



## The role of brachytherapy in organ preservation for penile cancer: A meta-analysis and review of the literature

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### ABSTRACT

**PURPOSE:** A meta-analysis is presented comparing the overall survival (OS) and local control (LC) rates between penectomy and brachytherapy for penile cancer.

**METHODS AND MATERIALS:** A PUBMED search was conducted with the MeSH terms, “penis, penile, cancer, brachytherapy, penectomy, surgery, treatment” in various combinations. Nineteen retrospective studies published between the years 1984–2012, detailing OS and LC were included. Data were collected per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

**RESULTS:** A total of 2178 males, median age 61 years, were included with 1505 in the surgery group and 673 in the brachytherapy group. The 5-year OS with surgery was 76% compared with 73% with brachytherapy, odds ratio = 1.17 (0.95–1.44,  $p = 0.128$ ). Penectomy was associated with a higher 5-year LC rate of 84% compared with 79% with brachytherapy, odds ratio = 1.45 (1.09–1.92,  $p = 0.009$ ). The organ preservation rate for brachytherapy treatment was 74%. Among the surgery patients in a Stage I/II subset, the 5-year OS and LC was 80% ( $n = 659$ ) and 86% ( $n = 390$ ), respectively. Of the 209 early stage patients who received brachytherapy, the 5-year OS was 79% and LC was 84%. Chi-square testing demonstrated no difference for either OS or LC for early stage disease.

**CONCLUSIONS:** This meta-analysis is limited by the retrospective nature and inherent selection bias of the data. While penectomy provided better control, there was no survival benefit, implying that in most cases failed brachytherapy could be salvaged with surgery. Additionally, in early stage tumors there was no survival or control difference. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

### Keywords:

Penis; Penile; Cancer; Brachytherapy; Penectomy

### Introduction

Comprising less than 1% of all male cancers in the United States (1), squamous cell carcinoma of the penis currently has few treatment guidelines, none of which are based on randomized evidence (2). Early stage (I or II) cancers are tumors that do not invade the corpora cavernosa or metastasize to the inguinal lymph nodes, whereas locally advanced disease tends to be more extensive with regional

lymph node involvement (3). The distinction is important as stage predicts prognosis and perhaps determines treatment recommendations. The cause-specific survival of penile cancer at 5 years is 62%; 20–60% with lymph node involvement and 85% without regional disease (4, 5). The gold standard for treatment is full or partial penectomy, regardless of the tumor’s depth of invasion. Moh’s surgery is an emerging organ-sparing alternative in which the tumor is excised with minimal margins, although outcome data are currently limited. Radiotherapy, particularly brachytherapy, offers an alternative to surgery in early stage penile cancer, which has been shown to be as effective as penectomy for overall survival (OS) in some studies (6).

Radiotherapy for penile cancer has been available for decades, but it is still not considered the standard of care.

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Part of the reason is the rarity of the tumor, especially in developed countries and subsequently the scarcity of physicians who can offer brachytherapy or organ-sparing surgery. Penectomy is effective for disease control but is also associated with higher rates of depression and suicide (7), and therefore may not be a superior option to organ-sparing therapy for select patients. However, OS, control, safety, and propensity to undergo successful salvage therapy with penectomy alternatives is not well known. A review of 101 cases by Sarin *et al.* observed that radiation resulted in worse outcomes when compared with penectomy (8); conversely, Crook *et al.* demonstrated that brachytherapy successfully treated early stage cancers with survival rates similar to penectomy (9). Other studies in the literature, many limited by a lack of power and heterogeneous patient selection, report varying outcomes with different treatment modalities for penile cancer. Therefore, we performed a comparative meta-analysis to evaluate the relative safety and efficacy of surgery, external beam radiation, and brachytherapy in penile cancer treatment.

## Methods

A PUBMED and Medline search with the MeSH terms, “penile cancer, penis squamous cell carcinoma, brachytherapy, radiotherapy, penectomy, surgery” was conducted in various combinations. The studies were then selected for meta-analysis based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. An initial abstract search yielded 1227 articles, among which only retrospective or prospective studies detailing survival and/or control outcomes of penile cancer treated by either radiation or surgery were selected for full text eligibility. No prospective data were discovered, and of the 35 remaining retrospective reviews, 15 were excluded for the following reasons: 6 reported duplicate data (10–15), 5 discussed only organ-sparing surgeries (16–20), 2 failed to report survival and/or control at 5 years (21, 22), 1 only reported on adjuvant external beam radiation therapy (EBRT) (23), and 1 reviewed only 10 patients with endpoints before 5 years (24). A flow diagram depicts the selection process on Figure 1. In total the meta-analysis includes 20 retrospective reviews published between 1984 and 2012. Four were large series reporting penectomy alone, 10 solely regarding brachytherapy, two comparing brachytherapy and penectomy, and four comparing external beam radiation and penectomy. For the purposes of the meta-analysis, survival, control, and toxicity data were combined and compared between surgery, brachytherapy, and external beam radiotherapy cohorts. We also conducted a subset analysis between penectomies and brachytherapy for early stage cancers; however, the data were limited to approximately one-third the total number of patients.

Patients of any age or performance status with squamous cell carcinomas of the penis were included in the study, with the exception of metastatic disease. Tumor maximum

diameter was not well reported in the penectomy literature but was almost always less than 4 cm in the brachytherapy studies, as recommended by current guidelines (25). Outcome data of each study were collected for the same endpoints, including disease-free progression, local control (LC), and OS at 5 years. Survival rates were not reported in one study (26) and recurrence rates were lacking in two studies within the penectomy group (27, 28). One article did not report 5-year survival (29) and another did not mention disease-free progression among the brachytherapy studies (30). Cases reviewed in different countries and at different time periods with at least 20 subjects were considered for the systematic analysis.

For consistency, clinically remarkable and biopsy-proven inguinal lymph nodes were considered positive. Pathologic nodes following inguinal lymph node dissection were only noted in a few penectomy studies and therefore were not considered as positive nodes for the purposes of the meta-analysis. The penectomy group included penile cancer of any stage treated with penectomies and partial penectomies, with or without lymph node dissection, adjuvant chemotherapy, or adjuvant external beam radiation. Studies that reported organ-sparing partial penectomies, such as one from Philippou *et al.* (31), were included in the penectomy stratification. However, Moh's surgery, cryotherapy, and circumcision were excluded.

The brachytherapy arm included high dose rate, low dose rate, and pulse dose rate between 50 and 70 Gy (median 65), with or without adjuvant external beam radiation, chemotherapy, or lymph node (LN) dissection. External beam radiation to the penis to a median dose of 51 Gy (40–60 Gy), with or without additional radiation to the pelvis or adjuvant chemotherapy was included in the EBRT category. Penectomy with adjuvant EBRT was included in the surgery group, and EBRT with a brachytherapy boost was included in the brachytherapy group. Data were extracted from each study based on inclusion criteria and results were pooled into separate outcome categories, if available, via the random effects model. Weighted means were used to account for variability in study population, chi-square testing was used to test for heterogeneity, and odds ratios (OR) were used for statistical analysis of the endpoints via MedCalc.

## Results

### *Patient and disease characteristics*

The total number of patients in the penectomy, brachytherapy, and EBRT arms were 1505, 673, and 155, with median followup of 59, 67, and 62 months. The median age for the entire systematic analysis is 61 years (21–98 years). Table 1 details the differences in patient characteristics between the surgery and brachytherapy cohorts. Notably, the brachytherapy group had a 15% lower positive LN rate ( $p = 0.004$ ) than the penectomy group, as well as

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