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Does a groin node dissection in vulvar cancer affect groin recurrence and overall survival?: Results from a population-based cohort study

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HIGHLIGHTS

- This cohort showed no significant difference in groin recurrence with or without GND.
- There was not enough power for a significant association between GND and survival.
- Risk of death before recurrence is a competing risk with groin recurrence.

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ABSTRACT

Background. To determine, in a population-based cohort of vulvar cancer patients, if groin node dissection (GND) decreases the risk of groin recurrence and increases overall survival.

Methods. This population-based retrospective cohort study includes all cases of invasive squamous cell carcinoma identified in a provincial cancer registry from 1998 to 2007. Data collection was completed for all clinical and pathologic factors by chart abstraction. Cumulative incidence functions for recurrence were estimated, accounting for death before recurrence as a competing risk. Multivariable Cox regression models examined the associations between GND and groin recurrence, and overall survival.

Results. Clinical and pathologic data were collected for 1109 patients, of which 1038 patients were eligible for GND. 647 patients (62%) had a GND, while 391 patients (38%) did not. Median follow-up was 2.8 years. Cumulative incidence plots demonstrate that the risk of death without recurrence was consistently higher than groin recurrence in each year after diagnosis. On multivariate analysis, GND was not significantly associated with decreased groin recurrence (HR 0.91, 95% CI 0.58–1.44, $p = 0.70$). The hazard of death was 15% lower for women who received GND (HR 0.85, 95% CI 0.63–1.16, $p = 0.32$), but this difference was not statistically significant.

Conclusions. There was no significant difference in groin recurrence or overall survival in those with or without GND in this population-based cohort, raising questions whether a subgroup of patients may not benefit from GND. Patients had a higher probability of dying before groin recurrence could occur. Future trial design should consider death as a competing risk.

1. Introduction

Vulvar cancer is an uncommon malignancy which accounts for 4–5% of all cancers of the gynecologic tract [1]. This has made it difficult to evaluate new treatment strategies in prospective randomized trials and requires multi-institutional involvement.

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Among the existing published literature there are two landmark trials coordinated by the Gynecologic Oncology Group (GOG). GOG 37 was a trial where 114 women post radical vulvectomy and bilateral groin node dissection with positive lymph nodes were eligible. Patients were randomized to either radiation of the inguinal and pelvic nodes or pelvic lymph node dissection [2]. Interim analysis revealed there was a significant survival advantage for patients in the adjuvant radiation group (68% vs. 54%, $p = 0.03$) with a lower rate of recurrence in the groin nodes (5% vs. 24%, $p = 0.02$), resulting in early trial termination. These results highlighted the critical importance of nodal control to achieve cure.

In the second trial, GOG 88, patients with resectable vulvar cancers were randomized to either groin node dissection (GND) or to groin radiation therapy. There were only 52 patients randomized in this trial (25 to GND, 27 to groin radiation). Five of the 27 patients in the radiation group (18.5%) recurred in the groin, compared to no recurrences in the GND group, resulting in early trial termination. Additionally, the 3-year overall survival was significantly improved in the GND group (88% vs. 63%, $p = 0.035$) [3]. This study has been criticized for its inadequate radiation technique [4]. Yet, this is the only randomized trial comparing groin radiation to groin surgery. There is insufficient evidence to suggest that primary radiation therapy to the groin is as effective as surgery in controlling tumor in the groin, and there are no other randomized trials evaluating adequate and modern groin radiation vs. groin surgery. Therefore, in current management of invasive vulvar cancer, surgery remains the treatment of choice for groin nodes [5].

However, GND is associated with high complication rates, including wound breakdown (49%) and chronic lymphedema (27%) [6]. In a disease which typically arises in an elderly population and related comorbidities, these complications can be particularly morbid. Patient characteristics from randomized trials may not be reflective of those in the general population, and therefore recommended therapies on trial may not always be generalizable.

Our group has conducted a population-based analysis of all patients diagnosed with invasive vulvar carcinoma from 1998 to 2007 in the province of Ontario, Canada. The rate of GND among 1109 patients was 68%. Factors significantly associated with the lack of GND included increasing age, comorbidities, lower socio-economic status, and having a non-gynecologic oncologist at time of vulvar resection [7]. Using this population-based cohort of invasive vulvar cancer patients, we evaluated whether the presence or absence of GND affects risk of groin recurrence, as well as overall survival.

2. Methods

The cohort for this study was identified using administrative data sources, and augmented by primary data collection. This methodology of data collection has been previously described and published [7].

2.1. Administrative data sources

The Ontario Cancer Registry (OCR) captures at least 95% of provincial cancer cases resulting in a comprehensive population-based cancer registry [8,9]. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) has procedure and diagnosis codes from all inpatient and outpatient hospital admissions. In re-abstraction studies, it has a maximum discrepancy rate of 10% [10]. The Registered Persons Database (RPDB) has demographic information on all residents in the province who are eligible for the Ontario Health Insurance Plan (OHIP) [11]. Canada's 2006 Census contains information on neighbourhood income quintiles [12].

2.2. Case ascertainment and chart abstraction

This is a retrospective population-based cohort study. All consecutive cases of invasive squamous cell carcinoma of the vulva (ICD-9 codes 184.1–184.4, ICD-10 codes C51) in the province diagnosed from January 1, 1998 to December 31, 2007 were identified in the cancer registry (OCR).

Abstraction of clinical data was performed by three trained abstractors who reviewed individual charts at all of the major cancer centers in Ontario. These abstractors travelled to an additional 75 institutions across the province in order to collect local hospital chart data of patients who were never assessed at a cancer center, or where the cancer center chart was missing key data elements. Research ethics board approval was obtained from each institution.

All of the available vulvar cancer pathology reports were obtained from the cancer registry and abstracted by two investigators (LB, LG). Merging of the collected data for analysis was done by linking a unique identifier at the Institute for Clinical Evaluative Sciences (ICES).

The final cohort excluded patients identified by the cancer registry but who had missing chart numbers or charts that could not be located, patients where chart abstraction was completed but there was no available pathology data, and patients incorrectly identified in the registry as having invasive vulvar cancer.

2.3. Variable definitions

2.3.1. Outcome variables

2.3.1.1. Groin recurrence. was collected by a combination of clinical chart review and pathology reports. Groin recurrence and dates of recurrence were collected from the clinical chart. Any pathology reports of groin node biopsies >6 months from diagnosis date confirming presence of metastatic disease were also classified as groin recurrence, with dates abstracted from these pathology reports. Either a clinical or pathologic diagnosis could be used to determine presence or absence of groin recurrence.

2.3.1.2. Overall deaths. Patient deaths and dates of deaths were collected from the patient chart. Date of last follow up was recorded for all patients who did not have a death date at the end of the study period.

2.3.2. Exposure variable

2.3.2.1. Groin node dissection (GND). Groin node procedures that took place as part of the initial management of the patient's vulvar cancer were collected from the patient chart. For the purposes of this study, GND was defined as any of the following procedures: bilateral or unilateral superficial and deep GND, sentinel lymph node dissection, or debulking of enlarged groin nodes, completed within 6 months of diagnosis. Office biopsies or fine needle aspirations were excluded. For this study cohort between 1998 and 2007, only one center started sentinel node procedures in 2006, and the vast majority were done in conjunction with a GND on a trial basis only.

2.3.3. Patient variables

2.3.3.1. Age. Age at diagnosis was collected from the OCR. Comorbidities: The Adult Comorbidity Evaluation (ACE)-27 Comorbidity Index was used to calculate a comorbidity score. This index has been validated in the ambulatory cancer population, and has demonstrated the viability of its collection from chart data [13]. The highest ranked single ailment defined the overall comorbidity. Severe comorbidity was defined as severe decompensation (grade 3) of a single ailment, or two or more moderate decompensation (grade 2) ailments occurring in different organ systems.

2.3.4. Tumor variables

2.3.4.1. Depth of invasion and lymphovascular space invasion (LVSI). were obtained from the pathology reports. When available, the data from

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