Long-term Outcome of Seropositive HIV Patients with Head and Neck Squamous Cell Carcinoma Treated with Radiation Therapy and Chemotherapy

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Abstract. *Aim: To report the outcome of radiation therapy (RT) +/- chemotherapy in HIV-seropositive patients with Head and Neck Squamous Cell Carcinoma (HNSCC). Patients and Methods: This is the largest single-Institution retrospective study to date, consisting of 73 HIV patients with HNSCC treated from January 1997-2010. The median age at RT, HIV diagnosis and the duration of patients being HIV seropositive were 51, 34, and 11 years, respectively. Seventy patients had SCC and one had submandibular salivary duct carcinoma. Stages I-II, III and IVA/B were: 22%, 27% and 51%, respectively. Primary cancer sites comprised the larynx (37%), oropharynx (32%), oral cavity (13%), hypopharynx (7%), nasopharynx (4%), unknown primary (MUP) (4%), nasal cavity (3%), and submandibular salivary duct (1%). All patients had an ECOG performance scale of ≤1 and were treated with RT +/- chemotherapy. Fifty patients (70%) were on highly active anti-retroviral therapy (HAART) during treatment, and the median CD4 count was 290 (range: 203-1142). Median dose of 70, 63, and 54 Gy were delivered to the gross disease, high-risk neck, and low-risk neck respectively. Median duration of treatment was 52 (range: 49-64) days. Twelve patients (17%) underwent neck dissection for N3 disease. Results: After a median follow-up of 47 months (range: 7-140), the 4-year locoregional control (LRC) and overall survival (OS) were 69% and 55% respectively. Seven patients (10%) developed second primary sites within the first 5 years of completing RT (2 anal SCCs and 5 HNSCCs). The LRC for Stages III/IV larynx and oropharynx SCC (which represent the majority of the cohort) were 76% and 70%, respectively. Chemo/RT-related late toxicities were dysphagia of grade≤2, 3, and 4 found in 74%, 15% and 11% of patients, respectively. Hoarseness (grade 1) was reported in 10% of patients; no patient experienced grade ≥2. Xerostomia grade ≤2, and 3 was found in 77% and 23% of patients, respectively. A Chi-square test and univariate analysis showed statistically significant relationships between LRC and duration of RT ($p<0.001$), as well as positive trends for weight loss (<10%) and absence of second malignancy. Conclusion: Definitive RT +/- chemotherapy for HIV-seropositive patients with HNSCC appears to be less effective compared to the observed rates of LRC and OS of other HNSCC without HIV. Due to advances in the HAART which prolongs HIV patients' survival, it is extremely important to establish better treatment strategies to improve therapeutic ratio in this growing patient population.*

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The advent of highly active anti-retroviral therapy (HARRT) has significantly improved the life expectancy of patients infected with the human immunodeficiency virus (HIV) in the last two decades. While this remarkable progress has resulted in reductions in the incidence of acquired immune deficiency syndrome (AIDS)-defining malignancies, such as Kaposi's sarcoma and non-Hodgkin's lymphoma, an increasing proportion of patients are developing cancers that were previously not associated with AIDS (1, 2). These non-AIDS-defining cancers, such as squamous cell carcinoma

(SCC) of the anus and of the head and neck, tend to present with a more aggressive behavior, more advanced disease at diagnosis and are less often cured than the HIV-negative patient population (3), which is responsible for poorer patient outcomes.

While surgery is the mainstay of treatment in oral cavity carcinomas, adverse pathological features such as positive lymph nodes or close margins of excision indicate the need for adjuvant RT or concurrent chemoradiation (4). Nevertheless, previous studies have reported that RT is poorly-tolerated, particularly for those treated for anal cancer, and have recommended that modifications such as lower radiation doses and/or smaller field sizes to be considered in response to increased toxicity (5, 6). There is little information on RT of head and neck SCC (HNSCC) in HIV-positive patients (7) and specific therapeutic recommendations for HNSCC are lacking at present. Recent studies on RT management of HNSCC in this specific population, albeit small, have reported acceptable outcomes and toxicities compared to HIV-negative patients with HNSCC (8-13). Authors of these studies suggested that aggressive regimens commonly employed in HNSCC RT should be offered to HIV-positive patients with newly-diagnosed HNSCC. Therefore, we conducted a retrospective analysis of 71 HIV-seropositive patients treated at our cancer Center for HNSCC. Here we report the largest and longest single-Institution study, to date, on the treatment outcomes of RT for patients with HNSCC and co-existing HIV.

Patients and Methods

Patient population and eligibility. This study represents a single-Institution retrospective investigation and was fully-approved by our Institutional Review Board. Between 1997 and 2010, 70 HIV-seropositive patients who had pathologically-proven SCC and one HIV-seropositive patient with submandibular salivary duct carcinoma were treated. 49 patients (69%) were male with a median age of 51 years (range 32-72 years). The median age of HIV diagnosis and the duration of being HIV-seropositive were 34 years (range: 25-50 years) and 11 years (range: 6-20 years), respectively. While there was no acute RT-related fatality, two patients died before starting RT. One patient, with stage IVA base of tongue SCC, died from induction chemotherapy (TPF) while the other patient, with stage III tonsil SCC, died from bleeding after transoral robotic surgery (TORS). Both patients were not included in the current analysis of 71 patients. Tumor staging of AJCC 7th Edition (2009) was used to stage patients as follows: stages I, 6 patients (8%); stage II, 7 patients (10%); stage III, 17 patients (24%); stage IVA, 29 patients (41%) and stage IVB, 12 patients (17%). Various primary cancer sites and percentages of patients with each type of HNSCC are summarized in Table I. The median age of HIV diagnosis and the duration of these patients being HIV-seropositive were 34 years (range: 25-50 years) and 11 years (range: 6-20 years), respectively. Fifty patients (70%) were on HAART during treatment and the median CD4 count of the whole cohort was 290 (range: 203-1142).

Treatment. All patients were treated with curative intent using a continuous course, sequential boost, of once-daily RT. RT was delivered using either three-dimensional conformal RT (3DcRT) for 38 patients (54%) or intensity-modulated RT (IMRT) for 33 patients (46%). Patients were treated once daily receiving 1.8-2 Gy per fraction, to a total dose of 70 Gy (median 70 Gy; range: 66-70 Gy). Definitive RT was given as follows: 70, 63, and 54 Gy to the gross disease, high-risk ipsilateral involved neck, low-risk neck (uninvolved neck or low neck), respectively. The lateral retropharyngeal nodes (RPN) received elective dose of 54 Gy when clinically-indicated (*e.g.* SCC of the hypopharynx, oropharynx, MUP). Forty-six patients (65%) with stages III (n=5/17, 29.4%) and IVA/B (41/41, 100%) underwent concurrent chemo-RT. Cisplatin (CDDP) was the main chemotherapy regimen received by the patients, however, carboplatin or cetuximab were prescribed as a replacement for CDDP in cases of poor performance status or renal impairment. Twelve patients (17%) underwent neck dissection (ND) for N3 disease. Median duration of treatment was 52 days (49-64 days).

Follow-up. Each patient had follow-up appointments every 3 months during the first year, 4 months in the second, and every 6 months in years 3-5, then annually after 5 years. Each follow-up included a complete history and comprehensive physical examination, as well as a direct and indirect laryngoscope examination. All patients were followed for a minimum of 5 years, or until death. No patients were lost to follow-up. Flurodeoxyglucose (FDG) PET or CT was performed three months after completion of RT and every 6 months afterwards during the first three years, then once yearly. TSH levels were considered for all patients. Dental prophylaxis, rehabilitation and speech/swallowing evaluations were performed where needed. Complications were defined as per the RTOG toxicity scale. Patients who were unable to swallow during RT to the extent that a percutaneous endoscopic gastrostomy (PEG) tube was necessary were coded as grade 3 toxicity, while permanent PEG tube dependency was coded as grade 4 toxicity.

Results

Primary RT was the preferred treatment for HIV-positive patients with HNSCC treated at our Institution during the time of this study; therefore, all 71 (100%) patients received definitive RT. In the whole cohort, 49 (69%) patients were male. The median age was 51 years (range: 32-72 years). Twelve patients (17%) with N3 disease underwent ND. Our institutional ND experience has been previously reported (18). Chemo/RT-related late toxicities at median follow-up of 4 years were mainly dysphagia, hoarseness of voice and xerostomia. Dysphagia developed in 46% (grade 1), 28% (grade 2), 15% (grade 3) and 11% (grade 4) of patients, where as grade 4 dysphagia led to PEG dependence. Xerostomia grades ranging from 1 to 3 developed in 45% (Grade 1), 32% (grade 2) and 23% (grade 3) of patients. Seven patients (10%) developed second-primary within the first 5 years of completing RT (two patients with anal SCC and five patients with HNSCC) (Table I). All local and distant failures were observed within the first 3.5 years of treatment with a median time of 22 months (range: 3-43

Table I. *Primary sites of cancer and pattern of failure.*

Primary Site	Patients (%)	Pathology	Stage	LC	LRF	2nd Primary
Oropharynx	23 (32%)	SCC	III/IV	16 (70%)	7 (30%)	3 (13%)
Larynx	25 (35%)	SCC	I-IV	19 (76%)	6 (24%)	1 (4%)
Oral Cavity	9 (13%)	SCC	I-IV	7 (78%)	2 (22%)	3 (33%)
Hypopharynx	5 (7%)	SCC	IV	0	5 (100%)	0
Nasopharynx	3 (4%)	SCC	III/IV	2 (67%)	1 (33%)	0
Unknown Primary	3 (4%)	SCC	IV	3 (100%)	0	0
Nasal Cavity	2 (3%)	SCC	III/IV	1 (50%)	1 (50%)	0
Submandibular duct	1 (1%)	Salivary D.	II	1 (100%)	0	0
Total received RT	71 (100%)		49 (69%)	22 (31%)	7 (10%)	

Two patients died before starting RT and were not included in the current analysis. One died from induction chemotherapy (TPF) for stage IVa base of tongue carcinoma and the other with stage III tonsil died from uncontrolled bleeding few weeks after TORS.

months).The median overall survival (OS) for the group of patients that developed local recurrence (LR) was 10 months while the median OS for the group that developed distant metastasis (DM) was 5 months.

Locoregional control and survival. After a median follow-up of 47 months (range: 7-140 months), the four-year locoregional control (LRC) (Figure 1) and OS (Figure 2) for the whole cohort was 69% and 55%, respectively. The four-year actuarial LRF by primary tumor sites (Figure 3) were as follows: hypopharynx, 100%; nasal cavity, 50%; nasopharynx, 33%; oropharynx, 30%; larynx, 24%; oral cavity, 22%; metastatic SCC of unknown primary (MUP) and submandibular salivary duct tumor, 0%. The LRC for Stages III/IV larynx and oropharynx SCC (which represents >67% of the cohort) was 76% and 70% respectively. A Chi-square test and univariate analysis showed a statistically significant relationship between LRC and the duration of RT ($p<0.001$). A Chi-square test also showed significant relationship between lower CD4 counts and higher viral load ($p=0.001$). Positive trends were observed between weight loss ≤10% and LRC as well as between absence of second malignancy and OS ($p=0.271$).

Discussion

RT is a reputable treatment modality in the definitive management of HNSCC. The increase in the use of IMRT has significantly improved the outcomes associated with RT in the head and neck region (14, 15). HNSCC with co-existing HIV, however, remains a challenging clinical problem as there is very little information on the outcome and efficacy of RT for this population. Definitive RT+/- chemotherapy has been utilized for HNSCC in HIV-positive patients at our institution for over 14 years and our RT strategy was not modified with regard to dose and technique compared to immunocompetent patients with HNSCC. Given the varying CD4+ cell counts, end-points, diverse primary cancer sites and RT techniques, an exact comparison of toxicity with HNSCC in HIV-negative patients is difficult. However, a recent review article on the various published reports of outcomes using IMRT+/- concurrent chemotherapy for HNSCC in immunocompetent patients suggests HIV status does affect outcome of RT (16). In the present report, observed rates of LRC and OS for SCC of oropharyngeal, laryngeal/hypopharyngeal, nasopharyngeal and unknown primary site were (median 93%, 84%, 98% and 86.5%) and (92%, 83%, 89% and 75%), respectively (16). These data indicate significantly better outcome for HNSCC treated with RT+/- chemotherapy in immunocompetent patients compared to our observed rate of LRC (55%, Figure 1) and OS (69%, Figure 2) in HIV-positive patients with HNSCC. This finding is critical as there is no consensus on the best treatment modality for this population beyond what is commonly utilized for immunocompetent patients with HNSCC. Notably, a Chi-square test and univariate analysis showed a statistically-significant relationship between LRC and the duration of RT ($p<0.001$) in our patient population. Moreover, positive trends with weight loss <10% and absence of a second malignancy was noted. However, this analysis was limited as our multivariate analysis did not show any statistically-significant relationship, likely due to the relatively small sample size with diverse primary cancer sites. For example, we found all three patients with metastatic SCC of unknown primary did not experience Locoregional failure (LRF) whereas all five patients with stage IV disease of the hypopharynx developed LRF (Table I). Whether such difference in failure reflects the difference in behavior of primary cancer site require larger sample volume examination.

Comparison of our treatment outcome with previous smaller size single-institutional reports on RT for HNSCC in HIV-positive patients is also alarming (Table II). Sanfilipo *et al*. reviewed treatment results of 13 HIV-positive patients

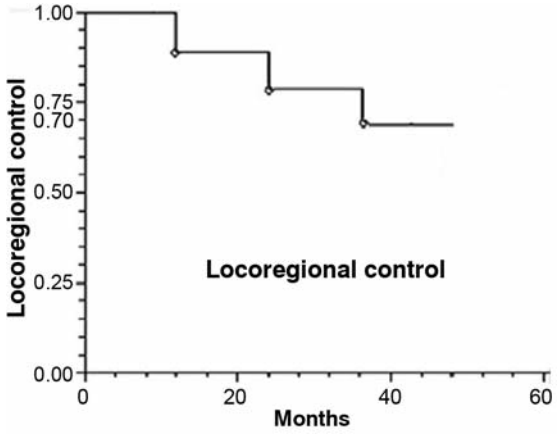

Figure 1. *The 4-year locoregional failure rate for the entire patient post RT +/- chemotherapy.*

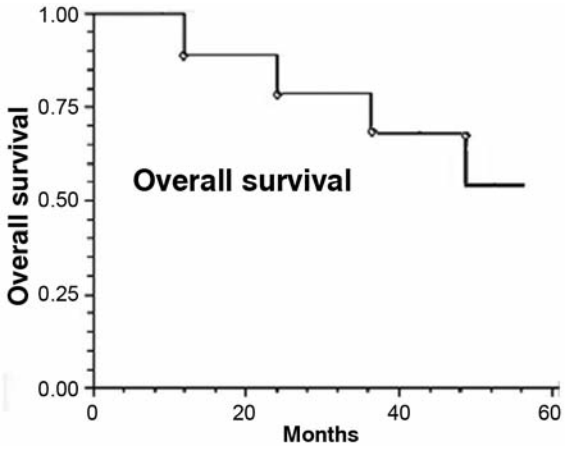

Figure 2. *The 4-year overall survival rate for the entire patient post RT +/- chemotherapy.*

with head and neck cancer who underwent RT, where 6 patients (46%) also received concurrent chemotherapy (9). Analysis from this study revealed higher OS rates compared to our study (83% *vs*. 69%), while a similar control rate (66% disease-free *vs*. 55% LRC patients) was found. Similarly, Klein *et al*. reviewed treatment results of 12 HIV-positive patients with HNSCC and also reported higher OS rates compared to our study (78% *vs*. 69%), however, a much higher rate of LRC was reported compared to our study (92% *vs*. 55% LRC) (8). While the authors of these studies concluded that the outcomes of RT for HNSCC in HIV-positive patients were relatively good, our study found poorer LRC and OS. Given the similar patient population, RT modalities employed and treatment duration between the studies, it is possible that the difference in the rates of LRC and OS could be attributed to the difference in the median follow-up duration as these studies had a shorter median follow-up duration of 2 years (9) and 3 years (8) compared to our study. Accordingly, we found that approximately 25% of all patients developed late Grade 3 to 4 RT toxicities, which is much higher than the reported late events by other studies with shorter follow-up (Table II). Additional consideration in the comparison of efficacy and outcome of RT includes varying $CD4^+$ cell count between the studies. Interestingly, local control and disease-specific survival rates in HIV-positive patients receiving RT are worse than in immunocompetent patients when CD4 counts are less than 200 cells/μl (16). Additionally, Hoffman *et al*. has reported identifying a CD4 count of less than 200 cells/μl as a predisposing factor to hospitalization with an increased likelihood of experiencing RT-related toxicities compared to those without HIV (17). An excellent LRC rate of 92% was found in Klein *et al*.'s study, where the median CD4 cell count was above 400 cells/μl, which was higher than either Sanfillipo *et al*.'s study or our study (Table II). While none

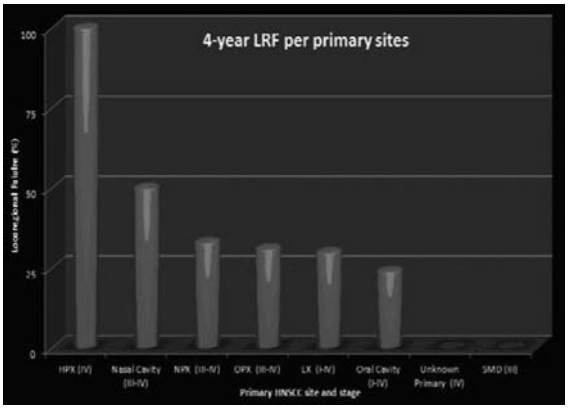

Figure 3. *The 4-year locoregional failure rate per primary cancer site post RT +/- chemotherapy. HPX; Hypopharynx, NPX; nasopharynx, OPX; oropharynx, LX; larynx, SMD; submandibular, and salivary duct carcinoma.*

of our patients had a CD4 count below 200 cells/μl and an univariate analysis found that only the duration of RT was associated with LRC, it remains a possibility that with larger patient volumes and longer follow–up, significant differences may emerge. Given the small number of patients in our study, however, it is not surprising that relatively few statistical conclusions could be drawn regarding the possible prognostic factors and variables.

Finally, the strengths of our study include: largest single-Institution experience with the longest median follow-up, reported in the literature. All RT were designed by two radiation oncologists (LBH and KSH) and all statistical analyses being performed by an independent statistician uninvolved with data abstraction. The caveats include: a non-randomized retrospective analysis, relatively small number of patients,

Table II. *A detailed comparison of studies for tolerance and RT-induced side-effects of HNSCC in HIV-seropositive patients receiving definitive RT.*

Study	Kao *et al*. 1999 (7)		Sanfilipo *et al*. 2010 (9)	Klein *et al*. 2011 (8)	Mourad *et al*. 2013
Patients (n)	4 with KS	4 without KS	13*(12 SCC & 1 lymphoma)	12	73 (71+2* patients died before RT starts)
Median age (years, range),	39 (30-44)	42 (33-53)	53 (42-65)	N/A	51 (32-72)
Gender (% Male)	N/A	N/A	69%	N/A	69%
CD4+ (cells/mm3) (median, range)	40 (20-70)	100 (60-140)	201 (125-458)	460 (222-800)	290 (203-1142)
HIV viral load (copies/mL) before RT	N/A	N/A	<50 (undetectable-46.600)	N/A	undetectable
Primary sites (#. Pts / %)	OPX		OPX 6 (46.1%)	OPX 25 (49%)	OPX 23 (32%)
Squamous Cell Carcinoma (SCC)	Oral Cavity		LX 3 (23.1%)	LX/ HPX 3 (25%)	LX 25 (35%)
Kaposi's Sarcoma (KS)			Oral Cavity 1 (7.7%)	NPX 2 (17%)	Oral Cavity 9 (13%)
Diffuse Histiocytic Lymphoma (DHL)			Paranasal sinus: 1 (7.7%)	MUP 1 (8%)	HPX 5 (7%)
			Skin (face): 1 (7.7%)		MUP 3 (4%)
			Parotid: 1 (7.7%)		Nasal Cavity: 2 (3%)
					Submandibular gland: 1 (1%)
Tumor stage (AJCC)	N/A	II: 2 (50%)	I: 1 (7.7%)	I: 2 (17%)	I: 6 (8%)
(Patients %)		IV: 2 (50%)	II: 1 (7.7)%	II: 2 (17%)	II: 7 (10%)
		Recurrent: 8%	III: 3 (23.1%)	III: 2 (17%)	III: 17 (24%)
			IV: 6 (46.1%)	IV: 6 (50%)	IVa: 29 (41%)
			Recurrent: 1 (7.7%)	AJCC 6th edition	IVb: 12 (17%)
			(one patient was not staged)		AJCC 7th edition
Treatment modality (%)	3DcRT: 100%		IMRT: 6 (46%),	IMRT: 50%,	IMRT: 46%,
			3DcRT: 6 (46%)	3DcRT: 50%	3DcRT 54% +/-
			Electron beam: 6 (8%)		Chemotherapy
					ND: 12 (17%)
					(for N3 disease)
HAART	0%		N/A	75%	70%
Treatment duration (median in days)	N/A		51 (15-61)	53 (47-79)	52 (49-64)
Median follow-up (months)	23.5 (13-32)	36.5(25-48)	22 (13-44)	33 (9-76)	47 (7-140)
Weight loss (lbs)	12.8	0.22	10 (3-25)	14 (0-37)	20 (6-40)
Treatment breaks (median in days)	N/A	N/A	0 (0-7)	33 (9-76)	5 (>10:5%, 7-10:13%, ≤5:15%)
Median Follow-up (years)	2 year		2 year	3 year	4 year
Late toxic events	Only morbidity score was reported. Median 3 *vs*. 1		Dysphagia Gr 1, 2, ,3, 4: 16%, 0%, 8%, 0%	Worsening dysphagia: 17% Grade N/A: none needed PEG-tube.	Dysphagia Gr 1, 2, 3, 4: 46%, 28% 15%, 11% Hoarseness Gr 1: 10% Xerostomia Gr 1, 2, 3: 45%, 32%, 23%
Reported end-results (reported CR or DF %)	Complete response: 100%	75%	Disease free: 66% (2 year)	Complete response: 92%	
OS (%, years)	(25%, 3 year)	(75%, 3 year)	(83%, 3 year)	78% (3 year)	69% (4 year)
LRC (%, years)	N/A	N/A	N/A	92% (3 year)	55% (4 year)
Other	Patients died of multiple system failure related to progression of the HIV infection and probably not directly attributable to the oral cavity SCC, KS or the local radiation.		Late toxicities were found in 2 patients that received CRT for SCC of oropharynx (grade 1) and in a patient treated for SCC of larynx (grade 3). One patient had persistent disease after RT and another experienced local recurrence after 1 year.	5 patients (45%) experienced treatment breaks in excess of 10 cumulative days. None of the patients required hospitalization during treatment. There were no treatment-related fatalities during RT.	One patient experienced grade 4 toxicities requiring hospitalization. There were no treatment-related fatalities during RT. Two patients died before starting RT and were not included in the current study. One died from induction chemotherapy (TPF) and the other died from uncontrolled bleeding few weeks after TORS.

OPX: Oropharynx, LX: larynx, NPX: nasopharynx, HPX: hypopharynx, MUP: metastatic squamous cell carcinoma of unknown primary site, TORS: Transoral Robotic surgery. RT; radiotherapy, Gr: grade, HAART: highly active anti-retroviral therapy. KS: Kaposi's sarcoma, SCC: squamous cell carcinoma, HNSCC: head-and-neck squamous cell carcinoma, DLH; diffuse histiocytic lymphoma, 3DCR; 3-dimensional conformal RT, IMRT; intensity-modulated RT, CRT; chemoradiotherapy, TPF; docetaxel, cisplatin and fluorouracil. OS; overall survival. LRC; locoregional control rate, N/A; data not available, ND; neck dissection, PEG; percutaneous endoscopic gastrostomy, and CDDP; cisplatin.

dependence upon accuracy of documentation, vulnerability to selection bias, as well as poorly-documented smoking history. Nevertheless, our data strongly suggest the need for modification of the current regimen in the management of HNSCC for HIV-positive patients to improve outcome.

Conclusion

HNSCC treatment in HIV-positive patients remains a challenging clinical problem. Our data show that definitive RT +/- chemotherapy for HIV-positive patients with HNSCC appears to be less effective compared to the observed rates of LRC, and OS of other HNSCC in patients without HIV. As HIV-positive patients' survival and life expectancy continues to improve, the likelihood to non-AIDS-defining malignancy increases. Hence, it is extremely important to establish better effective regimens to improve outcomes of treatment for HNSCC.

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Conflicts of Interest

None of the Authors report conflicts of interest or have financial disclosures to make. This article contains no copyrighted information.

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