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Which patients with inoperable vulvar cancer may benefit from brachytherapy in addition to external beam radiation? A Surveillance, Epidemiology, and End Results analysis

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ABSTRACT

PURPOSE: It is unknown whether brachytherapy after external beam radiation (EBRT + BT) results in improved outcomes compared with EBRT alone for patients with inoperable vulvar cancer. The purpose of this study was to compare survival outcomes for patients who received these treatment modalities.

METHODS AND MATERIALS: Data between 1973 and 2011 from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database were analyzed. Patients with Federation of International Gynecologists and Obstetricians stage I-IVA vulvar cancer treated with definitive EBRT + BT or EBRT alone were included. Patients with prior surgical resection were excluded. Disease-specific survival (DSS) and overall survival were compared using the Kaplan−Meier method and Cox proportional hazard models.

RESULTS: A total of 649 patients were analyzed, of which 617 received EBRT alone and 32 received EBRT + BT. Median follow-up was 33 months in surviving patients. The use of brachytherapy declined from 16% of cases treated in 1973−1980 to 4% in 2001−2011 ($p = 0.04$). EBRT + BT vs. EBRT alone was not significantly associated with improved DSS (45% vs. 33% at 5 years) or overall survival (34% vs. 24% at 5 years) on univariate or multivariate analyses. On post hoc subgroup analyses, brachytherapy consolidation was associated with higher 5-year DSS in a composite subgroup that included patients with stage IVA disease, tumor >4 cm, or node-positive disease (52% vs. 27%, $p = 0.02$).

CONCLUSIONS: Utilization of BT consolidation with EBRT for vulvar cancer is declining in the United States. EBRT + BT is not associated with improved survival compared with EBRT alone in the overall group of patients. Certain subgroups of patients might benefit from brachytherapy, but this hypothesis requires validation in future studies.

Keywords: Vulvar cancer; Radiation; Brachytherapy; Surveillance, Epidemiology, and End Results (SEER)

Introduction

Vulvar cancer represents approximately 4% of all gynecological malignancies, with an incidence of 2.5 per 100,000 women in the United States (1). Several notable risk factors for vulvar cancer have been identified with greater than 50% of cases occurring in women over the age of 70 and greater than 50% of cases linked to high-risk human papillomavirus type infections (2, 3). Furthermore, given the advancing age of our general population and the high prevalence of high-risk human papillomavirus in sexually active individuals, it is not surprising that over the last decade, the incidence and the death rates of vulvar cancer have steadily risen on an average of 0.6% and 0.7% each year, respectively (4).

Vulvar cancer treatment remains complex due to the radiosensitivity of surrounding organs, tumor shape irregularities, and the relatively low incidence of the

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disease. Surgical resection is the most common treatment modality for patients with tumors confined to the vulva or perineum with or without local spread (Federation of International Gynecologists and Obstetricians [FIGO] stage I−II) (5). Radiotherapy in the preoperative or postoperative setting has proven useful in reducing the need for more radical surgery as well as decreasing the rate of local relapses in patients with FIGO stage III−IV disease. However, in patients with inoperable tumors or in those who elect nonsurgical therapy, achieving complete tumor response and durable local control remains challenging (6−8). For instance, the complete clinical response rate to chemoradiation of 5760 cGy with weekly cisplatin for unresectable vulvar cancer in the phase II Gynecologic Oncology Group 205 study was 64% (9). In addition, 50% (29 of 58) of enrolled patients had a complete pathological response. Although the long-term outcomes of the Gynecologic Oncology Group study have yet to be reported, the locoregional control rate is not likely to exceed the pathological complete response rate without additional local therapy. Indeed, in a retrospective study from our institution, the 3-year actuarial rate of locoregional control was 42% in patients treated with definitive radiation or chemoradiation (10).

External beam radiation (EBRT) has been used for vulvar cancer treatment but has limitations including the ability to safely escalate the radiation dose. Intensity-modulated radiation therapy is quickly becoming a standard radiotherapeutic option for vulvar cancer given its ability to better spare regional critical structures compared with 3D conformal radiotherapy; as such, intensity-modulated radiation therapy, has now been incorporated in radiotherapy treatment guidelines and recent prospective trials (11). For tumors located near critical structures such as the urethra, bladder, rectum, or vagina, delivery of high-dose radiation via EBRT may be difficult without exceeding dose tolerances to normal structures. Interstitial brachytherapy (BT) consolidation after EBRT may be one solution that allows for safe and conformal dose escalation. In addition, BT consolidation may be useful for patients with residual disease after EBRT or for those who develop early progression.

Several studies on the use of interstitial BT for vulvar cancer have been reported; however all of these studies had small patient cohorts. Given such limited available data, the role of BT has not been clearly defined in vulvar cancer treatment guidelines (12−14). Furthermore, to the best of our knowledge, there are no studies directly comparing patient outcomes after EBRT + BT vs. EBRT alone for inoperable vulvar cancer. The aim of this study is to assess the impact of BT in addition to EBRT on survival in patients with inoperable vulvar cancer, and to define patient subgroups that may benefit the most from BT in addition to EBRT.

Methods

SEER database

This analysis was conducted with data from 18 registries of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The SEER 18 registries cover about 30% of the U.S. population and consist of data from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey. The SEER program registries collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status.

Patient population

After filing a completed research agreement, a retrospective analysis was performed using data gathered from an individual case query on the SEER database (15). Selection criteria included diagnosis year 1973−2011, age 18−85, female sex, first primary cancer, vulva site, no surgery, and treatment with radiation. Allowed histology codes were 8070−8078 and 8140−8146 corresponding to squamous cell carcinoma and adenocarcinoma, respectively. A case file of 843 patients was downloaded. After review, 194 patients were excluded from the study due to predefined exclusion criteria (unknown stage, incomplete staging data, metastatic disease at diagnosis, treatment with BT alone, or follow-up of less than 1 month). A total of 649 remaining patients with FIGO stage I−IVA disease were included in the study.

Vulvar cancer staging was defined using the FIGO 1989 system (16). This staging information was included in the SEER case listing file for patients diagnosed 2004 and later. FIGO 1989 staging was derived from extent of disease codes for patients treated from 1973 to 2004. The FIGO 1989 staging system was used because the most recent FIGO 2009 system (17) incorporates pathological features such as extracapsular extension and number of lymph nodes that are not readily available from patients who did not receive surgery in SEER. In addition, the FIGO 2009 staging system could not be determined from extent of disease codes in patients diagnosed before 2004.

Treatment

This study is limited to patients who received either EBRT alone or EBRT + BT. The EBRT dose, BT dose, fractionation, and radio-isotope used are not available in the SEER database. The use of concurrent chemotherapy with definitive radiation is also not available. The reason why patients did not receive surgery was also compared between the two groups.