Toxicity of Head and Neck Cancer Radiotherapy in HIV-positive Patients: A Systematic Review

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Introduction

The advent and widespread use of highly active anti-retroviral therapy (HAART) since 1996 has led to an increased life expectancy of people living with Human Immunodeficiency Virus (HIV)[1] along with increased incidence of non-acquired immunodeficiency syndrome (AIDS)-defining cancers.[2]

Multiple studies have reported patients with HIV/AIDS have a two to four-fold increased risk of head and neck cancer (HNC) at all subsites, with some reports suggesting increased rates of HPV-related head and neck malignancies, such as oropharyngeal squamous cell carcinoma (SCC).[3]

Radiation and chemoradiation are standard non-surgical treatment modalities used in management of head and neck malignancies, but their efficacy and tolerability have not been well-studied in the HIV-positive population. There have been studies analyzing toxicity and survival after radiotherapy in patients with HIV and other cancers with reported increased toxicity rates to chemoradiation.[4] Multiple studies have illustrated that patients with HIV/AIDS and Kaposi sarcoma of the oropharynx or oral cavity experience exaggerated and severe mucositis in response to even small amounts of radiation. There are relatively scarce data evaluating treatment response and toxicity in patients with HIV receiving radiotherapy for non-AIDS-defining HNC.

The aim of the current study was to review current literature in order to describe demographic trends of patients with HIV and HNC, to clarify their tolerance of radiation and/or chemoradiation, and more specifically, to detail radiation toxicity events and survival outcomes in this patient population.

Methods

Peer-reviewed scientific databases were searched using key terms “head and neck cancer” AND “HIV” AND “radiation” for studies published from January 1, 1996, until January 1, 2022, that included toxicity and survival outcomes related to radiotherapy in patients with HIV and HNC. Only studies involving more than one human patient were included. PRISMA guidelines were followed for proper study inclusion and data extraction. The primary outcomes assessed were radiation toxicity and overall survival.

Figure 1. PRISMA Flow Diagram

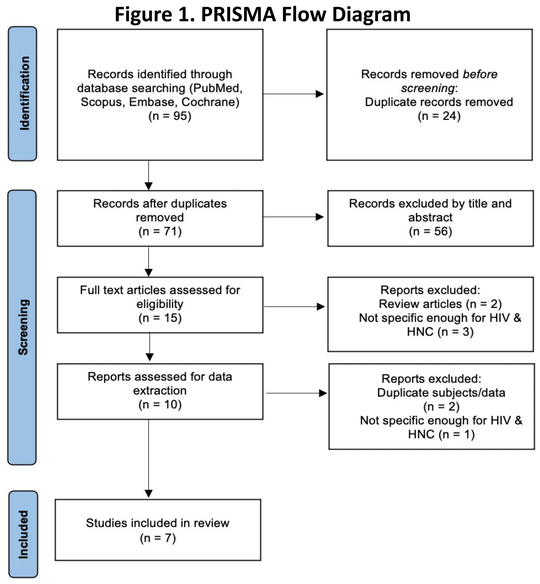

Table I. Overview of Demographic, Cancer and HIV-related Patient Characteristics

Author (year)	MINORS score (quality)	Patients (n)	% Male	Age (years)	Malignancy types	Early stage (I-II) (n)	Late stage (III-IV) (n)	Subsites involved	HPV+ (n)	(n) on ART	Median follow up (n)
Kao (1999)[5]	10 (moderate)	8	N/A	42 (33-53)	KS – 4 SCC – 3 DHL – 1	2 (50%)	2 (50%)	OC – 2 OP – 2	N/A	8 (100%)	36.5 mo (25-48)
Klein (2011)[6]	7 (low)	12	N/A	N/A	SCC – 12	4 (33%)	8 (67%)	OP – 6 LX/HPX –3 UNK – 1 NP – 2	N/A	9 (75%)	33 mo (9-76)
Mourad (2013)[7]	11 (moderate)	71	69%	51 (32-72)	SCC – 70 SDC – 1	13 (18%)	58 (82%)	OC – 9 OP – 23 LX/HPX – 30 UNK – 3 SAL – 1 NP – 5	15 out of 30	50 (70%)	48 mo (12-144)
Grew (2014)[8]	10 (moderate)	24	83%	53 (32-67)	SCC – 23 SpCC – 1	3 (12%)	21 (88%)	OC – 2 OP – 12 LX/HPX – 6 UNK – 2 NP – 1 PS – 1	2 out of 3	19 (86%)	21 mo (N/A)
D’Souza (2014)[9]	9 (moderate)	94	90%	50 (46-57)	SCC - 94	16 (21%)	60 (79%)	OC – 38 OP – 31 LX/HPX – 22 Multi - 3	14 out of 46	55 (77%)	23 mo (10-51)
De Felice[10] (2017)	10 (moderate)	13	92%	39 (30-56)	DLBCL - 13	5 (38%)	8 (62%)	OC – 7 LX/HPX – 1 NP – 1 PS – 4	N/A	N/A	152 mo (N/A)
Brickman[11] (2019)	15 (moderate)	37	92%	52 (N/A)	SCC - 37	4 (12%)	30 (88%)	OP – 37	14/23	14 (58%)	30 mo (N/A)

**SCC: Squamous cell carcinoma; KS: Kaposi’s sarcoma; DHL: Diffuse histiocytic lymphoma; SDC – Salivary ductal carcinoma; SpCC: Spindle cell carcinoma; DLBCL: Diffuse large B cell lymphoma; OC: Oral cavity; OP: Oropharynx; LX/HPX: Larynx/hypopharynx; UNK: Unknown primary; NP: Nasopharynx, nasal cavity; SAL: Parotid or submandibular gland; PS: Paranasal sinus*

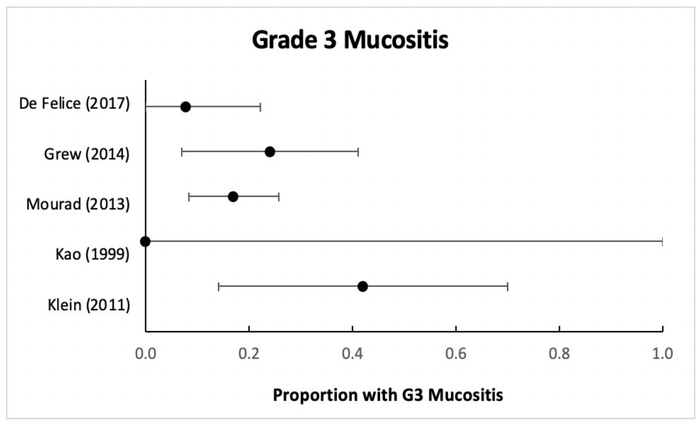

Figure 2. Percentage of patients with Grade 3 mucositis amongst included studies

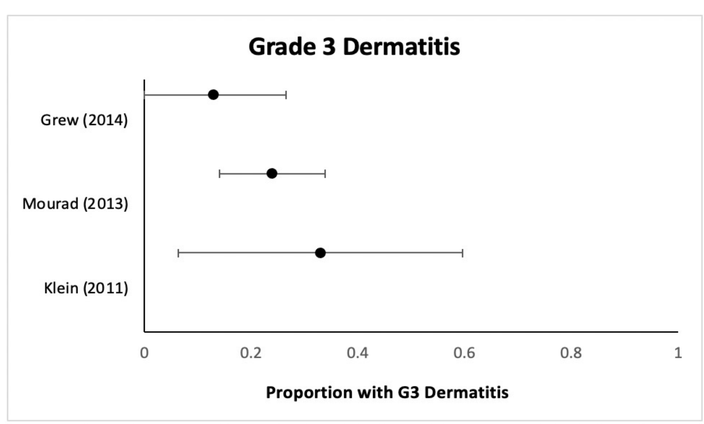

Figure 3. Percentage of patients with Grade 3 dermatitis amongst included studies

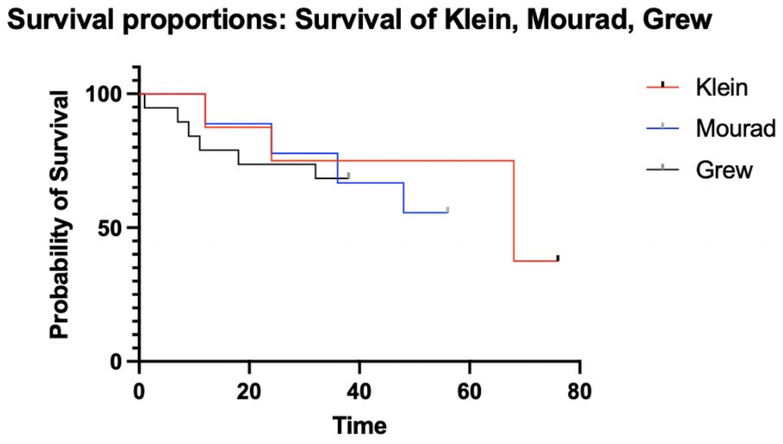

Figure 4. Survival curves for included studies, time in months

Results

A total of 95 articles were identified. Fifteen articles that included key search terms and were relevant to our study aims were read completely in full-text form. Seven studies included adequate survival or toxicity data in 259 patients with HIV and HNC and were analyzed in this review (**Figure 1**). Of these patients, 84% were male and relatively young with median age at diagnosis ranging from 39 to 53 years old. The majority of patients presented with advanced stage (Stage III or IV) HNC (80%), and the oropharynx was the most common subsite involved in the 255 cases of HNC (44%), followed by the larynx/hypopharynx (24%), and oral cavity (23%). HPV status was frequently unavailable. See **Table I** for further details.

There was significant diversity in the reporting of toxicity rates and overall survival data amongst the various studies. Studies inconsistently reported each toxicity and grade experienced by patients and instead reported the percentages of patients that developed grade 2, grade 3, or higher toxicities. Pooled weighted average **grade 3 mucositis and dermatitis rates** from the five studies that adequately reported toxicity data were calculated at **19.3%** and **22.5% which compare favorably to historical radiation toxicity rates reported in the literature for HNC in the general population**.[12,13] See **Fig. 2-3** for mucositis and dermatitis rates by study.

Survival was reported inconsistently across studies. **Pooled estimated overall survival was 73%.** Estimated overall survival at 36 months ranged from 62% to 83% across six studies. See **Fig. 4** for survival curves.

Discussion/Conclusions

This review sought to evaluate if patients with HIV and HNC who are treated with radiation or chemoradiation have poorer toxicity and survival outcomes than HNC patients without HIV. **Our review suggests patients with HIV and HNC tolerate radiotherapy, including chemoradiation, relatively well without significant need for de-intensification of radiation doses or significant treatment breaks.**

Acute and late radiation toxicity rates in HIV patients were further suggestive of acceptable tolerance and comparable to rates historically reported in the HIV-negative population with HNC.[12,13]

Late toxicity was less stringently reported and was often ungraded in the studies included in this review. When mentioned, late toxicity generally consisted of varying degrees of dysphagia with a low rate of permanent feeding tube dependence. It is possible that late toxicity occurs more frequently but was underreported due to relatively short median follow-up times ranging from 2-4 years.

Comparison of overall survival in HIV versus non-HIV patients with HNC was rare due to most studies in this review consisting of case series without comparative groups. Two included studies did include comparative groups and found that although patients with HIV and HNC were more frequently diagnosed at an advanced stage compared to the non-HIV HNC patients (60% vs. 20%), survival was not significantly different between the two groups, but HIV-positive patients were significantly more likely to experience disease recurrence.[9,11]

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