# The Relationship of Circumcision With Clinical Tumor Staging of Penile Cancer

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## Abstract

In this report, we look at the relationship between prior circumcision and presenting stage of penile cancer. We performed an analysis of an international, multicenter database of 1254 penile cancer patients diagnosed from 1980 to 2019 in the United States, Europe, Brazil, and China, and analyzed the relationship between circumcision and presenting T and N stage. A total of 710 patients met the inclusion criteria and were statistically analyzed. We found that uncircumcised men with locally advanced tumors (T3–T4) had significantly higher risk of lymph node metastasis compared with circumcised men.

The genital microbiome is the only shared human microbiome[1]. Since circumcised men harbor different bacterial communities than uncircumcised men[2], we hypothesized that circumcised men may present with a different penile squamous cell carcinoma (PSCC) disease burden than uncircumcised men. Were this the case, it could manifest as a difference in either the T or N stage of the subsequent disease. To our knowledge, no prior study has discussed the relationship of prior circumcision with the presenting tumor stage. In order to do so, we performed a retrospective cohort study.

Large clinical datasets of patients with PSCC are uncommon given the rarity of the disease[3]. We have collaborated on an international, multicenter retrospective database of 1254 penile cancer patients diagnosed from 1980 to 2019 in the United States, Europe, Brazil, and China. Previous publications from our group have discussed correlates of chemotherapy and lymph node dissection use by participating institutions[4–6], and association between human papillomavirus (HPV) infection and radiosensitivity[7]. For this report, we analyzed the relation between circumcision and presenting T and N stage. Patients treated with circumcision during the surgery of the primary lesion or those without data on time of circumcision were excluded.

## Key Words

Penile cancer, cancer staging, circumcision

## Competing Interests

None declared.

## Article Information

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For this analysis, 710 patients met the inclusion criteria (Figure 1). Patient characteristics are summarized in Table 1. Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuous variables. The statistical significance of differences in medians and proportions between circumcised and uncircumcised men with penile cancer was tested with the Kruskal-Wallis and chi-square tests, respectively.

Analyses were organized in several steps. First, we explored predictors of inguinal lymph node metastases (ILNM) among several variables including circumcision, histology (squamous cell versus non-squamous cell), T stage (T< 2 versus T2 versus T3–T4), age at penile cancer diagnosis, use of perioperative chemotherapy, surgical procedure to the primary (total penectomy versus partial penectomy versus no surgery/local surgical procedures). The choice of the predictors for this multivariable model has been made based on clinical relevance. Second, to assess whether the higher risk of ILNM in locally advanced tumors (T3–T4) was different by circumcision status, we tested an interaction with T stage and circumcision. Third, we depicted the probability of inguinal lymph node metastases for circumcised and uncircumcised men with penile cancer across T sub-stages.

**FIGURE 1.**

Inclusion/exclusion criteria and study population

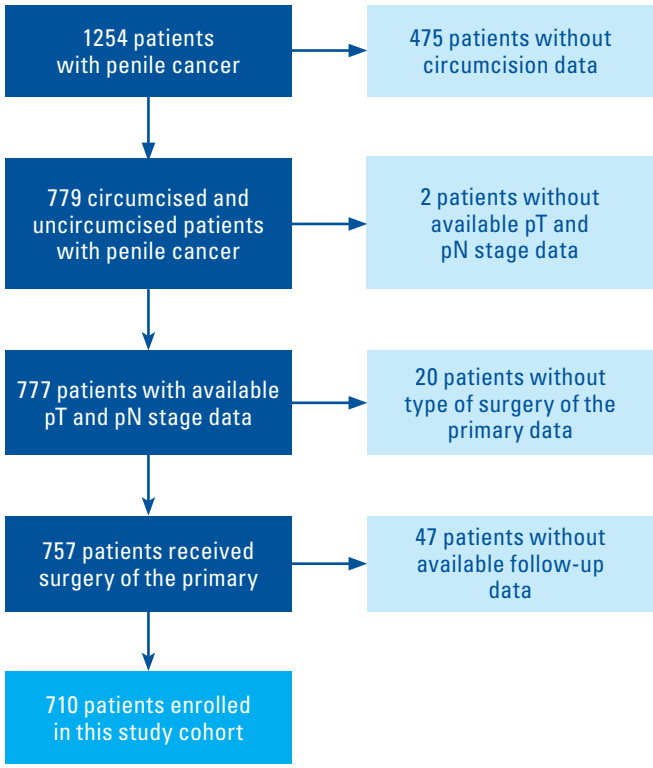



**TABLE 1.**

Epidemiological, geographical, and disease-specific characteristics of 710 penile cancer patients treated within 9 tertiary referral institutions

| Variable | | Overall (n = 710) | Circumcised (n = 550) | Not circumcised (n = 160) | *P*-value |
|---|---|---|---|---|---|
| **Median age at diagnosis (range)** | | 59 (50–69) | 59 (50.2–68.8) | 58 (48.8–69) | 0.98 |
| **Median ILMN (range)** | | 13.3 (4.3–25) | 13.3 (4.8–25) | 12.5 (0–26.8) | 0.89 |
| **Geographical areas (%)** | **Europe** | 388 (54.6) | 304 (55.3) | 84 (52.5) | < 0.001 |
| | **Brazil** | 173 (24.4) | 145 (26.4) | 28 (17.5) | |
| | **United Kingdom** | 77 (10.8) | 66 (12) | 11 (6.9) | |
| | **United States** | 72 (10.1) | 35 (6.4) | 37 (23.1) | |
| **HPV infection (%)** | **Yes** | 371 (52.3) | 284 (51.6) | 87 (54.4) | 0.21 |
| | **No** | 38 (5.4) | 26 (4.7) | 12 (7.5) | |
| | **NA** | 301 (42.4) | 240 (43.6) | 61 (38.1) | |
| **Smoking habit (%)** | **Current or former** | 246 (34.6) | 204 (37.1) | 42 (26.2) | 0.04 |
| | **Never** | 166 (23.4) | 121 (22) | 45 (28.1) | |
| | **NA** | 298 (42) | 225 (40.9) | 73 (45.6) | |

*CHT: chemotherapy; ILNM: inguinal lymph node metastasis; LND: lymph node dissection; RT: radiotherapy; SCC: squamous cell carcinoma*

**TABLE 1.**

Epidemiological, geographical, and disease-specific characteristics of 710 penile cancer patients treated within 9 tertiary referral institutions

| Variable | | Overall (n = 710) | Circumcised (n = 550) | Not circumcised (n = 160) | *P*-value |
|---|---|---|---|---|---|
| **Histology (%)** | **SCC** | 622 (87.6) | 477 (86.7) | 145 (90.6) | 0.21 |
| | **Non-SCC** | 88 (12.4) | 73 (13.3) | 15 (9.4) | |
| **pT stage (%)** | **pT<2** | 277 (39) | 190 (34.5) | 87 (54.4) | < 0.001 |
| | **pT2** | 279 (39.3) | 235 (42.7) | 44 (27.5) | |
| | **pT3-4** | 154 (21.7) | 125 (22.7) | 29 (18.1) | |
| **pN stage (%)** | **Nx-N0** | 230 (32.4) | 182 (33.1) | 48 (30) | 0.60 |
| | **N1-N2** | 193 (27.2) | 151 (27.5) | 42 (26.2) | |
| | **N3** | 287 (40.4) | 217 (39.5) | 70 (43.8) | |
| **Inguinal LND (%)** | **Bilateral** | 479 (67.5) | 364 (66.2) | 115 (71.9) | 0.01 |
| | **Unilateral** | 143 (20.1) | 107 (19.5) | 36 (22.5) | |
| | **Not performed** | 88 (12.4) | 79 (14.4) | 9 (5.6) | |
| **Node metastasis side (%)** | **Negative ILNM** | 112 (15.8) | 78 (14.2) | 34 (21.2) | 0.1 |
| | **Bilateral ILNM** | 174 (24.5) | 133 (24.2) | 41 (25.6) | |
| | **Unilateral ILNM** | 158 (22.3) | 120 (21.8) | 120 (21.8) | |
| | **ILND not performed** | 21 (3) | 19 (3.5) | 2 (1.2) | |
| | **NA** | 245 (34.5) | 200 (36.4) | 45 (28.1) | |
| **Type of surgery of the primary penile lesion (%)** | **Total penectomy** | 162 (22.8) | 141 (25.6) | 21 (13.1) | < 0.001 |
| | **No surgery/ local procedures** | 97 (13.7) | 40 (7.3) | 57 (35.6) | |
| | **Partial penectomy** | 451 (63.5) | 369 (67.1) | 82 (51.2) | |
| **Perioperative CHT (%)** | **No CHT** | 328 (46.2) | 249 (45.3) | 79 (49.4) | 0.02 |
| | **CHT** | 258 (36.3) | 193 (35.1) | 65 (40.6) | |
| | **NA** | 124 (17.5) | 108 (19.6) | 16 (10) | |
| **Perioperative RT (%)** | **No RT** | 509 (71.7) | 388 (70.5) | 121 (75.6) | < 0.01 |
| | **RT** | 82 (11.5) | 57 (10.4) | 25 (15.6) | |
| | **NA** | 119 (16.8) | 105 (19.1) | 14 (8.8) | |
| **Pelvic LND (%)** | **No** | 366 (51.5) | 271 (49.3) | 95 (59.4) | 0.01 |
| | **Yes** | 264 (37.2) | 207 (37.6) | 57 (35.6) | |
| | **NA** | 80 (11.3) | 72 (13.1) | 8 (5) | |

*CHT: chemotherapy; ILNM: inguinal lymph node metastasis; LND: lymph node dissection; RT: radiotherapy; SCC: squamous cell carcinoma*

**TABLE 2a.**

Univariable and multivariable analysis testing the risk of ILMN according to several predictors

| | Univariable analysis | | | | Multivariable analysis | | | |
|---|---|---|---|---|---|---|---|---|
| Covariates | OR | 5% | 95% | *P*-value | OR | 5% | 95% | *P*-value |
| Previous circumcision | 0.72 | 0.46 | 1.14 | 0.2 | 0.63 | 0.36 | 1.10 | 0.1 |
| Non-SCC histology | 5.19 | 2.10 | 17.28 | 0.002 | 2.82 | 1.00 | 10.17 | 0.07 |
| pT2 stage (ref T < 2) | 1.36 | 0.87 | 2.14 | 0.2 | 1.82 | 1.06 | 3.15 | 0.03 |
| pT3-T4 stage (ref T < 2) | 2.22 | 1.25 | 4.14 | 0.009 | 2.83 | 1.42 | 5.86 | 0.004 |
| Age at diagnosis | 1.01 | 0.99 | 1.02 | 0.4 | 1.01 | 0.99 | 1.03 | 0.2 |
| Perioperative CHT unknown (ref. no perioperative CHT) | 13.62 | 4.11 | 84.31 | < 0.001 | 7.36 | 1.92 | 48.71 | 0.01 |
| Perioperative CHT (ref. no perioperative CHT) | 9.59 | 5.40 | 18.42 | < 0.001 | 10.57 | 5.88 | 20.54 | < 0.001 |
| Total penectomy versus no surgery/local surgical procedures | 0.90 | 0.46 | 1.83 | 0.9 | 2.42 | 0.97 | 6.20 | 0.06 |
| Total penectomy versus partial penectomy | 0.96 | 0.58 | 1.56 | 0.9 | 1.28 | 0.71 | 2.26 | 0.4 |

*CHT: chemotherapy; OR: odds ratio; SCC: squamous cell carcinoma*

**TABLE 2b.**

Interaction between circumcision and pT stage for prediction of lymph node invasion adjusted for all the other covariates: histology, age, perioperative CHT, surgical procedure on the primary penile lesion

| Variable | OR | 5% | 95% | *P*-value |
|---|---|---|---|---|
| Previous circumcision*T2 stage | 0.48 | 0.14 | 1.61 | 0.2 |
| Previous circumcision*T3-T4 stage | 0.21 | 0.04 | 0.92 | 0.03 |

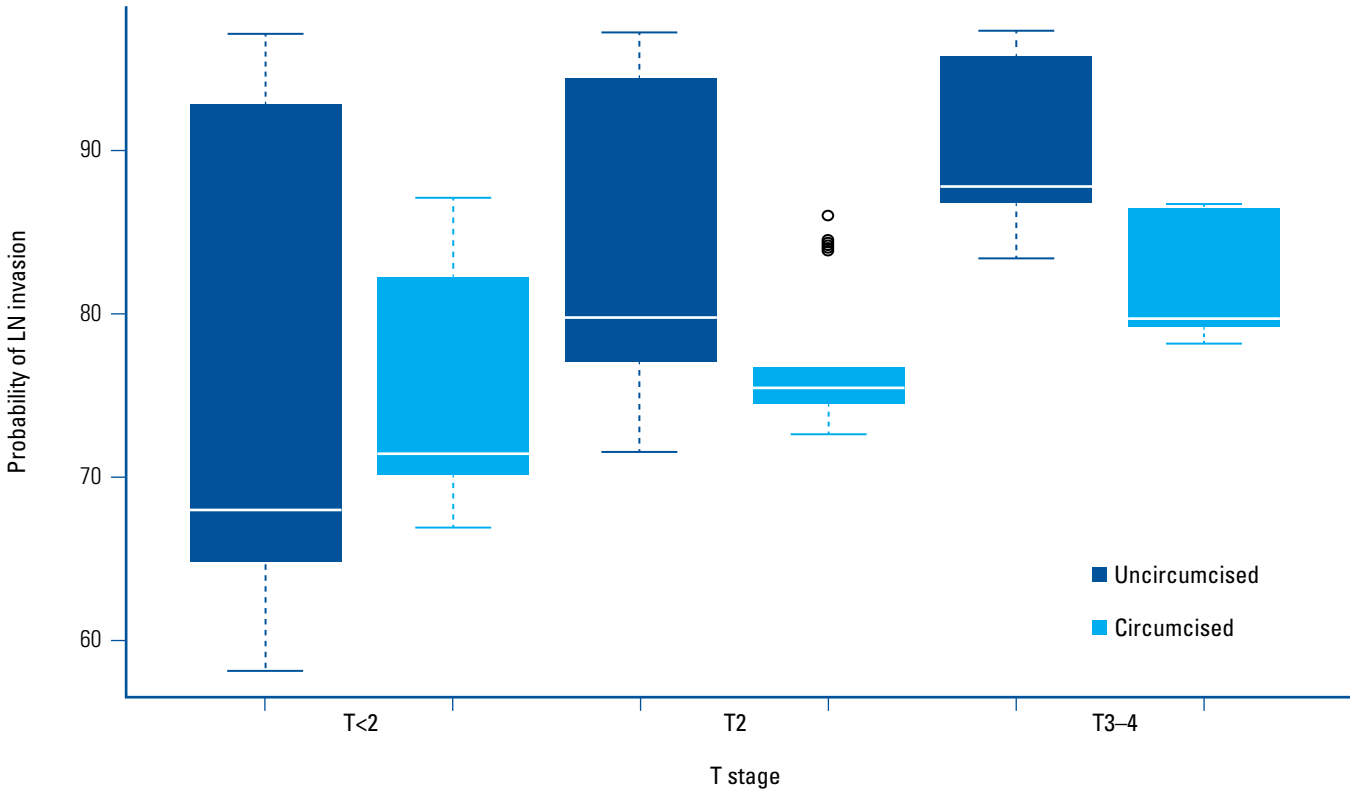
Uncircumcised patients harbored T< 2 tumors more frequently than did circumcised men (54.4% versus 34.5%; $P < 0.001$) (Table 1). No statistical difference was found regarding N stage between circumcised and uncircumcised men. Furthermore, circumcision rates differed with smoking and geographic patient variables, and with several treatment variables including extent of surgery and delivery of chemotherapy and radiotherapy. Multivariable analyses showed a clear and expected association between advanced pT stages and higher risk of ILNM, as well as between use of perioperative chemotherapy and higher risk of ILNM. Conversely, no association was found between circumcision and the risk of ILNM. Nevertheless, we found that circumcision, compared with no-circumcision, conferred a lower risk of ILNM (Table 2) in patients with locally advanced tumors (T3–T4). The risk of ILNM according to T stage in circumcised versus uncircumcised penile cancer patients is depicted in Figure 2.

Debate continues about the potential role of circumcision in subsequent development of PSCC[8,9]. To our knowledge, no prior study has discussed the association of prior circumcision with tumor stage at presentation. Our data reveal correlations between circumcision and PSCC staging. First, there is an association of prior circumcision with presenting T stage on multivariable analysis. Second, there is no association of circumcision with presenting N stage. These findings suggest there may be a difference in local microbiota in uncircumcised compared with circumcised individuals, which might contribute to development of PSCC.

Limitations of this analysis include a lack of broad generalizability, since data are lacking from Africa, India, and most of South America, and we consider our coverage of North America and Europe to be suboptimal. Lack of data on HPV status on these patients is a limitation in terms of understanding its potential etiology in penile cancer, most notably in non-circumcised men. Specific analysis of large populations with equal access to health care would help clarify the potential role of the genital microbiome in this process.

**FIGURE 2.**

Risk of ILNM according to T-stage in circumcised versus uncircumcised penile cancer patients




*ILNM: inguinal lymph node metastasis*

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