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Improved survival with definitive chemoradiation compared to definitive radiation alone in squamous cell carcinoma of the vulva: A review of the National Cancer Database

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HIGHLIGHTS

- We compared definitive CRT vs RT for vulvar cancer in NCDB.
- Definitive CRT was associated with improved survival compared to RT alone.
- Survival benefit was observed in most subgroups (except in FIGO stage I) and in propensity matched analysis.

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ABSTRACT

Background. It is unclear whether definitive chemoradiation (CRT) results in improved overall survival compared to radiation therapy (RT) alone in patients with vulvar cancer who are not candidates for surgery. We compared these treatment strategies in the National Cancer Database (NCDB).

Methods. We identified 1352 patients with pathologically-confirmed squamous cell carcinoma of the vulva treated with definitive RT ($n = 353$) or definitive CRT ($n = 999$) between 2003 and 2014 in the NCDB. Exclusion criteria were metastatic disease at diagnosis, RT dose <4000 cGy, follow-up <6 months, and surgical treatment. Overall survival was compared using Kaplan-Meier method with log-rank test. Cox proportional hazard modeling, propensity score matching, and subgroup analyses were performed.

Results. The median age overall was 66 (23–90) years. The CRT group was younger ($p < 0.001$) and had more advanced FIGO staging ($p < 0.001$) compared to the RT group. Median radiation dose was 5940 (4000–7920) cGy. The median follow-up for living patients was longer in the CRT group (45.2 months [6.0–131.6]) than RT (34.4 months [6.1–127.6]) ($p = 0.004$). The 5-year overall survival was higher in the CRT group compared to RT (49.9% vs. 27.4%, $p < 0.001$). On multivariate analysis, CRT was associated with a reduced hazard of death compared to RT (HR: 0.76 [0.63–0.91], $p = 0.003$). The effect remained significant after propensity score matching (HR: 0.78 [0.63–0.97], $p = 0.023$). On subgroup analysis, patients with FIGO stage I only had a trend towards improved survival with CRT ($p = 0.058$).

Conclusions. In the NCDB, definitive chemoradiation was associated with higher overall survival compared to radiation alone in patients with squamous cell carcinoma of the vulva who did not receive surgery. These findings suggest that concurrent chemoradiation may be beneficial for select patients in the definitive setting.

1. Introduction

Vulvar carcinoma is a rare malignancy that accounts for 6% of gynecologic malignancies. In 2017, an estimated 6020 women will be diagnosed with vulvar cancer and 1150 are expected to die from the disease [1]. Traditionally, vulvar cancer has been primarily managed with radical surgery followed by adjuvant radiation or chemoradiation. Radical surgeries used to involve *en bloc* radical vulvectomy with

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bilateral inguinofemoral lymphadenectomy, and potentially resection of urethra, vagina, anus or pelvic exenteration procedures for patients with more advanced disease. More recently, these techniques have largely been replaced by three-incision and other more limited operations, but locally advanced tumors still involve extensive resection. While these surgeries are effective, they may cause significant postoperative complications, short-term and long-term morbidity, and impact quality of life [2–4]. Therefore, efforts have been made to move away from primary surgery in locally advanced vulvar cancer, especially in elderly or medically inoperable patients, or in patients for whom primary surgery has a high probability of unacceptable toxicity.

In search for alternatives to pelvic exenteration, Boronow [5] and Hacker [6] pioneered the incorporation of preoperative radiation therapy in the management of locally advanced vulvar cancer the 1970s–1980s. Boronow and Hacker independently reported high complete clinical response and low tumor recurrence rates after preoperative radiation therapy. These impressive results inspired the first prospective clinical trials with chemoradiation in vulvar cancer, Gynecologic Oncology Group (GOG) protocol 101. GOG 101 examined the effect of preoperative chemoradiation with cisplatin and 5-fluorouracial in patients with locally-advanced squamous cell carcinoma of the vulva with unresectable primary [7] and unresectable nodes [8]. External beam radiation therapy delivered using a planned split course regimen to a moderate dose of 4760 cGy in 170-cGy fractions was associated with a 48% complete clinical response and a 31% complete pathologic response rate.

More recently, GOG 205 investigated a higher radiation dose of 5760 cGy in 180-cGy fractions with cisplatin alone, which resulted in a complete clinical response (CR) rate of 64% and a pathological complete response rate of 50% [9]. Patients with clinical CR and confirmed pathologic CR on incisional biopsy or FNA were spared additional surgery and had an outcome comparable to patients treated with primary surgery. A Cochrane analysis also showed similar survival outcomes of primary chemoradiation compared to primary surgery [10]. Indeed, the most recent GOG protocol for locally advanced vulvar cancer (protocol 279) evaluates the use of dose escalated intensity-modulated radiation therapy (IMRT) of 6400 cGy and concurrent weekly cisplatin and gemcitabine [11].

As definitive chemoradiation emerged as a possible alternative to radical surgery, there remains limited data on whether the addition of chemotherapy improves overall survival compared to RT alone. Since chemotherapy also confers its own toxicities and risks of treatment-related mortality, it is important to carefully select for candidates for this multi-modality treatment. In this study, we reviewed the NCDB to compare overall survival in vulvar cancer treated with definitive chemoradiation and definitive radiation alone.

2. Methods

2.1. Data source and study population

The NCDB is a joint project of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its CoC accredited hospitals. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually from >1500 CoC accredited facilities, and contains >34 million historical records. Data elements are collected and submitted to the NCDB from commission-accredited oncology registries using standardized coding and data item definitions, including details not available from the Surveillance, Epidemiology, and End Results (SEER) registry, such as radiation dose/technique, chemotherapy use/timing, and comorbidity. This project was exempted by the institutional review board.

The NCDB was queried for adult women (≥18 years) with pathologically proven squamous cell carcinoma (histology code 8070–8084) of the vulva diagnosed from 2004 to 2013 who received either definitive RT or definitive CRT. Radiation modalities included either external beam RT (EBRT) or a combination of EBRT and brachytherapy. Exclusion criteria included incomplete staging information, metastatic disease, in situ disease, primary surgical treatment, death before intended sequential chemotherapy administration, RT dose <4000 cGy, and follow-up duration <6 months from diagnosis. Variables included in the analysis were patient demographics (age, race, Charlson-Deyo comorbidity score [12], insurance type, income, educational attainment level, residential setting), treatment characteristics (year of diagnosis, facility type, facility location, facility distance, type of radiation therapy and chemotherapy), tumor status (stage, tumor size), and patient's vital status. Chemotherapy was defined as concurrent if the start date of chemotherapy and RT are ≤4 weeks apart and as sequential if the start dates are >4 weeks apart.

Staging was reported in NCDB as the American Joint Commission on Cancer (AJCC), 6th or 7th edition, which are equivalent to the International of Federation of Gynecologists and Obstetrician (FIGO) staging systems reported in 1989 [13] and 2009 [14], respectively. It is not possible to exactly convert between FIGO 2009 and FIGO 1989 stage using data available in NCDB due to considerable differences in nodal staging between the two systems. Therefore, for the purposes of this study, the patients were analyzed and reported using the 1989 or 2009 FIGO group stage and AJCC 6th or 7th edition TNM stage. The primary analysis included the staging system as an adjusted covariate to confirm that this confounding factor did not affect the conclusions regarding the use of chemoradiation.

2.2. Statistical analysis

Chi-square test and *t*-test were used to compare the categorical and continuous patient demographics, tumor and treatment variables. Overall survival was defined as the time from diagnosis to last follow-up or death. The univariate Kaplan-Meier method with log-rank test for statistical significance was used to assess actuarial outcomes. Multivariate Cox proportional regression modeling was performed using forward conditional selection ($p = 0.05$ for model entry and for removal). Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were reported. A p-value of <0.05 was considered as statistically significant and all the p-values were obtained from two-sided tests. The statistical tests were performed using SPSS version 22.

To better assess the effect of chemotherapy on overall survival, propensity score analysis with 1:1 match without replacement was performed. Propensity scores were calculated based on multivariable logistic regression using age, race, insurance status, income, education, urban/rural, Charlson/Deyo Score, and TNM staging. The propensity score matching tool in SPSS version 22 was used to generate the propensity scores and then patients were matched using the "FUZZY" package version 1.3.0 extension in Python version 2.7.1. The patients were matched with a caliper width of 0.05, which was calculated based on 0.2 multiplied by the standard deviation of the propensity scores of the entire cohort. This caliper width was estimated to eliminate 98% of the bias from the baseline variables [15]. The effect of CRT versus RT on overall survival was assessed in pre-defined subgroups based on age, Charlson-Deyo score, FIGO stage, and lymph node involvement.

3. Results

3.1. Patient characteristics

Within the NCDB, 1352 patients with pathologically-confirmed squamous cell carcinoma of the vulva treated with definitive RT or definitive CRT between 2003 and 2014 were identified. Of the 1352 patients, 353 (26.1%) received RT and 999 (73.9%) received CRT. The

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