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Gender disparities in head and neck cancer chemotherapy clinical trials participation and treatment

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ABSTRACT

Objectives: To characterize the representation of women in clinical trials directing the National Comprehensive Cancer Network (NCCN) guidelines for chemotherapy use in head and neck squamous cell carcinoma (HNSCC), as well as the relationship between gender and chemotherapy administration in the definitive treatment of HNSCC in the United States.

Methods: A review of all HNSCC chemotherapy clinical trials cited by the 2018 NCCN guidelines was performed. Sex-based proportions were compared with the corresponding proportions in the general U.S. population of patients with HNSCC between 1985 and 2015, derived from the Surveillance, Epidemiology, and End Results (SEER) program. A second analysis using the National Cancer Database (NCDB), identified 63,544 adult patients diagnosed with stages III-IVB HNSCC between 2004 and 2014 and treated with definitive radiotherapy or chemoradiotherapy. Univariable and multivariable logistic regression analyses were used to identify predictors of chemotherapy administration.

Results: While women comprised 26.2% of U.S. patients with HNSCC between 1985 and 2015, they comprised only 17.0% of patients analyzed in U.S. NCCN-cited chemotherapy clinical trials between 1985 and 2017. On multivariable analysis, women had decreased odds of receiving chemotherapy (Odds Ratio [OR]: 0.875; 95% Confidence Interval [CI]: 0.821–0.931; $p < 0.001$).

Conclusion: Women are underrepresented in HNSCC chemotherapy clinical trials cited by the national guidelines. Additionally, women are less likely than men to receive definitive chemoradiotherapy as oppose to definitive radiotherapy. Reasons for these disparities warrant further investigation as well as re-evaluation of eligibility criteria and enrollment strategies, in order to improve relevance of clinical trials to women with HNSCC.

Introduction

Over two decades have passed since Congress legislated the National Institute of Health (NIH) Revitalization Act mandating the inclusion of women and minorities in NIH-funded research due to concerns about unequal access to clinical trials and result applicability [1]. Since then, research concerning gender-based participation disparities in clinical trials for common cancers, such as lung and colorectal, has produced equivocal results [2–4]. Analysis of gender-based participation in clinical trials for head and neck squamous cell carcinoma (HNSCC), which accounts for approximately 4% of all cancers in the United States [5], has been minimal. A 1999 study by the Southwest Oncology Group (SWOG) investigated clinical trial participation among 11 cancer types and reported a 7% discrepancy between the proportion of women enrolled in SWOG HNSCC clinical trials and the proportion of women with the disease in the U.S. population [6]. Although women can be 2–3 times less likely than men to have HNSCC [7,8], proportional inclusion in clinical trials is paramount to understanding relevance and generalization of trial results to women. While several studies investigated whether patients with HNSCC receive guideline-recommended therapy, the prevalent focus was on differences by age and race [9–11]. A few cancer studies found gender disparities in the

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administration of chemotherapy [12–15] including oropharyngeal cancer [16].

In treatment of HNSCC, addition of chemotherapy to radiotherapy in the non-operative, definitive setting for locoregional advanced disease, became standard following several pivotal trials suggesting improved locoregional control and/or survival. These trials included the Veterans Affairs trial for laryngeal cancer, the European Organization for Research and Treatment of Cancer (EORTC) trial 24,981 for hypopharyngeal cancer, the French Head and Neck Oncology and Radiation Group (GORTEC) trial 9401 for hypopharyngeal cancer, and the Head and Neck Intergroup trial for the major upper aerodigestive tract cancers [17–20]. The proportion of women analyzed in these trials was low, ranging from 3 to 12% of all participants.

Given these gender-based discrepancies, the objective of our study was to characterize the representation of women in chemotherapy HNSCC clinical trials cited by U.S. national guidelines, and describe patterns of care by gender. Specifically, we investigated whether women are proportionally represented in chemotherapy clinical trials cited in the National Comprehensive Cancer Network (NCCN) guidelines, and whether gender affects the guideline-recommended administration of definitive chemotherapy in addition to radiotherapy for non-surgically treated patients with locoregionally advanced HNSCC [21].

Methods

Data sources

Data were extracted from 3 sources – the NCCN clinical trials reference section, Surveillance, Epidemiology, and End Results (SEER), and the National Cancer Database (NCDB). The NCCN clinical practice guidelines are the recognized standard for clinical practice in oncology and are regarded as the most comprehensive clinical practice guidelines available in medicine. Given their inclusive nature across all stages of head and neck cancer we employed the regimens cited in the guidelines as a convenient and up-to-date accounting of trials which impact standard of care. We reviewed all HNSCC chemotherapy randomized clinical trials cited by the NCCN 2018 guidelines and computed the total number of analyzed patients, stratified by sex [21]. The SEER registry includes 28% of cancers in the U.S and are selected to be representative of the entire population [22]. We used SEER data between the years 1985–2015 to estimate the proportion of patients with HNSCC who were women. The NCDB is a national cancer registry program and has been widely used and described [23]. We used data from the NCDB from 2004 to 2014 to analyze the association of gender with chemotherapy administration.

Clinical trial and SEER cohort and analysis

We identified all clinical trials of oral cavity, oropharynx, hypopharynx, larynx, and sinonasal tract cancer cited in the P*rincipals of Systemic Therapy* section of the NCCN Head and Neck Cancer guideline version 2.2018 [24].We excluded trials without data on participants' sex, and those describing further follow-up on already included trials to prevent patient duplication. In total, 38 clinical trials that enrolled patients between 1985 and 2017 were included (Fig. 1 and eTable 2 in Supplement). We identified the number of participating patients, stratified by sex and whole years of trial enrollment, from each of the reviewed trials' published manuscripts. Patient number was identified from the analyzed cohort. The cumulative proportion (%) of women participating in all clinical trials was computed by dividing the number of participating women by the total number of patients. The number of patients enrolled in each year was estimated by assuming equal patient distribution per year of enrollment in each clinical trial. A cumulative number of patients enrolled per year was derived and the proportion (%) of women enrolled in each year was computed by dividing the number of women by the number of total patients in each enrollment year. We characterized the trials by participating country (later stratified into U.S. and non-U.S.), sample size (above and below the median), phase, randomization (yes or no) and number of arms. Trial characterization by exclusion criteria included upper age limit (yes or no), prior malignancy (yes- including those with specified timeline from remission, or no), pregnancy/lactation (yes or no), including only recurrent or M1 disease (yes or no). Criteria were extracted from the manuscript text and supplemented from clinicaltrials.gov identifier whenever available. We used chi-square analysis to compare the proportion of women stratified by trial characterization and conducted an identical subgroup analysis including only U.S. trials.

Using *Incidence-SEER 18 Registries Research Data* between 1985 and 2015 we identified cases of HNSCC using the *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3), histology codes for squamous cell carcinoma (8070–8076, 8078, 8083, 8084, 8094) and topography codes for the following anatomic head and neck subsites: oropharynx (C09.0-C09.9 [tonsil], C10.0-C10.4 [other oropharynx], and C01.9 [base of tongue]), oral cavity (C00.3-C00.5 [lip mucosa], C02.0-C02.9 [other/unspecified tongue], C03.1-C03.9 [gum], C04.0-C04.8 [floor of mouth], C05.0-C05.9 [palate], C06.0-C06.9 [other/unspecified parts of mouth]), hypopharynx (C12.9 [pyriform sinus], C13.0-C13.9 [hypopharynx]), sinonasal tract (C30.0 [middle ear], C31.0-C.9 [accessory sinuses]), and larynx (C32.0-C32.9 [larynx]). We excluded patients < 18 years of age at the time of diagnosis. The proportion (%) of women with HNSCC in the U.S. was estimated assuming SEER-derived cases and proportions are representative of the U.S. population, and was computed by dividing the number of women with HNSCC by the number of all patients with HNSCC between 1985 and 2015, for both the cumulative time and per year.

We computed the absolute difference between the proportion of women among patients diagnosed with HNSCC in the U.S. and the proportion of women among patients: 1. participating in all chemotherapy clinical trials, and 2. participating only in clinical trials including the U.S. We used a chi-square test of homogeneity to assess statistical significance of the differences. We aggregated the proportion of women in the three groups into 5-year intervals and derived corresponding 95% confidence intervals and percent change over time.

NCDB cohort, variable definitions, and analysis

Our final study population included 63,544 patients with clinical stage III-IVB primary HNSCC of the oropharynx, hypopharynx, larynx and sinonasal tract diagnosed between 2004 and 2014 and treated non-surgically with either definitive radiotherapy (RT) or definitive chemoradiotherapy (CRT). According to national guidelines, the addition of chemotherapy to radiotherapy should be considered for curative intent in this cohort [21]. Complete cohort exclusion criteria are shown in Fig. 2.

We analyzed clinical, socioeconomic, and institutional variables from the NCDB, categorized as shown in Table 1. Treatment was stratified to RT and CRT. We considered patients to have received RT if they received external-beam radiation. Patients were considered to have received chemotherapy if they received any chemotherapy, regardless of type or number of agents used. Oropharyngeal HPV status is available after 2010 and patients were classified positive if any high-risk HPV (including HPV types 16 and 18) was recorded. Annual facility case volume was calculated as number of diagnosed HNSCC cases, divided by 11 (the number of NCDB years analyzed). Upon stratification of hospitals into quartiles, cases were classified ≤ 1.7, $> 1.7–\leq 3.5$, $> 3.5–\leq 7$, > 7 cases per year.

Clinical, socioeconomic, and institutional characteristics were compared between women and men via χ^2 analysis. Univariable binary logistic regression was performed to identify predictors of CRT. Factors with $p < 0.2$ were included in a multivariable logistic regression analysis. AJCC cT and cN staging were left out due to collinearity with

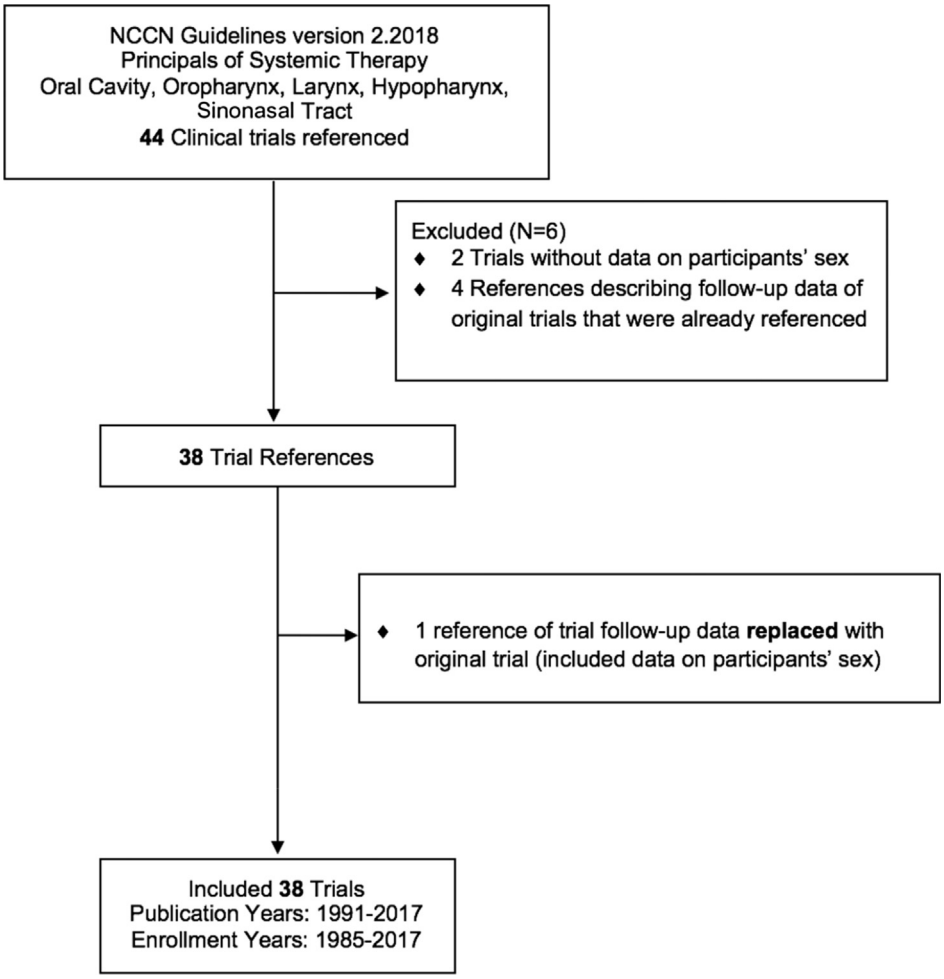

Fig. 1. Clinical Trial Selection with Exclusion Criteria. NCCN = national comprehensive cancer network.

prognostic clinical stage. Statistical significance was determined at the $p < 0.05$ level. All data analysis was performed using SPSS statistical software (version 25.0; IBM Corporation, Armonk, NY).

Results

Representation of women in chemotherapy clinical trials

We identified 38 HNSCC chemotherapy clinical trials that enrolled patients between 1985 and 2017 (Fig. 1). Total number of participating patients was 9146, of whom 1291 (14.1%) were women. Total number of participating patients in U.S. trials was 5388, of whom 915 (17.0%) were women. We identified 197,313 patients diagnosed with HNSCC between 1985 and 2015 in the SEER database, of whom 51,744 (26.2%) were women. Overall, there was a 9.2 percentage point difference ($p < 0.001$) in the proportion of women participating in U.S. NCCN-cited clinical trials and the proportion of U.S. HNSCC patients who were women. This changed over time. The proportion of women in U.S. clinical trials increased 0.3% per five-year interval and the proportion of women among new HNSCC cases decreased 0.6% per interval (Fig. 3). In the earliest interval (1985–1989) the difference in proportions was 14.9% compared to 8.4% in the latest interval (2015–2017).

Most trials (21/38, 55.3%) were conducted in the U.S. The majority (94.1%) of the 17 trials conducted outside of the U.S. were centered in Europe (France n = 6; Spain n = 4; multiple European sites n = 4) and 1 trial (5.9%) was from India. The median number of patients across all trials was 208. The majority of trials were phase III (55.3%), randomized (65.8%), excluded patients with a prior malignancy (53.9%), and did not state pregnancy/lactation under their exclusion criteria (57.9%). Most did not include an upper age limit (73.7%), while 4 (10.5%) and 6 (15.8%) trials excluded patients < 70 and < 75 years of age, respectively. All trials excluded patients < 18 years of age and had a statement excluding patients with any possible contraindication to receiving chemotherapy. Across all trials, women were less represented in trials conducted outside of the U.S. (10.0% vs. 17.0%, $p < 0.001$), larger trials (above the median sample size) (13.7% vs. 15.7%, $p = 0.024$), trials with an upper age limit (12.9% vs. 14.8%, $p = 0.016$), and a prior malignancy-based exclusion (13.4% vs. 15.0%, $p = 0.023$). Surprisingly, women had higher participation in trials with a pregnancy/lactation exclusion statement (15.5% vs. 13.1%, 0.002). Across U.S. trials only, the proportion of women was significantly lower in trials excluding patients with prior malignancies (15.9% vs. 18.1%, $p = 0.036$). The remaining trial characteristics compared by gender and country are presented in Table 2.

NCDB patient characteristics

Of the 63,544 non-surgically treated patients with clinical stage III-IVB HNSCC in whom chemotherapy should be considered in addition to radiotherapy, 81.0% were men and 19.0% women (Table 1). Most patients were white (80.7%), younger than 65 (69.4%), had no co-morbidities (80.0%), had stage IV disease (72.4%), had primary tumor of the oropharynx (62.1%), and received CRT (89.1%). Women tended to be older (36.7% women vs. 29.2% men were over 64 years of age, $p < 0.001$), presented at earlier clinical stage (32.8% women vs. 26.4% men had stage III disease), were less likely to have HPV positive

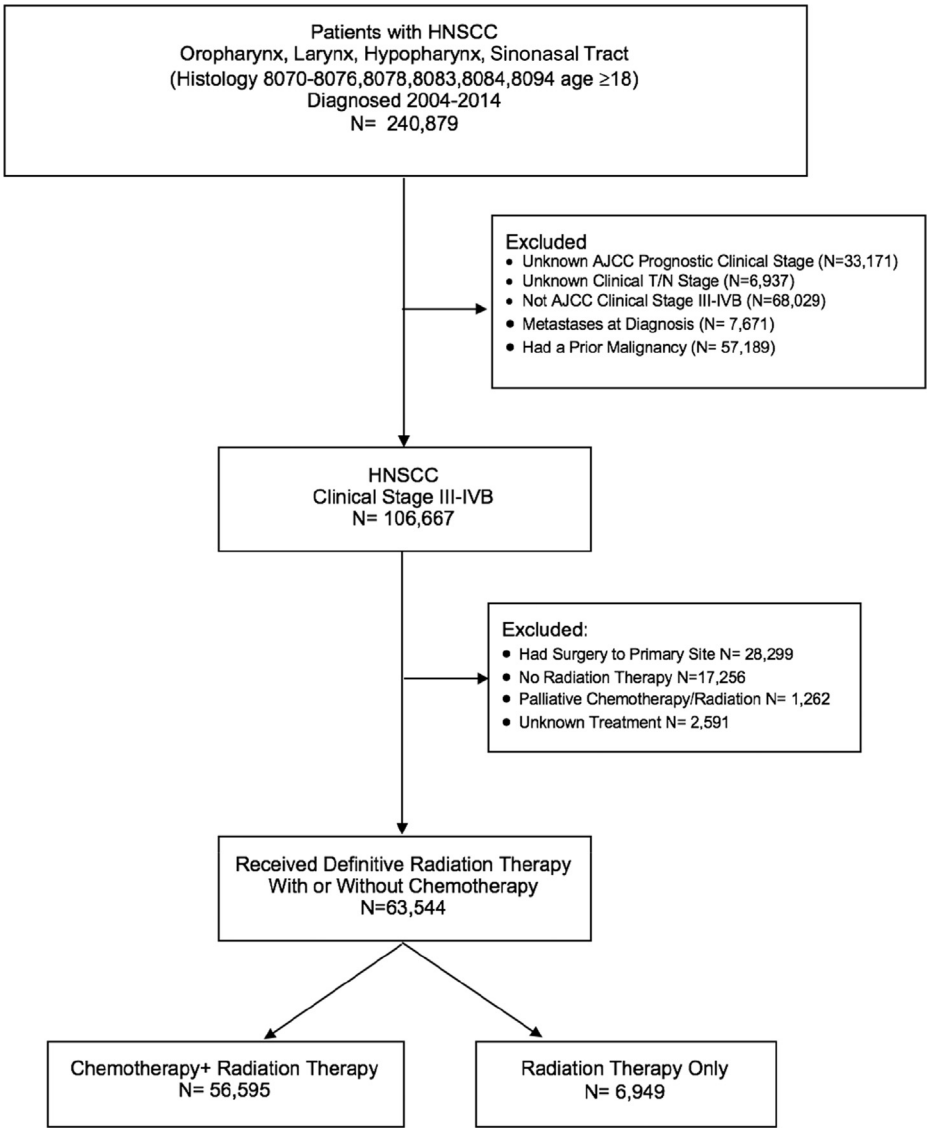

Fig. 2. NCDB Cohort Selection Criteria. a. NCDB = national cancer database. HNSCC = head and neck squamous cell carcinoma. b. Patients with oral cavity cancer subsite were excluded given that definitive radiotherapy is not part of the recommended treatment. c. Many patients were excluded for multiple criteria.

OPSCC (25.0% women vs. 35.3% men, $p < 0.001$) and were less likely to have private insurance (35.1% women vs. 44.5% men, $p < 0.001$). Women were less likely to receive chemotherapy (86.2% women vs. 89.7% men, $p < 0.001$) (Table 1).

Predictors of CRT

In multivariable analysis (Fig. 4), women were less likely to receive CRT (odds ratio [OR]: 0.875; 95% confidence interval [CI]: 0.821–0.931). Older age, higher Charlson-Deyo comorbidity score, nonwhite race, non- private insurance, lower median income, and facility location in the south or west were also associated with decreased likelihood of CRT. Compared to patients with tumors in the larynx, those with tumors in the sinonasal tract were less likely to receive CRT, while those with oropharyngeal origin were more likely to receive CRT, as were patients with clinical stage IV disease. There was no difference in likelihood of CRT receipt by facility academic affiliation or case volume. HPV status also did not affect CRT likelihood as 91.7% and 91.9% of HPV positive and negative patients, respectively, received CRT. Further detail is shown in Supplemental eTable 1.

Discussion

Our study found that women were underrepresented in the NCCN-cited chemotherapy clinical trials for treatment of head and neck cancer, although with modest representation improvement over time in U.S.-based trials. While women comprised 17.0% of patients analyzed in U.S. trials, and 14.1% in all trials, they comprised approximately 26.2% of U.S. patients with HNSCC. Additionally, we found that women with HNSCC AJCC clinical stages III-IVB treated in the non-operative definitive setting were significantly less likely than men to receive chemotherapy that should be considered in this cohort according to guidelines. Given the comprehensive nature of the NCCN guidelines across all stages of head and neck cancer, we employed the regimens cited in the guidelines as a comprehensive, convenient and up-to-date accounting of trials which strongly impact and standard of care.

While there was a trend for increased U.S. trial participation and decreased disease burden for women from 1985 to 2017, it was modest at 0.3% and 0.6% per each 5-year period, respectively. Additionally, an 8.4% gap remained at the latest time period (2015–2017), although it decreased from 14.9% at the earliest time period (1985–1989). A number of studies have examined changes in the participation of women and minorities in cancer clinical trials since the 1993 NIH

Table 1
Univariate chi-square analysis of baseline patient characteristics stratified by sex (patients with HNSCC, clinical stages III-IVB, who received definitive radiotherapy with or without chemotherapy).

	All N = 63,544 (100%)	Male N = 51,464 (81.0%)	Female N = 12,080 (19.0%)	*P*
Clinical Factors				< 0.001
Age at Diagnosis				
18–54	19,767 (31.1%)	16,160 (31.4%)	3607 (29.9%)	
55–64	24,319 (38.3%)	20,280 (39.4%)	4039 (33.4%)	
65–74	13,594 (21.4%)	10,820 (21.0%)	2774 (23.0%)	
≥75	5864 (9.2%)	4204 (8.2%)	1660 (13.7%)	
Charlson-Deyo Score				< 0.001
0	50,824 (80.0%)	41,672 (81.0%)	9152 (75.8%)	
1	9706 (15.3%)	7561 (14.7%)	2145 (17.8%)	
≥2	3014 (4.7%)	2231 (4.3%)	783 (6.5%)	
AJCC Clinical Stage				< 0.001
III	17,556 (27.6%)	13,590 (26.4%)	3966 (32.8%)	
IV	45,988 (72.4%)	37,874 (73.6%)	8114 (67.2%)	
Clinical T Stage				< 0.001
T1	8126 (12.8%)	6764 (13.1%)	1362 (11.3%)	
T2	19,581 (30.8%)	16,015 (31.1%)	3566 (29.5%)	
T3	21,044 (33.1%)	16,762 (32.6%)	4282 (35.4%)	
T4	14,793 (23.3%)	11,923 (23.2%)	2870 (23.8%)	
Clinical N Stage				< 0.001
N0	10,503 (16.5%)	8116 (15.8%)	2387 (19.8%)	
N1	11,750 (18.5%)	9093 (17.7%)	2657 (22.0%)	
N2	37,228 (58.6%)	30,763 (59.8%)	6465 (53.5%)	
N3	4063 (6.4%)	3492 (6.8%)	571 (4.7%)	
Anatomic Site				< 0.001
Larynx	17,177 (27.0%)	12,804 (24.9%)	4373 (36.2%)	
Oropharynx	39,456 (62.1%)	33,222 (64.6%)	6234 (51.6%)	
Hypopharynx	5974 (9.4%)	4824 (9.4%)	1150 (9.5%)	
Sinonasal Tract	937 (1.5%)	614 (1.2%)	323 (2.7%)	
HPV Status Oropharynx (2010–2014)				< 0.001
Positive	6975 (33.7%)	6177 (35.3%)	798 (25.0%)	
Negative	3557 (17.2%)	2826 (16.2%)	731 (22.9%)	
Unknown	10,136 (49.0%)	8474 (48.5%)	1662 (52.1%)	
Treatment				< 0.001
Radiotherapy	6949 (10.9%)	5282 (10.3%)	1667 (13.8%)	
Chemoradiotherapy	56,595 (89.1%)	46,182 (89.7%)	10,413 (86.2%)	
Socioeconomic Factors				
Race				< 0.001
White	51,267 (80.7%)	41,742 (81.1%)	9525 (78.8%)	
Non-White	12,277 (19.3%)	9722 (18.9%)	2555 (21.2%)	
Insurance				< 0.001
Private	27,135 (42.7%)	22,896 (44.5%)	4239 (35.1%)	
Not Insured	4688 (7.4%)	3840 (7.5%)	848 (7.0%)	
Medicare/Other Government	22,168 (34.9%)	17,356 (33.7%)	4812 (39.8%)	
Medicaid	8432 (13.3%)	6458 (12.5%)	1974 (16.3%)	
Unknown	1121 (1.8%)	914 (1.8%)	207 (1.7%)	
Median Income Quartiles (2008–2012)				< 0.001
< $38,000	13,756 (21.6%)	10,795 (20.9%)	2961 (24.5%)	
$38,000–$47,999	15,708 (24.7%)	12,581 (24.4%)	3127 (25.9%)	
$48,000–$62,999	16,457 (25.9%)	13,401 (26.0%)	3056 (25.3%)	
$63,000+	16,766 (26.4%)	13,987 (27.2%)	2779 (23.0%)	
Unknown	857 (1.3%)	700 (1.4%)	157 (1.3%)	
Institutional Characteristics				
Facility Type				0.003
Community Cancer Program	6222 (9.8%)	4966 (9.6%)	1256 (10.4%)	
Comprehensive Community Cancer Program	24,062 (37.9%)	19,435 (37.8%)	4627 (38.3%)	
Academic	25,434 (40.0%)	20,769 (40.3%)	4665 (38.6%)	
Integrated Network Cancer Program	6980 (11.0%)	5684 (11.0%)	1296 (10.7%)	
Unknown	846 (1.3%)	610 (1.2%)	236 (1.9%)	
Urban/Rural				0.149
Metropolitan	50,703 (79.8%)	40,996 (79.7%)	9707 (80.3%)	
Urban	9573 (15.1%)	7821 (15.2%)	1752 (14.5%)	
Rural	1215 (1.9%)	980 (1.9%)	235 (1.9%)	
Unknown	2053 (3.2%)	1667 (3.2%)	386 (3.2%)	
Facility Location				< 0.001
Northeast	12,515 (19.7%)	10,053 (19.5%)	2462 (20.4%)	
South	24,978 (39.3%)	20,290 (39.4%)	4688 (38.8%)	
Midwest	16,215 (25.5%)	13,026 (25.3%)	3189 (26.4%)	

(*continued on next page*)

Table 1 (*continued*)

	All N = 63,544 (100%)	Male N = 51,464 (81.0%)	Female N = 12,080 (19.0%)	*P*
West	8990 (14.1%)	7485 (14.5%)	1505 (12.5%)	
Unknown	846 (1.3%)	610 (1.2%)	236 (1.9%)	
Facility Case Volume (quartiles)				< 0.001
≤ 1.7 cases/year	2590 (4.1%)	2032 (3.9%)	558 (4.6%)	
1.7–3.5 cases/year	6932 (10.9%)	5564 (10.8%)	1368 (11.3%)	
3.6–7 cases/year	13,503 (21.2%)	10,779 (20.9%)	2724 (22.5%)	
> 7 cases/year	40,519 (63.8%)	33,089 (64.3%)	7430 (61.5%)	

[a]HNSCC = head and neck squamous cell carcinoma.

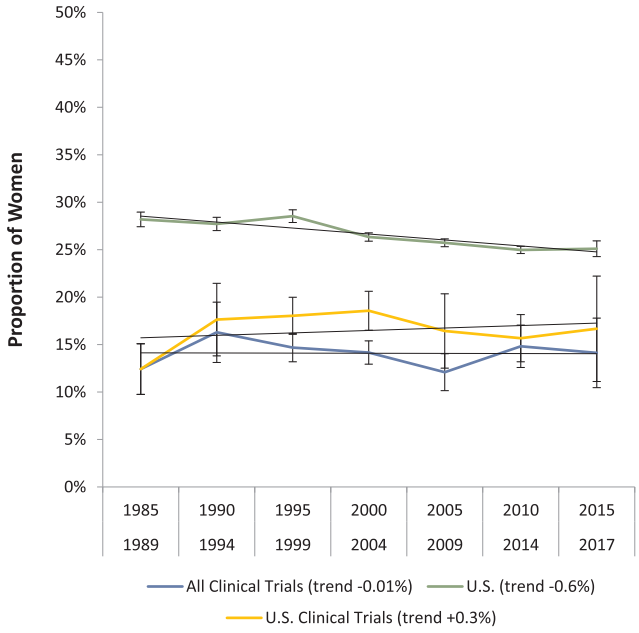

Fig. 3. Proportion of Women Analyzed in NCCN Cited Chemotherapy Clinical Trials (All countries and U.S. only) Compared with the Proportion of Women with HNSCC in the United States (with 95% Confidence Intervals). a. Enrollment years in the clinical trials cited by NCCN ranged from 1985 to 2017; SEER data available from 1985 to 2015. b. Trend line represents 5-year intervals percent change. c. Data derived from *Incidence- SEER 18 Registries Research Data 1973–2015.* d. NCCN = national comprehensive cancer network. HNSCC = head and neck squamous cell carcinoma.

revitalization act but, to the best of our knowledge, only one of these included head and neck cancers [2–4]. Among 11 types of cancers, the SWOG group found that although the overall enrollment rate for women in SWOG trials was similar to the proportion of women in the U.S. population of patients with cancer between 1993 and 1996, there was a significant negative difference for head and neck cancer as well as colorectal and lymphoma [6]. Additional studies of lung and colorectal cancers either continue to indicate underrepresentation of women [2,3], or show a closing gap towards proportional representation of younger, but not older, women [4].

Trying to elucidate the reasons for the observed underrepresentation we identified that among U.S. trials women had lower participation proportion if exclusion criteria included prior malignancy. Past studies in cancer trials, including lung cancer, identified this exclusion criteria as problematic since it significantly limited trial accrual but was often incorporated reflexively without a proven clinical risk [25,26]. Among all included trials, women had lower participation proportion if trials were conducted outside of the U.S.(mostly Europe), had above the median sample size, were phase III, had an upper age limit of 70 or 75, listed prior malignancy as an exclusion criteria, and were not limited to recurrent/M1 disease. European countries report similar HNSCC gender proportions (26% women) as the U.S.[27–29], making the NIH revitalization act a possible reason for better U.S. representation. Lower representation in larger and phase III trials could stem from increased trial intensity, but specific reasons can be further investigated. An upper age limit criteria can be re-evaluated given the current findings, although it was not significantly associated with lower participation proportions in U.S. trials only. Better participation of women with more advanced disease has been previously noted in the literature in studies which found that women's consideration of entering clinical trials increased if they had advanced disease and elevated anxiety from the disease [32,33]. Studies examining more common cancers, including breast cancer, found that women were less likely to be offered clinical trial participation if they had earlier stage disease, or were of older age regardless of criteria [30,31]. Additionally, women may independently be less likely than men to be willing to enter clinical trials [32]. Better understanding of trial conditions, and decreased financial barrier for trial transportation were previously identified to increase women's clinical trial participation [33]. While we observed an improved participation in U.S. trials over the years, a disparity remains and further efforts should be made to address it not only because clinical trials are considered to be the best strategy for cancer management [21], but also because generalization of trial results between the genders may not be warranted. The disparity may indicate unequal access to chemotherapy trials and, as could be suggested by our second analysis, be associated with under-treatment.

Our finding that women were less likely to receive chemotherapy in the definitive, non-operative setting has, to the best of our knowledge, only been documented in one HNSCC study of the oropharynx [16]. Similar findings were found in colorectal and lung cancers [12–15]. While older age and increased comorbidities [34,35] have been implicated as reasons for underuse of chemotherapy, our findings persisted after adjusting for these, and all other clinical, sociodemographic, and facility factors. Additional factors related to underutilization of cancer treatment such as beliefs in treatment efficacy, healthcare system trust and relationship with physicians were not available for our analysis and may differ by gender [34,36–38].

Interestingly, a growing body of evidence is calling for sex-specific investigation of chemotherapy regimens and treatment [39,40] due to differences in physiology-based pharmacologic responses [41,42], that are partially manifested by women experiencing higher rates of adverse effects such as nausea and vomiting, cardio- and neuro- toxicities, and oral mucositis [43,44]. These could potentially decrease chemotherapy use in women. Finally, it is also possible that the treatment gap we observed is a manifestation of an implicit bias against aggressive therapy in women, mimicking the commonly discussed gender gap in the management of coronary artery disease, where women are less likely than men to receive standard, invasive interventions independent of other clinical variables [45].

While the majority of our cohort received CRT, approximately 11% of patients were treated with radiotherapy alone. Other than gender, additional factors associated with decreased use of chemotherapy were older age, higher Charlson-Deyo comorbidity score, nonwhite race, non-private insurance, and lower median income. All of these factors have been previously identified as predictors of treatment

Table 2
Trial characteristics stratified by gender and country.

Trial characteristic	All Trials				U.S. Trials			
	Clinical Trials N (%)	Total Patients Analyzed	[a]Women N (%)	[b]P	Clinical Trials N (%)	Total Patients Analyzed	[a]Women N (%)	[b]P
Country (all)	38 (100%)	9146 (100%)	1291 (14.1%)	< 0.001	21 (100%)	5388 (100%)	915 (17.0%)	
U.S.	21 (55.3%)	5388 (58.9%)	915 (17.0%)					
Non U.S.	17 (44.7%)	3758 (41.1%)	376 (10.0%)					
Sample Size				0.024				0.362
Above median (> 208 patients)	19 (50%)	7292 (79.7%)	999 (13.7%)		10 (47.6%)	4201 (77.9%)	703 (16.7%)	
Below median (< 208 patients)	19 (50%)	1854 (20.3%)	292 (15.7%)		11 (52.4%)	1187 (22.0%)	212 (17.9%)	
Phase				0.047				0.116
I	3 (7.9%)	229 (2.5%)	38 (16.6%)		2 (9.5%)	192 (3.6%)	33 (17.2%)	
II	14 (36.8%)	1390 (15.2%)	219 (15.8%)		6 (28.6%)	760 (14.1%)	144 (18.9%)	
III	21 (55.3%)	7527 (82.3%)	1034 (13.7%)		13 (61.9%)	4436 (82.3%)	738 (16.6%)	
Randomized				0.119				0.313
Yes	25 (65.8%)	8135 (88.9%)	1132 (13.9%)		15 (71.4%)	4871 (90.4%)	819 (16.8%)	
No	13 (34.2%)	1011 (11.1%)	159 (15.7%)		6 (28.6%)	517 (9.6%)	96 (18.6%)	
Number of Arms				< 0.001				0.2462
1	13 (34.2%)	1011 (11.1%)	159 (15.7%)		6 (28.6%)	517 (9.6%)	96 (18.6%)	
2	18 (47.4%)	5279 (57.7%)	675 (12.8%)		9 (42.9%)	2855 (53.0%)	471 (16.5%)	
3	7 (18.4%)	2856 (31.2%)	457 (16.0%)		6 (28.6%)	2016 (37.4%)	348 (17.3%)	
Exclusion Criteria								
Upper age limit (70–75)				0.016				0.472
Yes	10 (26.3%)	3276 (35.8%)	424 (12.9%)		4 (19.0%)	1223 (22.7%)	216 (17.7%)	
No	28 (73.7%)	5870 (64.2%)	867 (14.8%)		17 (81.0%)	4165 (77.3%)	699 (16.8%)	
Prior malignancy				0.023				0.036
Yes	19 (50%)	4928 (53.9%)	658 (13.4%)		11 (52.5%)	2691 (49.9%)	428 (15.9%)	
No	19 (50%)	4218 (46.1%)	633 (15.0%)		10 (47.5%)	2697 (50.1%)	487 (18.1%)	
Pregnancy/lactation				0.002				0.352
Yes	16 (42.1%)	3776 (41.3%)	585 (15.5%)		12 (57.1%)	3224 (59.8%)	535 (16.6%)	
No	22 (57.9%)	5370 (58.7%)	706 (13.1%)		9 (42.9%)	2164 (40.2%)	380 (17.6%)	
Limited to Recurrent/M1				0.010				0.435
Yes	18 (47.4%)	3404 (37.2%)	522 (15.3%)		11 (52.4%)	2542 (47.2%)	421 (16.6%)	
No	20 (52.6%)	5742 (62.8%)	769 (13.4%)		10 (47.6%)	2846 (52.8%)	494 (17.4%)	

[a] % of women is calculated out of total analyzed patients for each row.
[b] P-value for chi-square test comparing proportion of women for each subcategory.

underutilization and extensively discussed in head and neck and other cancers [46–51]. Unlike some previous HNSCC studies, neither facility academic affiliation nor facility case volume were associated with chemotherapy administration [52,53]. However, facility location, namely in the south or west was associated with decreased chemotherapy use and may warrant further investigation.

There are multiple limitations to our study. Our clinical trials analysis was limited by the lack of patient-level data such as age, race and comorbidities that could have better informed participation rates, but our analysis of trial characteristics and representation by gender aimed to counteract this limitation. We also relied on assumption of an equal distribution of patients for each enrollment year which could have influenced the observed trend over time. While we only included trials referenced by the NCCN, and analyzed those conducted in Europe as well, we believe the comprehensive nature of the NCCN is a valid representation of the clinical trials which are at the center of guiding treatment decisions in the U.S. The number of participating patients was extracted from the analyzed patient pool, and we did not have original enrollment data which could have impacted results. Our proportion estimate of HNSCC cases in the U.S. relied on SEER registry data, which only includes a sample of all head and neck cancer cases. However, it is considered to be representative of actual population trends and has been extensively used to estimate the proportions of other cancers [54].

Our NCDB analysis is limited by its retrospective design and available information. We excluded a large number of patients due to missing data and the impact of these exclusions is unknown. Additionally, the NCDB does not provide information on specific chemotherapy drugs, and as an example, only distinguished traditional chemotherapy from chemoimmunotherapy such as Cetuximab, starting in 2013. This information could have been imperative in evaluating adequate chemotherapy administration. We also did not have information describing reasons for lack of chemotherapy administration. Furthermore, part of our patient population may have included patients with early stage regionally advanced tumors, such as T2N1, for which chemotherapy in addition to radiotherapy is only a category 2B recommendation. Nevertheless, we aimed to characterize the use of chemotherapy in a cohort in which chemotherapy should be considered according to guidelines and believe the identified discrepancies are relevant.

In conclusion, women are underrepresented in HNSCC chemotherapy clinical trials cited by the national guidelines. Furthermore, women are less likely than men to receive chemotherapy when it should be considered by national guidelines. Reasons for the above disparities warrant further investigation as well as adaptation of policies to correct inequalities.

Declaration of Competing Interest

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

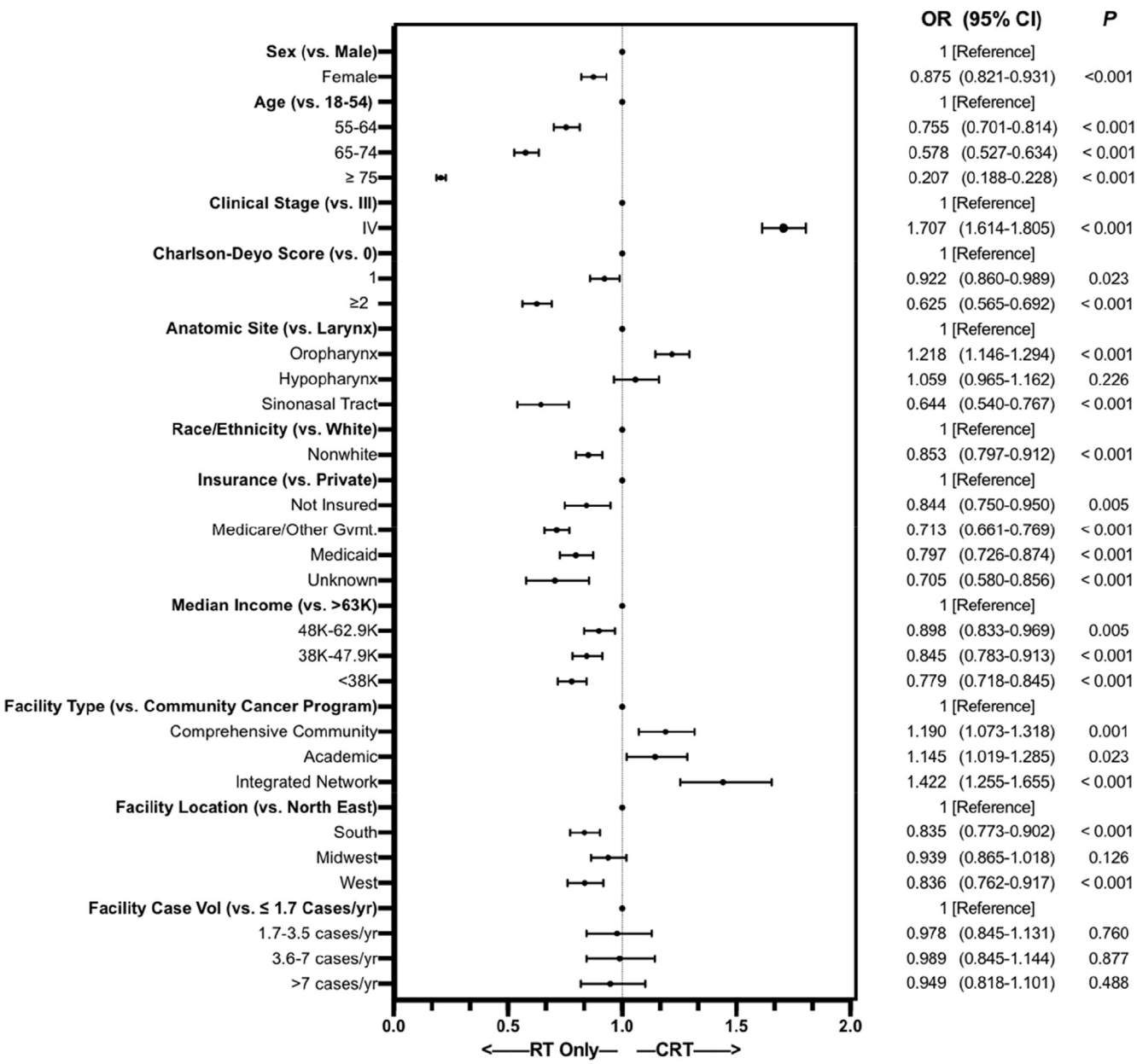

Fig. 4. Predictors of chemotherapy among patients with stage III-IVB HNSCC treated with definitive radiotherapy on multivariate logistic regression analysis. Notes: The error bars represent 95% confidence intervals (CI); OR: odds ratio RT: radiotherapy; CRT: Chemoradiotherapy; HNSCC: head and neck squamous cell carcinoma.

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Appendix A. Supplementary material

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