesthesia with direct laryngoscopy, computerized tomography (CT) or MRI, chest radiograph, and combined positron emission tomography with CT. Tumors were staged according to American Joint Committee on Cancer 6th edition criteria. Patients with stage III/IV without distant metastatic disease were eligible. Patients with T1N1-2 disease or tumor encasement of the carotid artery were excluded. Other exclusion criteria are described in the Figure 1 legend. Carotid ultrasounds were performed at initial screening and one month after CRT completion. Written informed consent was obtained on all patients prior to enrollment.

**Study Design**

This trial was an investigator-initiated, open label, non-randomized single institution study (clinicaltrials.gov NCT00140556) conducted under the US Food and
Drug Administration Investigational New Drug (IND) program (IND #12451) with approval for enrollment of up to 30 patients. The study was also approved by the Duke Cancer Center Protocol Review Committee and Institutional Review Board of Duke University Health System. The protocol schema is described in Figure 1. In the lead-in phase, patients were randomly allocated to receive 1) 10 mg/kg bevacizumab on days -14 and 0; 2) 100 mg erlotinib daily; or 3) both agents. These separate cohorts were designed to facilitate correlative studies that examined the physiologic changes in treatment naïve tumors induced by single versus dual biologic targeted therapy independent from another and separate from those induced by CRT. The reduced 100 mg erlotinib dose was chosen for additional safety, as both agents had not been previously combined in the CRT setting.

In the CRT phase, all patients received both targeted agents with cisplatin (CDDP) and twice-daily 1.25 Gy intensity-modulated RT Monday-Friday with a 6-hour interfraction interval to 70 Gy. A scheduled one-week treatment break was taken during week 4. CDDP was administered at 33 mg/m² on days 1-3 during weeks 1 and 5 of RT. Bevacizumab 10 mg/kg was given on day 1 of RT and repeated every 14 days for four doses. Erlotinib 100 mg was taken daily during RT except on days of CDDP administration. Adjuvant neck dissection was performed 10-12 weeks post-therapy in N2 patients with clinical or radiographic evidence of residual disease and all N3 patients irrespective of response.

**Statistical Design**

The primary objective of the study included safety and efficacy endpoints, monitoring both the ability to complete treatment and the clinical complete response
(CR) rate at the primary site (or nodal sites for unknown primary patients) within 30 days of therapy completion. This conservative time point was chosen to identify persistent disease and trigger stopping rules as soon as possible. Target accrual was 28 patients, 2 of whom were expected to be unavailable for response evaluation. A Simon two-stage optimal design with 1-sided alpha of 0.10 and power of 0.91 was used to test null and alternative hypotheses that the ability to complete treatment and the primary site CR rate was <70% and >90%, respectively. Only if 23 (82%) or more of the 28 patients achieved these outcomes would the null hypothesis be rejected. The first stage of the design required at least 7 of the first 9 patients to complete treatment and achieve CR’s to continue accrual.

Secondary endpoints of locoregional control (LRC), distant metastasis-free survival (DMFS), disease-specific survival (DSS), progression-free survival (PFS), and overall survival (OS) were defined from time on-study and estimated using the Kaplan-Meier method. The analysis of LRC included only local-regional recurrences as events; other failures were censored. DMFS was defined analogously. PFS included all failures as events except for death not due to disease, which was censored. DSS included disease-related deaths as events; other deaths were censored. OS included deaths due to any cause. Safety was assessed through collection of adverse events and laboratory tests based on Common Toxicity Criteria (CTC) version 3.0. Toxicity assessments were performed weekly during treatment, and post-treatment at one month and every three months through year two.

**DCE-MRI Scanning**

**Imaging Protocol**
An initial pretreatment DCE-MRI (Baseline) was performed. Patients received two weeks of lead-in targeted therapy, followed by a second MRI (Lead-in) prior to initiation of CRT. A third scan (Week 1) was performed after completion of the first week of CRT and synchronous targeted therapy. The fourth scan (End) was performed at CRT completion. Ultimately, this final scan was discontinued (see Results). Serum banking was performed with each DCE-MRI study for future correlative analyses.

DCE-MRI's were acquired on a 1.5T scanner (Signa Excite, GE Medical Systems, software version 11x and 14x)m5) prior to and following a single bolus injection of 0.1 mmol/kg of Gadolinium-DTPA using a dynamic coronal 3D fGRE sequence (fast gradient echo) with the following parameters: TR= 6.4 msec, TE = 2 msec, field of view (FOV) = 24 cm x 24 cm, acquisition matrix size: 238 x 128, single scan duration = 10 sec, number of scans = 31-33, 10 mm slice thickness using ZIP41 (48 slices), flip angle = 60°. The final size of each voxel per scan was 10 mm3. Imaging was done using the Linear Receive Anterior Neck Coil (GE Healthcare, Waukesha, WI), with no head and neck immobilization device specific to radiation treatments. Additional MR series, namely T1–weighted coronal fast spin echo (FSE) series were acquired consecutively before and after contrast administration, which provided better anatomic spatial resolution. In addition, before contrast, 3D fGRE sequences were acquired at variable flip angles (VFA) = 10, 45°. These sequences were used to calculate the tissue T10values pre-contrast agent administration (T10) using the VFA method(22).

Scans were obtained in the axial plane at the beginning of the trial, but difficulties distinguishing the boundaries between tumor volumes and immediately adjacent major

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1 ZIP is a function available on GE scanners that improves through plane resolution by interpolating the acquired scan data to create new images
salivary glands and/or major blood vessels mandated a change in strategy. Thereafter, image acquisition was performed in the coronal plane. Primary tumor and lymph node gross tumor volumes (GTV) were analyzed separately. Regions of interest (ROI) were defined as the entire GTV as delineated by a radiation oncologist (DMB or DSY) and a radiologist (JH) on either an early subtraction map or on the post-contrast FSE T1 images.

Image Processing

Monitoring of the temporal “wash in–wash out” of the contrast agent measures the vascular transfer constant ($K_{\text{trans}}$), which provides an estimate of vascular permeability, and the rate constant ($K_{\text{ep}}$). The extracellular, extravascular volume fraction ($V_e$) is described by the Tofts pharmacokinetic model ($V_e = \frac{K_{\text{trans}}}{K_{\text{ep}}}$) \cite{16}. $K_{\text{trans}}$ approximates perfusion in high permeability states such as untreated tumor \cite{16}. The images were analyzed using post-processing software from iCAD, Inc. (Nashua, NH) that uses All Time Point (ATP) pharmacokinetic image analysis \cite{23}. All applicable parameters and settings of the MRI exam were used to fit voxel enhancement curves to the appropriate formula for estimation of tissue parameters. A detailed description of the procedure is published elsewhere \cite{22}.

Data Analysis

The distribution of $K_{\text{trans}}$ values for each patient was summarized by calculating its 25th and 75th percentiles and each 10th percentile from the 10th to 90th percentiles (total 11 percentiles). Data were grouped according to whether they were obtained from primary tumor or lymph nodes. Comparisons were then performed within each group based upon whether or not a patient relapsed. The medians of each of the 11
percentiles were calculated and displayed with dot plots in which the x-axis represents the median $K_{trans}$ value for a given percentile and the y-axis is labeled with the names of the 11 percentiles. Box and whiskers plots were used to provide additional summary statistics describing the patient-specific distribution of the 50th percentile of $K_{trans}$. All analyses are descriptive rather than inferential because of the small sample size.

Results

Patient Characteristics

Twenty-nine patients were enrolled from October, 2005 – April, 2009. One patient withdrew prior to starting treatment. A second patient withdrew during therapy due to acute toxicity but is included in the analyses. For the lead-in phase, eight patients were allocated to the bevacizumab-alone cohort, ten received erlotinib, and ten received both agents. Table 1 describes patient and tumor characteristics. Eighty-two percent were T3/T4, and 79% had N2/3 disease. Mean gross primary and nodal GTV’s were 46 cc and 24 cc, respectively. Human papillomavirus (HPV) status was available in 15 patients (2 cervical nodes, 3 oral tongue, 10 oropharynx) by in-situ hybridization and/or p16 immunohistochemistry. Ten (67%) tested positive for HPV (1 cervical node, 9 oropharynx). Of the nine HPV-positive oropharynx patients, eight had a history of tobacco use. In the 10 oropharynx patients without HPV data, six had used tobacco.

Treatment Delivery

Median dose was 70 Gy (range 69.5-71.5 Gy), and median treatment time was 44 days (range 40-53 days). Twenty-six patients (93%) received the planned 2 cycles of
concurrent cisplatin. The median bevacizumab dose was 3905 mg (89.5% planned). Median erlotinib dose was 4900 mg (97% planned).

**Toxicity**

Table 2 shows the incidence and severity of acute and chronic toxicities. One patient withdrew from protocol due to mucositis-related pain but completed CRT without treatment break. Thirteen patients required inpatient hospitalization, primarily for feeding tube placement and pain control secondary to mucositis. One patient in the erlotinib-alone cohort required temporary intensive care support after development of global myocardial ischemia resulting in pulmonary edema and shock liver, both of which were transient. She received less than 50% of the planned doses of both bevacizumab and erlotinib.

Overall, 26 patients (93%) developed some degree of oropharyngeal mucositis. Grade 3 mucositis occurred in 14 patients (50%), while grade 3 dysphagia developed in eight patients (29%). Percutaneous feeding tubes were required prior to therapy in four patients. During protocol treatment, an additional 18 patients underwent placement of a nasogastric (NG) feeding tube. However, by 12 months post-therapy, no patient was feeding-tube dependent.

Grade 3 osteoradionecrosis (ORN) developed in 3 patients (11%), two with T3 tonsil primaries and one with unknown primary. One patient received both bevacizumab and erlotinib during lead-in but discontinued both (per request) during CRT after the scheduled treatment break, ultimately receiving 60% of the total planned doses of both agents. The other two patients were in the bevacizumab-alone lead-in cohort and had received all planned doses of bevacizumab, but only 41% and 85% of erlotinib during...
CRT. Soft tissue necrosis developed in two oropharynx patients. One patient in the erlotinib-alone cohort healed after antibiotics alone. The second patient in the combined lead-in cohort underwent adjuvant modified neck dissection followed by pectoralis muscle flap reconstruction for postoperative chyle leak and subsequently developed an orocutaneous fistula that healed after HBO without need for further surgical repair.

**Efficacy**

Primary site (or nodal sites for unknown primary patients) clinical CR was achieved in 27 of 28 patients, (96%; 95% confidence interval [CI] 82-100%). Of the 23 patients with pre-treatment nodal metastases, 17 (74%) had clinical CRs. Adjuvant neck dissections were performed in 11 patients (five CRs, six PRs), with residual nodal disease found in 4 of the partial responders.

Median follow-up for surviving patients was 46 months (range, 25-63 months). Five patients had documented disease progression post-treatment: 2 with local-only, 1 regional only, 1 regional plus distant metastasis, and 1 with distant-only failure. All of them have died. One additional patient died of unknown cause without evidence of disease or treatment-related toxicity six months after completion of CRT and neck dissection. No other patients have died. At 3 years, LRC and DMFS were 85% (CI, 65-94%) and 93% (CI, 74-98%), respectively (figure 2A). Three-year DSS, PFS, and OS were 89% (CI, 70-96%), 82% (CI, 62-92%), and 86% (CI, 66-94%), respectively (figure 2B).

**DCE-MRI**

The original protocol design included four DCE-MRI scans per patient. However, due to the high clinical CR rates, very few patients had lesions that could be
visualized radiographically at treatment completion. Consequently, a protocol amendment deleted the fourth scan. Baseline, Lead-in, and Week 1 scans were performed in 26, 24, and 24 patients, respectively. The first six patients were scanned in the axial plane; the others were imaged in the coronal plane. The median (25-75% range) of the pretreatment primary tumor GTV was 41.4 cm$^3$ (14-66 cm$^3$), and the median pretreatment nodal GTV was 12.8 cm$^3$ (8-31 cm$^3$). Thus, the median number of voxels scanned per primary tumor and nodal GTV was 4140 (1400-6600) and 1280 (800-3100), respectively.

Five of the 26 patients with Baseline DCE-MRI studies recurred, all within 2 years of treatment completion. Their scans were compared with those from patients who remained disease-free. The distributions of patient-specific 50th percentile $K_{\text{trans}}$ values for primary tumors and lymph nodes, respectively, for each of the three scanning time points are displayed in figures 3A and 3B.

Overall, both primary tumors and lymph nodes showed higher baseline $K_{\text{trans}}$ values for patients who did not recur than for those who did. Moreover, $K_{\text{trans}}$ values diminished in the early phases of treatment for patients who remained disease-free, while they increased in those who recurred. The median of 50th percentile $K_{\text{trans}}$ values obtained from primary tumors in patients who did not recur was 4.90 min$^{-1}$ at Baseline. $K_{\text{trans}}$ decreased to 3.77 at the end of Lead-in therapy and to 2.55 at Week 1 of CRT. The median of 50th percentile $K_{\text{trans}}$ values obtained from primary tumors in patients who recurred after treatment was 4.72 at Baseline, increased to 5.74 after Lead-in, and 5.77 at Week 1 of CRT. Dot plots present the medians of all 11 percentiles of $K_{\text{trans}}$ values.
from primary tumors in patients who did not recur (figure 4A) and those who did recur (figure 4B) from the serial scans obtained before and during treatment.

$K_{\text{trans}}$ values obtained from lymph nodes demonstrated similar patterns. In patients without recurrence, the median of 50th percentile $K_{\text{trans}}$ values was 7.56 at Baseline and decreased to 5.8 and 2.43 at Lead-in and Week 1 time points, respectively (figure 4C). For patients who recurred, the median of 50th percentile $K_{\text{trans}}$ values was 4.43 at Baseline, and increased to 5.61 at Lead-in and 6.55 at Week 1 (figure 4D).

**Discussion**

This study represents the first to integrate synchronous multi-agent molecular targeted therapy with curative intent cisplatin-based CRT in locally advanced, non-metastatic HNC. The results suggest that the combination of 10 mg/kg bevacizumab every 2 weeks and 100 mg erlotinib daily can be incorporated into a CRT platform.

Overall, treatment was feasible, with one patient not completing protocol-specified therapy. No on-treatment or treatment-related deaths were noted. The incidence of mucositis seen in the study (93% all grades, 50% grade 3) is consistent with historical rates for altered fractionation RT (56% grade 3-4), as well as those prospectively reported with concomitant RT and cetuximab (93% all grades, 60% grade 3-4)(10, 24). Of note, the study design incorporated a one-week treatment break due to concern for potential excess mucositis with treatment intensification, perhaps explaining the lower rates of grade 3 mucositis seen. Still, 22 patients (79%) required NG feeding tube placement at some point, and had World Health Organization (WHO) toxicity criteria been employed instead of CTC, the incidence of grade 3-4 mucositis would have been
higher. Importantly, no patient was feeding tube-dependent at 12 months, which compares favorably to the 83% (anytime) and 41% (12 months) feeding tube rates reported in RTOG 99-14, a phase II study of concurrent cisplatin with accelerated RT in locally advanced HNC patients(25).

The use of bevacizumab has been associated with severe bleeding events and poor wound healing. The current study had five patients (18%) develop grade 3 ORN or soft tissue necrosis, although three of them had not received full doses of both targeted agents. In a study of 43 recurrent/poor-prognosis HNC patients, bevacizumab added to FHX chemoradiation resulted in a 21% rate of ulceration/tissue necrosis or fistulas(8). Two-thirds of their study population had received prior irradiation. A subsequent phase II study comparing FHX versus FHX plus bevacizumab in stage II-III and select T4N0-1 HNC patients had three patients (16%) in the experimental arm requiring multiple surgeries for poor wound healing(26). Whether these rates would be lower in the setting of conventional once-daily RT or with different concurrent chemotherapy agents is unknown and warrants further investigation in the context of clinical trials.

The current trial utilized a modified twice-daily hyperfractionated regimen, which, at the time of its inception, had been shown to be superior to hyperfractionated RT alone in a randomized study(27). RTOG 0129, which compared concomitant boost accelerated fractionation CRT against standard once-daily fractionation CRT, has subsequently reported no differences in toxicity or efficacy between the two arms(28). The optimal RT fractionation regimen to use with molecularly targeted agents is not established. In the pivotal cetuximab trial, unplanned subset analyses suggested that the survival benefit was seen in patients treated with twice-daily or concomitant boost
The concomitant boost platform was chosen by the RTOG for its 0522 trial, which compared CRT versus CRT plus single agent cetuximab. Preliminary results showed higher rates of mucositis and skin toxicity but no improvements in PFS or OS(29).

The addition of single agent bevacizumab to CRT in treatment-naïve non-metastatic HNC patients was examined by Salama et al as described earlier(26). The study was terminated early after 26 patients due to unexpected locoregional progression in four of five T4N0-1 patients treated with bevacizumab and FHX. All four failures had unfavorable primary sites (two oral cavity, one pyriform sinus, one larynx). As their excellent results with FHX alone suggest, treatment intensification with bevacizumab may not be necessary in intermediate stage HNC patients. With only two T4N0-1 patients treated with FHX prior to early termination, the study appears too small to assess the efficacy of the combined regimen in more advanced disease.

Poor outcomes or resistance with single agent molecular therapy have spurred interest in strategies that synchronously target multiple signaling pathways(30). Cohen et al examined dual inhibition with erlotinib and bevacizumab in recurrent/metastatic HNC(15). The combination was well tolerated with a response rate of 15% and median PFS and OS durations of 4.1 and 7.1 months, respectively. However, co-administration has not always led to improved outcomes. The dual use of bevacizumab and erlotinib proved disappointing, with an estimated median time to progression of 40 days and median survival of 102 days in patients with gemcitabine-refractory pancreatic cancer (31). Even worse, the addition of cetuximab to bevacizumab and chemotherapy in first-
line treatment of metastatic colon cancer resulted in shorter PFS and poorer quality of life compared to bevacizumab and chemotherapy alone(32).

The use of dual inhibition in conjunction with CRT in the present study showed 3-year LRC and OS of 85% and 86%, comparing favorably to historical outcomes for locally advanced HNC. Comparisons amongst different studies are challenging, given different eras and patient populations. Concurrent RT and cetuximab in the Bonner study demonstrated 3-year LRC and OS of 47% and 55%(10). The concomitant boost CRT arm of RTOG 0129 showed 3-year LRC and OS of 71.8% and 70.3%(28). Two-year PFS and OS rates were 63% and 83% with CRT plus cetuximab in RTOG 0522(29).

As treatment strategies evolve, improved patient selection will be critical to identify those patients who may benefit most from therapeutic intensification. Retrospective review of RTOG 0129 found HPV status strongly correlated with survival in oropharyngeal cancers, with 82% 3-year OS for HPV-positive versus 57% for HPV-negative patients(28). Further analysis suggested that patients could be subdivided into low, intermediate, and high-risk groups for death based on HPV status, tobacco history, tumor stage, and nodal stage. Given that a majority of our study patients were smokers with large T3/T4 tumors and N2/3 disease, it is less likely that HPV status accounted for the encouraging outcomes seen. Of the 5 patients who progressed, HPV was positive in one (base of tongue primary - local only), negative in one (occult primary - regional and distant), and unknown in the remaining three (soft palate – regional-only; oral cavity – local-only; nasopharynx – distant-only).
Potential correlative biomarkers in HNC remain elusive. KRAS mutation status appears to predict tumor response to cetuximab in metastatic colon cancer but not in HNC(33). While high EGFR gene copy number was associated with worse survival in patients treated with gefitinib, EGFR expression did not predict for response to erlotinib in heavily pretreated recurrent/metastatic patients(34, 35). Seiwert et al showed that baseline VEGF plasma levels were neither prognostic nor predictive for response to bevacizumab(8). Changes in the tumor microenvironment, both by RT or molecularly targeted agents, can be monitored with FMI modalities such as DCE-MRI. FMI-derived data can potentially improve the a priori identification of patients at highest risk for failure and who might benefit most from therapeutic intensification, especially amongst heavy smokers with advanced HPV-negative disease. For these patients, treatment strategies that incorporate synchronous inhibition of multiple signaling pathways, induction chemotherapy regimens, and/or planned surgical resection may ultimately yield improved outcomes compared to CRT alone.

Conversely, FMI could facilitate the identification of patients who do NOT require more intensive therapy and could be spared from the risk of increased toxicity. This consideration is particularly relevant in HNC where standard treatment often eradicates disease but with very high cost, including severe and long-lasting mucositis, chronic xerostomia, dental disease, and long-term swallowing dysfunction. These considerations are more critical with the increasing incidence of HPV-related HNCs as investigators actively attempt to design and test de-intensified treatment regimens for this improved prognostic patient population.
Kim et al. used pretreatment DCE-MRI in 33 HNC patients to evaluate response to CRT. Pretreatment $K^{\text{trans}}$ values were 3-fold higher in complete responders compared to partial responders ($p=0.001$) (36). The current study, with its longer-term follow-up, showed similarly higher baseline $K^{\text{trans}}$ levels in primary tumors and lymph nodes from patients without subsequent disease recurrence, a more robust clinical endpoint than response. Moreover, these findings suggest that pretreatment $K^{\text{trans}}$ could provide prognostic information independent from conventional RECIST criteria given that nearly all patients in the study had a CR at the primary site.

$K^{\text{trans}}$ represents the vascular transfer coefficient and reflects vascular permeability as contrast moves out of the vasculature and into the interstitium. Permeability and perfusion closely approximate one another in an untreated tumor (16). Lyng et al. performed immunohistochemical analysis of uterine cervix squamous carcinoma and showed that patients whose tumors had high vascular density (a surrogate for perfusion) had better oxygenated tumors and better prognosis than those with low vascular density (37). The powerful adverse influence of tumor hypoxia on treatment outcome in HNC is well known (3). The association of higher baseline $K^{\text{trans}}$ values with a more favorable prognosis supports the concept of better perfusion being a favorable prognostic parameter.

Hoskin et al. performed second DCE-MRIIs after completion of accelerated RT in 12 HNC patients and compared them with pretreatment studies (38). They assessed the maximum signal enhancement (E) in a primary tumor or lymph node. Mean (+/- SD) baseline E fell from 0.76 +/- 0.09 to 0.67 +/- 0.04 after treatment in patients who were disease-free but rose from 0.81 (+/- .21) to 1.07 (0.25) in patients who subsequently
failed. Similarly, the time to maximum enhancement (Tmax) decreased after treatment in patients who were rendered disease-free by treatment, but it increased in those who recurred, similar to the rise in $K^{\text{trans}}$ in our trial. Both $E$ and $T_{\text{max}}$ are dependent upon $K^{\text{trans}}$ and would therefore be expected to move in step with this parameter(23).

Performance of serial scans at early and predetermined times during therapy is a unique aspect of the current trial. Comparison of pre-treatment versus post-treatment FMI parameters precludes modification of therapy based upon detection of adverse signals early during therapy. Early treatment-induced changes in $K^{\text{trans}}$ could be useful for real-time assessment of therapeutic efficacy.

Wedam et al treated 21 patients with locally advanced/inflammatory breast cancer using a combination of bevacizumab and cytotoxic chemotherapy. Four MRIs were performed: at baseline and after cycles 1, 4, and 7. They showed a 75% decrease in $K^{\text{trans}}$ over the course of treatment but did not detect a difference between responders and non-responders(20). Hayes et al performed DCE-MRI’s on 15 breast cancer patients before and after their first of six cycles of multi-agent chemotherapy. Responders had higher baseline $K^{\text{trans}}$ values, which diminished after chemotherapy compared to non-responders whose lower baseline $K^{\text{trans}}$ values increased(39). The overall patterns and changes in $K^{\text{trans}}$ in their study were similar to those in our trial.

The association between treatment-induced reductions in $K^{\text{trans}}$ and favorable outcomes seems paradoxical. However, these changes may reflect reductions in vascular permeability rather than perfusion, especially in the context of agents such as bevacizumab. Reductions in vascular permeability during treatment lead to reductions in interstitial fluid pressure (IFP)(40). Elevated IFP is strongly correlated with greater
risks of both local and distant recurrence in uterine cervix cancer independent of stage(41). Treatment-induced reductions in IFP would be expected to change hydrostatic gradients leading to net improvements in functional perfusion. Thus, treatment-induced reduction in $K_{\text{trans}}$ may reflect a net improvement in perfusion.

Caution must be exercised in the interpretation of the data from the current study. Only five relapses were observed in the study population, making statistical testing unreliable. Consequently, we did not compute $p$ values. The differences in baseline and temporal changes in $K_{\text{trans}}$ between patients who did and did not recur must therefore be viewed as hypothesis generating. We believe these apparent imaging differences are of sufficient clinical interest, however, to merit further investigation, especially given their correlation with a long-term endpoint rather than acute response to therapy.

Imaging of static anatomic parameters such as tumor size creates the tendency to attribute any subsequent changes to the intervening treatment. FMI measures dynamic physiologic processes subject to temporal fluctuations in the absence of any treatment, however. Therefore, treatment-induced changes in FMI parameters need to be interpreted with an understanding of the intrinsic temporal variability inherent to the tumors and/or normal tissues under investigation(42). Double baseline pretreatment PET studies demonstrate significant day-to-day variation in tumor oxygenation in up to 30% of HNC patients(43). Glucose metabolism may also fluctuate by 30-40% on a daily basis(44). Therefore, the intrinsic variability of $K_{\text{trans}}$, unknown for cancers in general and HNC in particular, constitutes a major focus of our present research.
Conclusion

The current study demonstrates acceptable safety and encouraging efficacy with the integration of dual EGFR and VEGF inhibitors with CRT in locally advanced non-metastatic HNC. The increased incidence of ORN and soft tissue necrosis may be associated with the use of bevacizumab. These results warrant further study in a larger multi-institutional and/or randomized setting. Identification of robust prognostic and predictive biomarkers may allow for more rational selection of patient populations who would benefit most from the addition of molecular targeted therapy. Using DCE-MRI to measure pre-treatment $K^{\text{trans}}$ and changes in $K^{\text{trans}}$ early in the course of treatment may prospectively identify HNC patients at high risk of treatment failure. Validation in a larger population could facilitate use of this tool to select or modify treatment strategies for individual patients.
Figure Legends

Figure 1
Protocol schema showing initial 2-week lead-in phase of molecular target agent(s), followed by 7-week concurrent chemoradiation regimen with synchronous bevacizumab and erlotinib administration. The timing of the DCE-MRI scans is also indicated. Additional protocol exclusion criteria included history of malignancy other than basal cell skin cancer, history of claudication, bleeding, or thromboembolic disorders, blood pressure of >150/100 mmHg, unstable angina, NYHA grade II or greater congestive heart failure, history of myocardial infarction or stroke within 6 months, major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to start of therapy, minor surgical procedures within 7 days prior to start of therapy, pregnancy or lactation, urine protein:creatinine ratio > 1.0 at screening, history of abdominal fistula, GI perforation, or intra-abdominal abscess within 6 months, serious non-healing wound, ulcer, or bone fracture, AST, ALT, bilirubin, PT or PTT >1.5x normal, platelets >100,000, WBC <2000, Hgb <10, creatinine clearance <60 mL/hr, or refusal to provide written informed consent.

Figure 2
Kaplan-Meier curves for (A) locoregional control and distant metastasis-free survival and (B) disease-specific survival, progression-free survival, and overall survival for all patients.

Figure 3
Box and whiskers plot of the distribution of the 50th percentile of $K^{\text{trans}}$ values in (A) primary tumors and (B) lymph nodes at baseline, after lead-in targeted therapy, and after week 1 of synchronous chemoradiation and targeted therapy. Each set of plots is grouped by clinical outcome. The horizontal lines show the median and the diamonds show the mean. The 25th and 75th percentiles are defined by the upper and lower boundaries of the boxes. The vertical lines illustrate the 10th and 90th percentiles.

Figure 4

Dot plots of the medians of all 11 percentiles of $K^{\text{trans}}$ values for the same time points as in Figure 3. Data from patients who did not fail are shown in panels A (primary tumors) and C (lymph nodes). Panels B (primary tumors) and D (lymph nodes) show the values for patients who did fail. $K^{\text{trans}}$ decreases during the early phases of treatment in both the primary tumor and lymph nodes in patients who do not recur and increases in those who do recur.
References


Cohort | Lead-In (2 wk) | Concurrent Chemoradiation (CRT) (7 wk) | Post-CRT (10-12 wk)
---|---|---|---
1 | B | RT 40 Gy; 1.25 Gy bid | REST RT 30 Gy; 1.25 Gy bid ± Adj ND
2 | E | CDDP | CDDP
3 | B | E | B

B: bevacizumab 10 mg/kg q2 weeks
CDDP: cisplatin 33 mg/m² x 3 days
E: erlotinib 100mg/day
ND: Neck dissection
DCE-MRI
Table 1. Patient and tumor characteristics

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Table 2. Acute and late toxicities

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Clinical Cancer Research

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David S Yoo, John Kirkpatrick, Oana Craciunescu, et al.

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