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Susanne M. Arnold
University of Kentucky, susanne.arnold@uky.edu

Mahesh Kudrimoti
University of Kentucky, mkudr0@email.uky.edu

Emily V. Dressler
University of Kentucky, emilydressler@uky.edu

John F. Gleason
Center for Cancer Care

Natalie L. Silver
The University of Texas MD Anderson Cancer Center

See next page for additional authors

Authors
Susanne M. Arnold, Mahesh Kudrimoti, Emily V. Dressler, John F. Gleason, Natalie L. Silver, William F. Regine, and Joseph Valentino

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Using low-dose radiation to potentiate the effect of induction chemotherapy in head and neck cancer: Results of a prospective phase 2 trial

Susanne M. Arnold MD [a,*], Mahesh Kudrimoti MD [b], Emily V. Dressler PhD [c], John F. Gleason Jr MD [d], Natalie L. Silver MD [e], William F. Regine MD [f], Joseph Valentino MD [g]

[a] *Department of Internal Medicine, Division of Medical Oncology, University of Kentucky, Markey Cancer Center, Lexington, Kentucky*
[b] *Department of Radiation Medicine, University of Kentucky, Markey Cancer Center, Lexington, Kentucky*
[c] *Division of Cancer Biostatistics, University of Kentucky, Markey Cancer Center, Lexington, Kentucky*
[d] *Center for Cancer Care, Huntsville, Alabama*
[e] *M D Anderson Cancer Center, Houston, Texas*
[f] *Department of Radiation Oncology, University of Maryland, Baltimore, Maryland*
[g] *Department of Otolaryngology Head and Neck Surgery, University of Kentucky, Markey Cancer Center, Lexington, Kentucky*

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Abstract

Purpose: Low-dose fractionated radiation therapy (LDFRT) induces effective cell killing through hyperradiation sensitivity and potentiates effects of chemotherapy. We report our second investigation of LDFRT as a potentiator of the chemotherapeutic effect of induction carboplatin and paclitaxel in locally advanced squamous cell cancer of the head and neck (SCCHN).

Experimental design: Two cycles of induction therapy were given every 21 days: paclitaxel (75 mg/m^2) on days 1, 8, and 15; carboplatin (area under the curve 6) day 1; and LDFRT 50 cGy fractions (2 each on days 1, 2, 8, and 15). Objectives included primary site complete response rate; secondary included overall survival, progression-free survival (PFS), disease-specific survival, and toxicity.

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Conflicts of interest: None.

* Corresponding author. Division of Medical Oncology, Markey Cancer Center, cc445, 800 Rose Street, Lexington, KY 40536
E-mail address: smarno0@uky.edu (S.M. Arnold)

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Results: A total of 24 evaluable patients were enrolled. Primary sites included oropharynx (62.5%), larynx (20.8%), oral cavity (8.3%), and hypopharynx (8.3%). Grade 3/4 toxicities included neutropenia (20%), leukopenia (32%), dehydration/hypotension (8%), anemia (4%), infection (4%), pulmonary/allergic rhinitis (4%), and diarrhea (4%). Primary site response rate was 23/24 (95.8%): 15/24 (62.5%) complete response, 8/24 (33.3%) partial response, and 1/24 (4.2%) stable disease. With median follow-up of 7.75 years, 9-year rates for overall survival were 49.4% (95% confidence interval [CI], 30.5-79.9), PFS was 72.2% (CI, 55.3-94.3), and disease-specific survival was 65.4% (44.3-96.4).

Conclusion: Chemopotentiating LDFRT combined with paclitaxel and carboplatin is effective in SCCHN and provided an excellent median overall survival of 107.2 months, with median PFS not yet reached in this locally advanced SCCHN cohort. This compares favorably to prior investigations and caused fewer grade 3 and 4 toxicities than more intensive, 3-drug induction regimens. This trial demonstrates the innovative use of LDFRT as a potentiator of chemotherapy.

Introduction

Locally advanced squamous cell carcinoma of the head and neck (SCCHN) remains a challenge to oncologists, with 12,290 deaths estimated in 2015 alone, despite aggressive multidisciplinary care.[1] Human papillomavirus (HPV) status has become a defining prognostic marker for survival in this disease, effectively delineating prognostic groups both in oropharyngeal sites[2-7] and others. Despite advances in our understanding of the molecular mechanisms of this disease, survival has improved only 5% in the past 20 years.[8] Although concurrent chemotherapy and radiation remains the standard of care in locally advanced disease of the oropharynx, hypopharynx, and larynx, the 5-year overall survival (OS) of varies from 10% to 82% depending on site, nodal involvement, race, HPV status, and comorbidities.[9-11]

Induction chemotherapy followed by concurrent chemoradiation therapy is 1 of several options available to patients in the treatment of locally advanced SCCHN,[12,13] but induction therapy carries the risk of acute toxicity, including neutropenia, fatigue, mucositis, and infection.[14-21] The combination of docetaxel, cisplatin, and fluorouracil has been the most widely used because of complementary mechanisms of action, improved radiation sensitization, and excellent response rates, albeit with increased toxicity[22]; however, the acceptance of induction therapy has been slow because of the perceived toxicity of induction, the success of combined modality therapy, and improved efficacy of other agents such as epidermal growth factor receptor–based immunotherapies, and induction therapy remains controversial.[13,16,23,24]

Induction therapy allows for rapid assessment of sensitivity to the regimen given, providing an excellent assessment of efficacy. We designed a novel induction regimen to study the synergy of low-dose fractionated radiation (LDFRT) combined with platinum-based doublet therapy. In this setting, LDFRT served as the third therapeutic agent in the induction treatment and was intended to provide an agent regimen that would remain less toxic than triplet chemotherapy.[25,26] Joiner and colleagues[27] recognized the therapeutic potential of low-dose radiation more than 20 years ago when they demonstrated an initial phase of hyperradiosensitivity (HRS) using doses from 0 to 80 cGy. The HRS observed with low-dose radiation is a unique radiobiologic phenomenon,[28] and was reported to enhance chemotherapy-induced the cell death by overcoming the antiapoptotic effects of bcl-2 and nuclear factor kappa-B[29] when delivered in 4 very low doses (termed ultrafractionation) in vitro.[29]

Preclinical data indicated optimal HRS at doses of 50 to 80 cGy given 4 times over 24 hours and led to the design and initial success of a clinical trial of paclitaxel, carboplatin, and LDFRT induction therapy in locally advanced SCCHN, without significant change in the toxicity profile over chemotherapy alone.[30] Long-term outcomes of this first trial have been reported[26] and led to a second trial examining a different schedule of LDFRT and chemotherapy with the primary endpoint of improved primary site complete response (CR) rate and secondary survival endpoints of nodal response, overall response rate (RR), OS, progression-free survival (PFS), and toxicity. Initial efficacy of this regimen has previously been presented in abstract form, and we report the mature phase 2 results of this treatment paradigm from our second clinical trial of chemotherapy and LDFRT as induction in SCCHN.

Methods and materials

Patient characteristics and eligibility criteria

Subjects were enrolled from December 19, 2002, until September 20, 2004. All patients signed informed consent approved by the University institutional review board.

Patients were required to have pathologically documented stage III or IV SCCHN (excluding distant metastatic disease) within 2 months of diagnosis. All patients underwent computed tomography (CT) or magnetic resonance imaging scan of the involved area of the head and neck, chest x-ray or chest CT scan, and direct laryngoscopy with biopsy of the affected area. Patients were required to have an Eastern Cooperative Oncology Group performance status of 2 or greater, no evidence of active cardiac abnormalities, adequate bone marrow reserve, serum total bilirubin $\leq$1.5 mg/dL, and a calculated or measured creatinine clearance greater than 60 mL/min. Patients were excluded if they had a history of malignancy within the past 5 years (other than nonmelanomatous skin cancer or carcinoma-in-situ of the cervix) or preexisting peripheral neuropathy greater than grade I. When this study was initially designed, HPV status was not routinely tested at our institution; however, where possible, HPV status is also reported.

Treatment and evaluation

Induction chemotherapy and radiation

The treatment scheme is shown in Fig 1. All chemotherapy was calculated using actual body weight and administered in the outpatient chemotherapy infusion center. Following standard premedication (steroid, H_1 and H_2 blockers, and physician choice of antiemetics), paclitaxel was diluted in 0.9% sodium chloride to a final concentration of 0.3 to 1.2 mg/mL and was given at a dose of 75 mg/m^2 intravenously over 1 hour on days 1, ,8 and 15 of a 21-day cycle. Following paclitaxel infusion on day 1, carboplatin, reconstituted in 0.9% sodium chloride to a final concentration of approximately 10 mg/mL, was given over 30 minutes at an area under the curve of 6, calculated using the Calvert formula (day 1 only). Two doses of 50 cGy radiation were given on days 1, 2, 8, and 15. The first fraction was given within 1 hour of completion of chemotherapy; the second fraction given 3 to 6 hours later with the third and fourth fractions given on day 2 separated by at least 3 hours (Fig 1). Patients were treated with shaped fields encompassing gross disease only (including the primary and gross nodal disease) with a maximum 2-cm margin. The primary site was treated with photons and lymph nodes with electrons, with spinal cord was excluded from the radiation field. Three-dimensional treatment planning was used in all patients. The total irradiation dose for induction therapy (total of 2 cycles) was 800 cGy (50 cGy $\times$ 8 fractions per cycle).

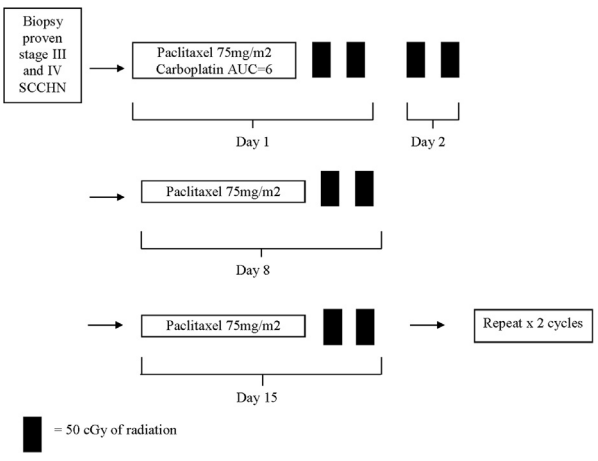

Figure 1 Schema describing the regimen of clinical trial 02-HN-15: low-dose fractionated radiation therapy + carboplatin and paclitaxel. Solid bars represent 50 cGy fractions of radiation. SCCHN, squamous cell cancer of the head and neck.

Dose modification

Chemotherapy dose modifications were required on days 8 and 15 for any of the following: absolute neutrophil count <800/μL, platelet count <50,000/μL, greater than grade 3 mucositis, grade 3 motor or sensory neuropathy, grade 3 arthralgias or myalgias, grade 3 fatigue, grade 2 or 3 hepatic dysfunction, or greater than grade 3 other nonhematologic toxicity. Patients were allowed a maximum of 2 dose reductions according to the following guidelines in Table 1.

Development of grade 4 sensory/motor neuropathy, arthralgias/myalgias, and fatigue or liver dysfunction required removal from protocol. Patients were required to have an absolute neutrophil count >800/μL and platelets >50,000/μL on day 22 to proceed with cycle 2 of therapy. No dose reescalation was permitted and treatment delays of longer than 2 weeks required removal from protocol.

Posttherapy evaluation

Radiographic tumor assessment by CT or magnetic resonance imaging scan and panendoscopy or indirect laryngoscopy, where appropriate, was performed within 4 weeks after the completion of the last dose or LDFRT. Biopsy was performed if there was a question of disease response. Response assessment used Response Evaluation Criteria in Solid Tumors, version 1.0.[31] Nodal response was assessed clinically and radiographically and was scored separately from the primary tumor response with overall response graded based on combined primary and nodal

Table 1 Dose modifications

Modification episode	Carboplatin (area under the curve)	Paclitaxel (mg/m^2)
0	6	75
-1	5	65
-2	4	55

response. Toxicities were scored using the National Cancer Institute's Common Toxicity Criteria, version 3.0.[32]

Definitive therapy

Definitive radiation began within 1 week after the completion of 2 cycles of induction, with decisions regarding therapy made by a multidisciplinary team. Response at the primary site was used to determine the total dose of definitive radiation: patients with CR to induction were treated with reduced dose of radiation at the primary site (reduced from 70 Gy to 60-66 Gy) and had 2 cycles of intravenous cisplatin (100 mg/m^2) instead of 3. Those with partial response or stable disease (SD) were treated with surgery and adjuvant therapy or with altered fractionation regimens. In calculating the planned total dose of radiation to be used for definitive therapy, the radiation oncologist incorporated the induction dose used into the final calculation for a maximum total dose (induction + definitive) of approximately 7640 cGy (once-daily fractionation, 180 cGy/fraction) or 8320 cGy (twice-daily fractionation, 120 cGy/fraction). In all definitive radiation treatment plans, either a 3- or 4-field setup was used, 3-dimensional-based treatment planning was used for all but 1 patient (who required intensity modulated radiation therapy), electrons were used to treat posterior neck nodes after spinal cord block and the spinal cord was limited to 45 Gy.

P16 expression

Surgical pathology slides from pretreatment tumor biopsies were collected for immunohistochemical evaluation. At the time of initiation of this study, p16 staining was not routinely performed; however, retrospectively adequate tumor samples were analyzable for p16 status in 11 patients (45.83%). Staining methods have been reported previously[33] and a blinded independent pathologist reviewed and characterized the formalin-fixed, paraffin-embedded, immunostained sections. Tumors were classified as positive when >75% showed diffuse nuclear and cytoplasmic staining.[34]

Statistical analysis

The primary endpoint for this study was pathologic primary site CR rate, with secondary endpoints of nodal response, overall RR, OS, PFS, disease-specific survival (DSS), and toxicity. For statistical purposes, the historical pathologic primary site CR to induction therapy for stage II (bulky), III, and IV SCCHN patients was considered to be 23% as documented in our previous experience with LDFRT induction.[30] We hypothesized improvement with this regimen to at least 50%; therefore, 25 patients would provide at least an 80% power to detect significant difference between the pathologic primary site CR for the proposed regimen to the prior reference regimen, assuming a 2-sided alpha level of 0.05.[35]

Primary site CR, nodal RR, and overall RR were estimated with corresponding 95% confidence intervals. Descriptive statistics including medians/ranges for continuous outcomes and frequency/percent for categorical variables are presented for both baseline and treatment-performance characteristics. Kaplan-Meier curves were constructed for OS, DSS, and PFS with log rank P values calculated to test for differences between p16 staining. All data analyses were conducted using SAS, version 9.3, for Windows (SAS Inc., Cary, NC).

Results

Patient characteristics

From December 2002 to September 2004, 25 patients with locally advanced SCCHN were enrolled and 1 was lost to follow-up; baseline characteristics are listed in Table 2. Median follow-up time of 93.08 months (range, 1.4-120 months) and primary sites included: oropharynx (62.5%), larynx (20.8%), oral cavity (8.3%), and hypopharynx (8.3%). All patients were chemotherapy naïve and this was their first diagnosis of SCCHN.

Acute and late toxicity

Grade 3 and 4 acute toxicities to induction therapy for all patients enrolled (n = 25) included: neutropenia 6/25 (24%), leukopenia 7/25(28%), dehydration and hypotension 2/25

Table 2 Patient characteristics (N = 24 evaluable)

Variable	N	%
Gender		
Male	22	91.7
Female	2	8.3
Age (y)		
Median (range)	54	(38-66)
Primary tumor site		
Oropharynx	15	62.5
Larynx	5	20.8
Oral cavity	2	8.3
Hypopharynx	2	8.3
Overall stage		
III	7	29.2
IVa	13	54.2
IVb	4	16.7
Nodal stage		
N0-N2a	12	50
N2b-N3	12	50
Tumor stage		
T1, T2	13	54.2
T3, T4	11	45.8

Table 3 Grades I-IV acute toxicity for all patients enrolled (N = 25)

Toxicity	NCI toxicity grade			
	I	II	III	IV
	N (%)	N (%)	N (%)	N (%)
Leukopenia	5 (20)	7 (28)	5 (20)	2 (8)
Neutropenia	3 (12)	7 (28)	6 (24)	-
Anemia	16 (64)	3 (12)	1 (4)	-
Thrombocytopenia	10 (40)	1 (4)	-	-
Infection/fever	1 (4)	2 (8)	1 (4)	-
Neutropenic	-	-	-	-
Nonneutropenic	1 (4)	2 (8)	1 (4)	-
Arthralgias/myalgias	1 (4)	1 (4)	-	-
Nausea	5 (20)	1 (4)	-	-
Alopecia	15 (60)	10 (40)	-	-
Diarrhea	2 (8)	1 (4)	1 (4)	-
Dyspepsia	-	3 (12)	-	-
Constipation	1 (4)	-	-	-
Hypotension/dehydration	-	2 (8)	2 (8)	-
Allergic rhinitis	-	1 (4)	-	-
Neuropathy	5 (20)	1 (4)	-	-
Fatigue/weakness	2 (8)	2 (8)	-	-
Nephrolithiasis	-	1 (4)	-	-
Dermatologic	1 (4)	-	-	-
Pulmonary (dyspnea)	-	-	1 (4)	-
Agitation	-	1 (4)	-	-
Epistaxis	1 (4)	-	-	-

NCI, National Cancer Institute.

(8%), anemia 1/25 (4%), nonneutropenic infection 1/25 (4%), pulmonary (dyspnea) 1/25 (4%), and diarrhea 1/25 (4%) (Table 3). No treatment-related deaths occurred. Late toxicities of the cohort (n = 24) included: 1/24 osteoradionecrosis, percutaneous gastrostomy tube dependence in 1/24, and lingual artery hemorrhage from local recurrence in 1/24. Induction therapy delays and dose reductions included 1 patient with a 1-week delay in therapy (during cycle 2) and 3 patients with dose reductions in the second cycle of chemotherapy.

Response assessment to induction and P16INK4a status

Primary site RR was 95.8% with 62.5% CR, 33.3% PR, and 4.2% SD. Of the 19 patients with nodal disease, nodal response was 84.2% (Table 4). Overall RR (primary and nodal) was 91.7%. p16 expression was available in 11 patients, with RR occurring in 3/4 (75%) p16-negative patients, 13/13 (100%) of p16 status unknown patients, and 6/7 (85.7%) p16-positive patients.

Definitive therapy

Fifteen patients (65.2%) received concurrent chemotherapy and radiation: 2 hyperfractionated with intra-arterial cisplatin, 1 hyperfractionated with intravenous cisplatin,[36] with 13 of these patients receiving once-daily fractionation with intravenous cisplatin; 4 (16.7%) patients received radiation alone, 1 patient had preoperative radiation and surgery, and 4 patients (16.7%) had surgery. Radiation was given without treatment interruptions except in 1 patient who refused radiation after 4000 cGy.

Table 4 Response to LDFRT, carboplatin, and paclitaxel at primary and nodal sites, presented as frequency (percent)

Response	N	CR	PR	SD	PD	RR
Primary site	24	15 (62.5)	8 (33.3)	1 (4.2)	-	23 (95.8)
Nodal	19	9 (47.4)	7 (36.8)	3 (15.8)	-	16 (84.2)
Overall	24	9 (37.5)	13 (54.2)	2 (8.3)	-	22 (91.7)

Response rates at primary site, nodes, and overall. Note that only 19 patients had nodal disease.
CR, complete response; LDFRT, low-dose fractionated radiation therapy; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.

OS and patient status

With a median follow-up of 93 months (7.75 years), 5-year OS was 79.2% and 9-year was 49.4%. Median OS was 107.2 months with median PFS and DSS not yet reached (Table 5, Fig 2). Although not statistically significant, median OS for p16-negative patients was 60.8 months, 107.2 months for p16 status unknown, and median not reached for p16-positive patients ($P = .0614$; eFigure 1; available as supplementary material online only at www.practicalradonc.org).

Patient status

Fourteen patients (58.3%) remain alive and well, 4 (16.7%) died of other causes, and 6 (25%) have subsequently died of progressive disease with a median survival time of 27.8 months (range, 15.2-107.2) following definitive therapy. Of those who have recurred, 1 larynx patient had a previous CR to induction therapy, 3 (2 oropharynx, 1 larynx) had a PR, and 2 (1 oral cavity, 1 oropharynx) showed SD during induction therapy. Patterns of recurrence included 2 locoregional, 3 distant, and 1 with

Table 5 OS, PFS, and DSS survival estimates

	OS	PFS	DSS
2 y	83.3 (69.7-99.7)	78.3 (63.1-97.1)	87.0 (74.2-100.0)
5 y	79.2 (64.5-97.2)	78.3 (63.1-97.1)	82.6 (68.5-99.6)
7 y	73.9 (57.8-94.5)	72.2 (55.3-94.3)	82.6 (68.5-99.6)
9 y	49.4 (30.5-79.9)	72.2 (47.8-86.7)	65.4 (44.3-96.4)
Median	107.2 (89.6-NA)	Not yet reached	Not yet reached

DSS, disease-specific survival; NA, not available; OS, overall survival; PFS, progression-free survival.

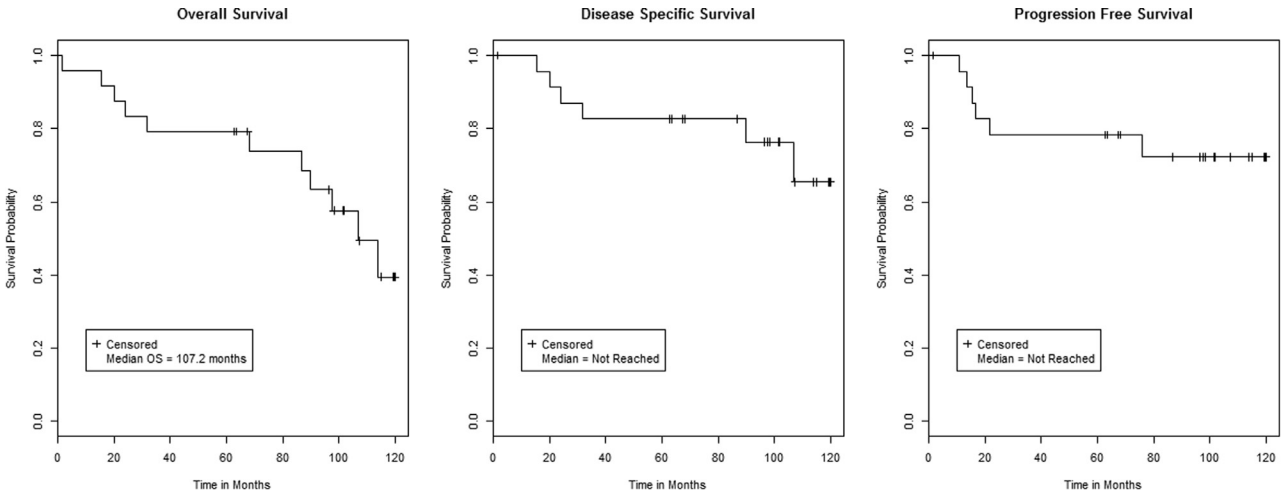

Figure 2 Overall (OS), progression-free, and disease-specific survival.

locoregional/distant metastatic failures. Second malignancies occurred as follows: prostate cancer (2), squamous cell skin cancer (2), second SCCHN (1), third SCCHN (1), non-small cell lung cancer, (2), small cell lung cancer (1), and skin cancer not otherwise specified (1).

Discussion

The use of LDFRT with chemotherapy provides a novel way to maximize tumor response, using radiation as a "biologic" agent in combination with chemotherapy (essentially, the third agent in this triplet combination). By potentiating the effect of chemotherapy, low-dose radiation targets area at highest risk (the tumor bed) and upregulates the apoptotic proteins bax and bcl-x[29,37] in the microenviroment that will most benefit from this upregulation. In this setting, radiation has a very different purpose than its traditional role in high-dose fractionation. Beyond very low doses of radiation (>50 cGy), there is a relative increase in the resistance to cell killing by radiation, termed induced radiation resistance (IRR).[33] The development of IRR is dependent on intact DNA repair mechanisms[25]; the induction of DNA repair pathways after DNA damage by radiation may be the regulator of IRR. The HRS response is independent of the DNA-dependent protein kinase complex used to repair double-stranded DNA damage.[25] This suggests that the HRS phenomenon is not dependent on DNA repair mechanisms[25] and that the use of LDFRT may selectively favor pro-apoptotic pathways[26]; therefore, HRS may provide a way to exploit radiation cell killing, without inducing DNA repair, thus providing a way to avoid the development of radiation resistance. Further exploration of the mechanism is ongoing.[34,35]

Induction therapy is a reasonable component of aggressive treatment of locally advanced SCCHN and was an excellent clinical model to allow us to evaluate the effect of low-dose radiation combined with chemotherapy. It is well-recognized that induction does add additional toxicity and triple-drug regimens increase the incidence of cytopenias and grade 5 toxicities. Using LDFRT as the third agent in a multidrug chemotherapy induction scheme did not add significant toxicity to the traditional side effects of chemotherapy. LDFRT potentiated the effect of induction chemotherapy as measured by an overall RR of 91.7%. This is the second report of the initial and long-term efficacy of induction therapy in SCCHN using a novel paradigm of LDFRT (ultrafractionation) and chemotherapy.[26,30,38-40] The use of radiation to potentiate the effect of chemotherapy, termed chemopotentiation, demonstrates long-term survival in this high-risk, locally advanced cohort of patients with SCCHN. Excellent primary site and overall RR of 91.7% are predictive of excellent local control and a 5-year OS of 79.2% and 9-year OS of 49.4%; indicating that this effect is durable in this population and has the potential to be translated to other cancer sites that use chemotherapy in the induction setting or as primary treatment. Our OS and PFS are also equivalent or superior to the largest induction regimens with long-term follow-up (TAX-234/235) with improved overall survival compared with historical controls (eTable 1). With regard to p16-positive patients, our findings mirror those of others; p16-positive oropharyngeal and nonoropharyngeal subsets had better outcomes than p16-negative cohorts.[6]

This combination of LDFRT, carboplatin, and paclitaxel is well-tolerated, with toxicities comparable to carboplatin and paclitaxel alone in a similar patient population.[23,24] In fact, there were no unexpected adverse events and no evidence that LDFRT increased the rate of radiation-induced grade 3/4 toxicities during induction therapy or long-term complication rates: 1 patient each with osteoradionecrosis, long-term percutaneous gastrostomy tube dependence, and arterial hemorrhage (resulting from cancer progression). When compared with reported toxicity rates of triplet therapy (docetaxel, cisplatin, and 5-fluorouracil), this study demonstrates reduced toxicity, chiefly in terms of

neutropenia and mucositis.[22,25] Definitive therapy did not have to be delayed (in the case of radiation or surgery) or interrupted (radiation) and did not affect the tolerability of subsequent therapy.

The primary endpoint of improved primary site CR was reached, with improvement from 28% in the first trial to 62.5% in this present study. The RRs of this trial are comparable to trials using 2-drug and[16,23,24] and 3-drug regimens[13,41] with less toxicity. The present study used only 2 cycles of induction and achieved a RR of 91.7% and enhanced the CR rate at the primary site from our previous study by more than 2-fold[30] as well as those of other induction therapy studies using similar agents (eTable 2). This improved control at the primary site allowed for dose deescalation of definitive chemoradiation without loss of efficacy, as previously reported in studies by Urba and Haraf.[17,42] Primary site CR rate served as a reliable surrogate marker of sensitivity to definitive radiation and is a significant endpoint for induction therapy studies. It is important with regard to patient toxicity in head and neck cancer because it can identify sensitive tumors that will respond to lower doses of definitive radiation and chemotherapy.

When comparing the present clinical trial with other neoadjuvant strategies that used 3- and 4-drug chemotherapy regimens,[15,16,18,30,31] chemotherapy and LDFRT provided similar results but less neutropenia (24% grade 3 and 4) and 24% grade 3 and 4 nonhematologic toxicity. In a strategy criticized for increased toxicity, this induction trial provides a 3-agent regimen, with no added toxicity.

Our findings are comparable to other reported outcomes in nonsurgical approaches, with 5-year OS, PFS, and DSS of 79.2, 78.3, and 82.6 months, respectively (Table 5). Compared with large phase 3 trials, this is favorable and shows the potential of chemopotentiating LDFRT combined with paclitaxel and carboplatin. This treatment paradigm, with an excellent 9-year OS of 49.4 months and median OS of 107.2 months, with median PFS and DSS not yet been reached is notable, especially coupled with the lower rate of grade 3 and 4 toxicities compared with more intensive, 3-drug induction regimens. This is the second innovative trial successfully using LDFRT as a potentiator of chemotherapy. Many other possibilities for harnessing the power of LDFRT exist, including ultrafractionation alone, combination with localized radiosensitizers, and combination with molecularly targeted agents and immunotherapy. Further investigation of this concept in a randomized trial is ongoing.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.adro.2016.06.003.

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