

Case series

Co-occurring substance use disorder: The impact on treatment adherence in women with locally advanced cervical cancer

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ABSTRACT

The purpose of this study was to identify the prevalence of substance use disorder and its association with adherence to treatment and survival in locally advanced cervical cancer patients treated with primary radiation therapy. This is a retrospective case series of locally advanced cervical cancer patients with substance use disorder in a single academic institution treated with radiation therapy between 2005 and 2016. Substance use disorder was identified through chart review. Those with substance use disorder were compared to those without in regards to demographics, Charlson comorbidity index, treatment details and outcomes. Of the 129 patients with locally advanced cervical cancer, 16 (12.4%) were identified as having substance use disorder. Patients with substance use disorder were younger (42.1 years vs 51.5 years, $p = .013$) and more likely to be smokers (81.3% vs 42.5%, $p = .004$). The majority of patients with substance use disorder received concurrent chemotherapy (93.8%) and brachytherapy in addition to external beam radiation therapy (81.3%). There was no significant difference in days to completion of radiation therapy between patients with and without substance use disorder. Radiation dose received, toxicities and survival were similar between groups. Among cervical cancer patients receiving treatment with radiation therapy, substance use disorder was not associated with poorer adherence, longer radiation treatment times or a difference in total dose of radiation received. Our experience demonstrates that patients with substance use disorder are able to adhere to complex, multimodal treatment plans resulting in similar cancer specific outcomes compared to patients without substance use disorder.

1. Introduction

Cancer patients with co-occurring substance use disorder (SUD) are a unique and understudied population. Cancer patients with SUD may be at particular risk for “chemical coping” or misuse of substances due to the emotional distress of diagnosis and treatment (Kwon et al., 2015). Chronic pain and other risk factors for substance use disorders are common among cancer patient populations (Childers et al., 2015). Although opioids are integral to treatment for cancer-related pain, current opioid misuse screening tools are not yet validated in cancer populations (Hojsted and Sjogren, 2007a), and true prevalence of substance misuse and SUD in this population is unknown. Reduced treatment adherence and poorer outcomes have been reported in cancer patients with SUD (Chang et al., 2014; Kisely et al., 2013).

Cervical cancer affects over 12,000 women in the United States yearly (Siegel et al., 2016). Primary treatment for locally advanced cervical cancer (LACC) involves multimodal therapy that includes chemotherapy and radiation. Protracted treatment courses correlate with poorer outcomes (Girinsky et al., 1993). The objective of this study is to identify the prevalence of SUD in LACC patients treated with primary radiation therapy (RT) and to evaluate its association with treatment adherence and survival outcomes.

2. Methods

Patient records with an ICD 9 or ICD 10 diagnosis code of cervical cancer at Virginia Commonwealth University Health System between January 2005 and December 2016 were reviewed following

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Institutional Review Board approval. Patients with LACC, (Federation of Gynecology and Obstetrics (FIGO) Stage IB2-IVA), who received definitive radiotherapy as initial treatment of disease were included. Data regarding patient demographics, smoking, substance use, medical comorbidities, histology, 2014 FIGO Stage, RT details, toxicities, and outcomes were abstracted from medical records of outpatient oncology visits and inpatient hospitalizations.

SUD was defined by presence of past or current use of alcohol, opioids, stimulants or other illicit drugs using DSM-5 guidelines. Data on tobacco was collected. Presence of medical comorbidities was categorized using the Charlson Comorbidity Index (CCI) (Kim et al., 2016). Radiation toxicities were captured and scored using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (Chhatre et al., 2014). Severe late toxicity was considered grade 3 or higher toxicity by CTCAE that occurred 90 days after completion of RT.

Descriptive data was summarized with mean and standard deviation for continuous variables and proportions and percentages for categorical variables. Patients with SUD were compared to those without SUD using chi square for categorical variables and student *t*-tests for continuous variables. The primary outcomes of treatment adherence were time to complete RT from first treatment date and total radiation dose received. Median progression free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method and compared with log rank tests. OS and PFS were calculated from date of diagnosis to date of death/ last known follow up and date of clinical recurrence respectively. Statistical analyses were performed using STATA version 15. A *p* value < .05 was considered significant.

3. Results

3.1. Patient characteristics

Of the 293 patients identified, 164 were excluded from analysis for the following reasons: 126 patients had early stage disease, 10 had metastatic disease, and 28 patients had incomplete medical records or were lost to follow up (See Fig. 1). Of the 129 patients included, 16 patients were identified as having SUD (12.4%, CI 0.07–0.2). No significant differences were identified between those with and without SUD in regards to BMI, race, insurance status, marital status or CCI (Table 1). Patients with SUD were younger (42.1 vs 51.5, *p* = .013) and more likely to smoke (81.3% vs 42.5%, *p* = .004) than patients without SUD.

Active SUD during treatment was present in 50% of patients, while the others were engaged in or had completed addiction treatment. The mean follow up time was 34.6 (range 1–143.7) months and was not

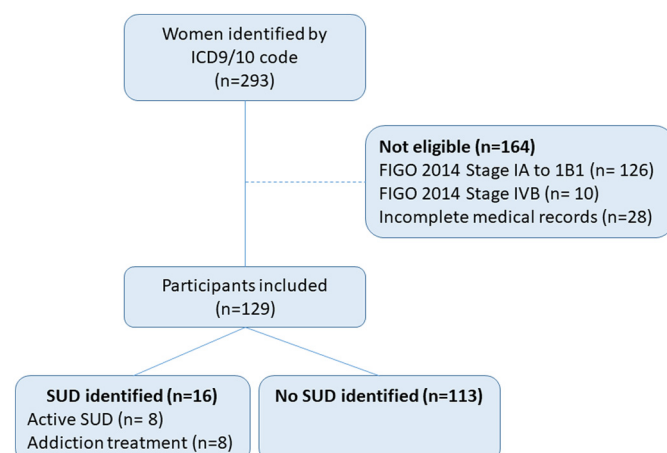


Fig. 1. Consort diagram for participants.

Table 1
Demographic and treatment characteristics of study population stratified by substance use disorder (SUD) co-morbidity.

	With SUD (n = 16)	Without SUD (n = 113)	<i>p</i> value
Age at diagnosis (years), mean ± SD	42.1 ± 8.9	51.5 ± 16.2	0.013
BMI (kg/m ²), mean ± SD	23.3 ± 6.6	26.8 ± 9.3	0.069
Race, n (%)			0.865
White	7 (43.8%)	52 (46.0%)	
Non-white	9 (56.3%)	61 (54.0%)	
Insurance status, n (%)			0.059
Private	0 (0.0%)	21 (18.6%)	
Public or uninsured	16 (100.0%)	92 (81.4%)	
Marital status, n (%)			0.549
Married	3 (18.7%)	29 (25.7%)	
Not married	13 (81.3%)	84 (73.3%)	
Smoking status, n (%)			0.004
Never or former	3 (18.8%)	65 (57.5%)	
Current	13 (81.3%)	48 (42.5%)	
Charlson comorbidity index quartile, n (%)			0.773
0	5 (31.3%)	46 (40.7%)	
1–2	7 (43.8%)	36 (31.9%)	
3–4	2 (12.5%)	19 (16.8%)	
≥5	2 (12.5%)	12 (10.6%)	
Days to completion of RT, mean (range) in days	62.7 (35–139)	57.2 (4–130)	0.818
Days to completion of RT, median	56	56	
Total radiation dose, mean (range) in Gray	82.25 (39–129)	81.1 (10–98.4)	0.596
Brachytherapy, n (%)			0.087
Yes	13 (81.3%)	103 (93.6%)	
No	3 (18.8%)	7 (6.4%)	
Concurrent chemotherapy, n (%)			0.727
Yes	15 (93.8%)	103 (91.2%)	
No	1 (6.3%)	10 (8.9%)	

BMI, body mass index. SUD, substance use disorder. *p* values < .05 are marked in bold.

significantly different when stratified by substance use disorder. Substances used included stimulants (*n* = 14, 87.5%), alcohol (*n* = 6, 37.5%) and opioids (*n* = 3, 18.8%). Half of those with SUD reported polysubstance use. The majority (81.3%) of those with SUD were smokers. In the SUD cohort, 43.8% were FIGO stage III at diagnosis, 31.2% were FIGO stage II, and 25% were FIGO stage I. The clinical characteristics of patients with SUD are detailed in Table 2.

3.2. Treatment adherence

The majority of patients with SUD received concurrent chemotherapy (93.8%) and brachytherapy (81.3%) with external beam radiation. One patient with SUD did not receive chemotherapy or brachytherapy due to treatment non-adherence. There were two SUD patients who received concurrent chemotherapy but not brachytherapy, and both were lost to follow up after completion of external beam radiation therapy. Comparison of treatment details between groups is summarized in Table 1. Median time to complete RT in both the SUD group and non-SUD group was 56 days. There were no differences in the mean number of days to complete RT in the SUD group compared to those without SUD (62.7 ± 24.8 vs 57.2 ± 21.4, *p* = .818). Radiation dose was similar between groups; patients with SUD received a mean dose of 82.2 ± 19 gray, and patients without SUD received 81.1 ± 16.8 gray (*p* = .596).

3.3. Treatment outcomes

There was no difference in rate of radiation toxicity between groups.

Table 2
Clinical details of patients with substance use disorder (SUD) comorbidity.

Patient number	Characteristic	Age	Race	FIGO stage	Substance use type	SUD status	Smoking status	EBRT plan	Brachytherapy	Concurrent chemotherapy	Total radiation dose, Gy	Treatment duration, days	Severe late toxicity
1	White	35	White	1B2	Opioids, AMP	Remission	Current	Unknown	Yes, unknown	Yes	126	74	RV, VV fistula
2	White	25	White	1B2	Cocaine, MDMA	Remission	Never	Unknown	No	Yes	76.5	Unknown	No
3	Black	54	Black	1B2	Opioids, cocaine, AMP	Remission	Never	3D	Yes, HDR	Yes	75	50	No
4	White	43	White	1B2	Cocaine, opioids	Remission	Current	3D	Yes, LDR	Yes	85	74	No
5	White	39	White	IIA	Cocaine	Current	Current	3D	Yes, HDR	Yes	84	56	No
6	White	42	White	IIB	Alcohol	Current	Current	3D	Yes, LDR	Yes	85	35	No
7	Black	32	Black	IIB	Alcohol	Current	Current	3D	Yes, HDR	Yes	74	81	TOA
8	Black	42	Black	IIB	Cocaine, alcohol	Remission	Current	3D	Yes, LDR	Yes	90.4	70	No
9	Black	34	Black	IIB	Cocaine	Remission	Current	3D	Yes, LDR	Yes	90.4	61	RV, VV fistula
10	Black	46	Black	IIB	Cocaine	Current	Current	3D	Yes, HDR	Yes	84	38	Ureteral stenosis
11	White	58	White	IIB	Cocaine	Current	Current	3D	Yes, HDR	Yes	93	52	No
12	Black	51	Black	IIB	Alcohol, cocaine	Current	Current	Unknown	No	No	39	139	Proctitis
13	Black	37	Black	IIB	Alcohol, cocaine	Current	Never	3D	Yes, HDR	Yes	82.3	52	SBO
14	Black	36	Black	IIB	Alcohol	Current	Current	3D	No	Yes	50.4	51	No
15	Black	48	Black	IIB	Cocaine	Remission	Current	IMRT	Yes, HDR	Yes	85	51	No
16	White	51	White	IIB	AMP	Remission	Current	3D	Yes, HDR	Yes	84	57	No

SUD, substance use disorder; EBRT, external beam radiation therapy; LDR, low dose rate; HDR, high dose rate; IMRT, intensity modulated radiation therapy; RV, rectovaginal; VV, vesicovaginal; AMP, amphetamine; TOA, tubo-ovarian abscess; MDMA 3, 4-methylenedioxy-methamphetamine (ecstasy); SBO, small bowel obstruction.

Gastrointestinal toxicities Grade 3 or higher were observed in 31.2% of patients with SUD and 17.9% of patients without SUD. Genitourinary toxicity rates were observed in 25% of patients with SUD and 9.8% of patients without SUD.

Survival was similar in patients with and without SUD (Fig. 2). PFS in the SUD group was 19.9 months compared to 30.7 months in those without SUD (HR 1.36, 95% CI 0.69 to 2.68). OS in the SUD group was 29.3 months in the SUD group compared to 38.7 months in those without SUD (HR 1.55, 95% CI 0.78–3.05). Median follow up in SUD group was 22.9 months with 10 recurrences and 10 death events during study period. Median follow up in non-SUD group was 23.3 months with 54 recurrences and 54 death events during study period.

4. Discussion

In this retrospective cohort of LACC patients treated with primary RT, SUD was common and associated with similar treatment adherence to patients without SUD. SUD patients were younger and more likely to use tobacco, but were otherwise demographically similar to those without SUD. Treatment regimens were similar among groups, and SUD was also not associated with radiation toxicity, lower PFS or lower OS.

Limited prior research regarding the prevalence of SUD among oncology patients is available and focuses primarily on opioids. Opioid addiction rates have been reported from 0 to 7.7% in cancer patients, however, these studies include data collected prior to the current opioid crisis (Hojsted and Sjogren, 2007b). Prior studies on opioid misuse risk in gynecologic population have shown that up to 29% of patients screen into moderate to high-risk categories for potential opioid misuse (Koyyalagunta et al., 2013), and cervical cancer patients may be at higher risk than those with other gynecologic malignancies (Garcia et al., 2017). In our cohort, risk of opioid misuse was not assessed, and the rate of opioid use disorder was low at 2.3%. Additionally, patients with SUD were more likely to be smokers, corroborating previous research that associates tobacco smoking history with other substance misuse (Kim et al., 2016).

SUD has been found to correlate with worse oncologic outcomes in other disease sites (Chhatre et al., 2014; Chang et al., 2010). In a study of advanced stage prostate cancer patients, SUD during treatment correlated to higher rates of inpatient hospitalizations, emergency room visits, healthcare costs and all-cause mortality (Chhatre et al., 2014). In hematologic malignancy, lifetime substance use disorder, in particular cocaine use disorder, correlated with six fold increased risk of death (Chang et al., 2010). Among colon cancer patients, substance use disorder is associated with higher overall and cancer specific mortality despite similar treatment rates (Baillargeon et al., 2011).

Cervical cancer patients are a vulnerable population, as the disease is associated with poverty and limited access to care (Freeman and Excess Cervical Cancer Mortality, 2005). Potential barriers to cervical cancer treatment exist from the individual to policy-level and can include financial constraints, transportation issues, geographic location remote from treatment center, and regulations for public health insurance coverage. In light of these well described barriers to care, we had expected SUD to exacerbate existing stressors. However, our results did not demonstrate a statistically significant effect on treatment adherence or outcomes. As a state designated safety net hospital, our study site may have additional services and support for patients. Cancer patients treated in this center have access to a dedicated social worker as well as a standardized protocol in the outpatient setting to screen for barriers and alert the care team of those likely in need of supportive services. Studies among cancer patients treated in the in the Veterans Affairs (VA) health system with similar findings for patients with mental health co-morbidities have hypothesized that such integration of care, as exists at the VA, addresses social determinants of health and may be driving such null results (Chang et al., 2014). Thus, our findings may be unique compared to other treatment settings where social services are less available.

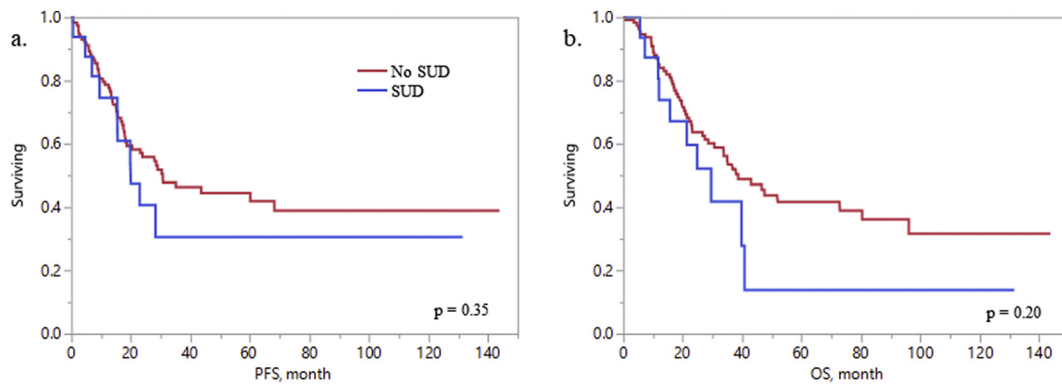


Fig. 2. Survival outcomes stratified by substance use disorder (SUD) comorbidity. a. progression free survival (PFS) in months b. overall survival (OS) in months.

The limitations of our study include its retrospective design and the inherent bias associated with this study type. Our sample size was small and we depended on medical record review to determine SUD. While there was no statistically significant difference in survival identified, there was an absolute difference of nearly one year in OS between groups. A larger or prospective study might highlight a clinically significant survival disparity. Individuals with both current SUD and those in recovery were included in the same cohort and severity of SUD was not quantified. Despite these limitations, this study evaluates the relationship between SUD and treatment outcomes in the LACC population following the start of the opioid crisis. The strengths of this study include a diverse patient population and extended follow up period.

In conclusion, little is known regarding co-occurring SUD in gynecologic oncology patients despite an ongoing opioid crisis in the United States. For patients with locally advanced cervical cancer undergoing primary RT, SUD was not associated with significant difference in treatment plan, treatment duration, toxicities or survival outcomes. These results suggest that patients with SUD can adhere to multimodal therapy, and treatment plans should not be altered in patients with co-occurring SUD. Future work should focus on confirming these findings in a larger population and evaluating the role linkage with services that address socioeconomic factors plays in treatment outcomes among cervical cancer patients with substance use disorders.

Conflict of interest statement

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Author contribution

Study concept/design: LR, MT, ST

IRB application and approval: LR, EF

Data collection: LR, EF

Data analysis and review: LR, MT, CM, WP, ST

Manuscript writing and editing: LR, MT, CM, WP, ST

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