|  |  |
| --- | --- |
| A graph of a number of months  Description automatically generated  **(A)** | A graph of a graph  Description automatically generated with medium confidence  **(B)** |
| A graph of a patient  Description automatically generated with medium confidence  **(C)** | A graph of a graph  Description automatically generated with medium confidence  **(D)** |
| A graph of a graph showing the growth of a patient  Description automatically generated with medium confidence  **(E)** | A graph of a patient  Description automatically generated  **(F)** |
| A graph of a graph  Description automatically generated with medium confidence  **(G))** |  |
| **Figure S1.** (A) Kaplan-Meier curve for follow-up detection of CIN2+ by HR-HPV post-LLETZ (p log-rank < 0.001). (B) Kaplan-Meier curve for follow-up detection of CIN2+ by margin status (p log-rank < 0.001). (C) Kaplan-Meier curve for follow-up detection of CIN2+ by margin status for positive HR-HPV post-LLETZ (p log-rank < 0.001). (D) Kaplan-Meier curve for follow-up detection of CIN2+ by margin status for negative HR-HPV post-LLETZ (p log-rank = 0.122). (E) Kaplan-Meier curve for follow-up detection of CIN2+ by age of the patients (p log-rank = 0.013). (F) Kaplan-Meier curve for follow-up detection of CIN2+ by age for positive HR-HPV post- LLETZ (p log-rank < 0.001). (G) Kaplan-Meier curve for follow-up detection of CIN2+ by age for negative HR-HPV post-LLETZ (p log-rank = 0.636). | |

**Table S1.** Univariate analysis of predictive factors associated with follow-up detection of CIN2+ after large loop excision of the transformation zone (LLETZ).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristics** | **Total**  **n** | **CIN2+**  **n (%)** | **HR** | **95% CI** | **P-value\*** |
| **Age at the time of LLETZ (years)** | | | | | |
| < 35 years old | 181 | 7 (3.8) | Ref. |  | Ref. |
| ≥ 35 years old | 251 | 25 (9.9) | 2.84 | (1.20-6.70) | **0.017** |
| **Age (years)** |  |  |  |  |  |
| Median (min-max) | 36.1 (18.3-77) | 39.2 (24-62) | 1.02 | (0.99-1.06) | 0.184 |
| **Smoking habit** |  |  |  |  |  |
| No | 195 | 14 (7.2) | Ref. |  | Ref. |
| Yes | 209 | 15 (7.2) | 0.93 | (0.45-1.93) | 0.850 |
| Unknown | 28 | 3 (10.7) | 1.51 | (0.42-5.41) | 0.526 |
| **Parity** |  |  |  |  |  |
| Nulliparous | 118 | 7 (5.9) | Ref. |  | Ref. |
| < 4 full term births | 264 | 18 (6.8) | 1.08 | (0.45-2.59) | 0.862 |
| ≥ 4 full-term births | 15 | 4 (26.7) | 4.99 | (1.46-17.1) | **0.010** |
| Unknown | 35 | 3 (8.6) | 1.19 | (0.30-4.75) | 0.802 |
| **Contraceptive method** |  |  |  |  |  |
| Nothing | 77 | 7 (9.1) | Ref. |  | Ref. |
| Hormonal | 113 | 10 (8.8) | 0.59 | (0.20-1.68) | 0.321 |
| IUD | 47 | 3 (6.4) | 1.04 | (0.39-2.72) | 0.944 |
| Condom | 130 | 7 (5.4) | 0.60 | (0.15-2.38) | 0.471 |
| Others | 19 | 2 (10.5) | 1.09 | (0.22-5.43) | 0.916 |
| **HPV vaccine prior to or after LLETZ** | | | | | |
| No | 326 | 24 (7.4) | Ref. |  | Ref. |
| Yes | 91 | 7 (7.7) | 1.19 | (0.51-2.78) | 0.696 |
| **HR-HPV result (HC2 and Cobas 4800)** | | | | | |
| **First HR-HPV post-LLETZ** |  |  |  |  |  |
| Negative | 332 | 12 (3.6) | Ref. |  | Ref. |
| Positive | 100 | 20 (20.0) | 5.98 | (2.92-12.3) | **< 0.001** |
| **First RLU HR-HPV post-LLETZ** | | | | | |
| Median (Min-Max) | 0.21 (0.06-3249.9) | 0.23 (0.07-561.43) | 1.00 | (0.99-1.01) | 0.604 |
| **First RLU HR-HPV post-LLETZ category** | | | | | |
| Negative | 301 | 12 (37.5) | Ref. |  | Ref. |
| 1-100 pg/ml | 60 | 7 (11.7) | 2.86 | (1.12-7.26) | **0.027** |
| > 100 pg/ml | 27 | 9 (33.3) | 11.0 | (4.60-26.2) | **< 0.001** |
| Unknown | 44 | 4 (9.1) | 2.98 | (0.93-9.56) | 0.067 |
| **Surgical specimen characteristics** | | | | | |
| **Margin status** |  |  |  |  |  |
| Clear | 232 | 8 (3.4) | Ref. |  | Ref. |
| Ecto+/endo- | 68 | 3 (4.4) | 1.43 | (0.38-5.38) | 0.600 |
| Ecto-/endo+ | 70 | 12 (17.1) | 5.64 | (2.30-13.8) | **< 0.001** |
| Ecto+/endo+ | 11 | 2 (18.2) | 6.86 | (1.45-32.5) | **0.015** |
| Endo+/deep+ | 2 | 0 (0.00)\*\* | 0.00 | (0.00) | 0.999 |
| All | 4 | 0 (0.00)\*\* | 0.00 | (0.00) | 0.998 |
| **Table 1.** (Continued) |  |  |  |  |  |
| **Characteristics** | **Total**  **n** | **CIN2+**  **n (%)** | **HR** | **95% CI** | **P-value\*** |
| Deep | 2 | 0 (0.00)\*\* | 0.00 | (0.00) | 0.999 |
| Uncertain | 43 | 7 (16.3) | 5.54 | (1.99-15.4) | **0.001** |
| **Margin status category** |  |  |  |  |  |
| Clear | 232 | 8 (3.4) | Ref. |  | Ref. |
| Involved | 157 | 17 (10.8) | 3.56 | (1.53-8.25) | **0.003** |
| Uncertain | 43 | 7 (16.3) | 5.53 | (1.99-15.4) | **0.001** |
| **Type of excision** |  |  |  |  |  |
| Type 11 | 141 | 12 (8.5) | Ref. |  |  |
| Type 22 | 199 | 15 (7.5) | 0.92 | (0.33-2.56) | 0.540 |
| Type 33 | 92 | 5 (5.4) | 0.71 | (0.22-2.29) | 0.272 |
| **Length (mm)**4 |  |  |  |  |  |
| Median (IQR) | 10.0 (7.0-15.0) | 9.5 (7.0-13.0) | 0.84 | (0.37-1.94) | 0.688 |
| **Thickness (mm)**5 |  |  |  |  |  |
| Median (IQR) | 10.5 (9.5-12.5) | 10.0 (9.0-13.0) | 0.34 | (0.08-1.44) | 0.143 |
| **Circumference (mm)**6 |  |  |  |  |  |
| Median (IQR) | 103.0 (90.6-120.0) | 99.0 (85.5-119.0) | 0.92 | (0.78-1.10) | 0.363 |
| **Volume Carcopino (cm³)**7 |  |  |  |  |  |
| Median (IQR) | 3.94 (2.27-6.18) | 3.66 (1.60-7.24) | 0.98 | (0.88-1.10) | 0.761 |
| **Volume Phadnis (cm³)**8 |  |  |  |  |  |
| Median (IQR) | 2.18 (1.31-3.50) | 1.96 (1.19-2.93) | 0.86 | (0.65-1.12) | 0.263 |
| **Quadrants involved** |  |  |  |  |  |
| 1-2 | 203 | 13 (6.4) | Ref. |  | Ref. |
| 3-4 | 158 | 16 (10.1) | 0.54 | (0.12-2.43) | 0.429 |
| Not valuable | 18 | 2 (11.1) | 0.93 | (0.21-4.09) | 0.933 |
| Unknown | 53 | 1 (1.9) | 0.19 | (0.01-2.18) | 0.185 |
| **Total** | 432 | 32 (7.4) |  |  |  |

CI, confidence interval; HR, hazard ratio; LLETZ, large loop excision of the transformation zone; IUD, intrauterine device; HPV, human papilloma virus; HR-HPV, high-risk human papilloma virus; RLU, relative light unit; Ecto, ectocervical; Endo, endocervical; IQR, interquartile range (25-75%). 1Length of <10 mm. 2Length of 10-15 mm. 3Length of 15-25 mm. 4The distance from the external margins to the internal margins, with data available from 307 cases for inclusion in the analysis.  5The distance from the stromal margins to the surface of the excised specimen. 6The perimeter of the excised specimen, formula: 2\*3.14159\*sqrt((cone amplitude^2+cone depth^2)/2), with data available from 363 cases for inclusion in the analysis. 7Volume = (1/2) (4/3) π x length x (circumference /2π) x thickness, with data available from 305 cases for inclusion in the analysis. 8Volume = 1/2 (4/3) π (a/2) (b/2) c [a: transverse diameter, b: longitudinal diameter, c: depth of the cone biopsy] with data available from 302 cases for inclusion in the analysis. Values in bold indicate significant differences between study groups. \*Log-likelihood ratio test p-value. \*\*No recurrences observed in the category.

**Table S2.** Association between type of excision, length of the cone, age of the women, and first HR-HPV post -LLETZ with ectocervical and endocervical margins of the surgical specimen in women treated with large loop excision of the transformation zone (LLETZ) for cervical intraepithelial neoplasia 2-3 (CIN2+).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **n = 138\*\*** | **EctocervicaL margin involvement**  **n= 68** | **EndocervicaL margin involvement**  **n = 70** | **OR (95% CI)** | **P-value\*\*\*** |
| **Type of excision** |  |  |  |  |  |
| Type 1, n (%)**\*** | 46 (33.3) | 23 (50.0) | 23 (50.0) | Ref. | Ref. |
| Type 2, n (%)**\*** | 70 (50.7) | 34 (48.6) | 36 (51.4) | 1.01 (0.44-2.32) | 0.985 |
| Type 3, n (%)**\*** | 22 (15.9) | 11 (50.0) | 11 (50.0) | 0.98 (0.32-3.20) | 0.979 |
| **Length (cm)** |  |  |  |  |  |
| Median (IQR) | 1.00 (0.70-1.37) | 1.00 (0.70-1.33) | 1.00 (0.70-1.37) | 1.29 (0.62-2.68) | 0.496 |
| **Age (years)** |  |  |  |  |  |
| < 35 years old, n (%)\* | 53 (38.4) | 30 (56.6) | 23 (43.4) | Ref. | Ref. |
| ≥ 35 years old, n (%)\* | 85 (61.6) | 38 (44.7) | 47 (55.3) | 0.767 (0.445-1.320) | 0.338 |
| **First HR-HPV post-LLETZ** | | | | | |
| Negative, n (%)\* | 110 (79.7) | 58 (52.7) | 52 (47.3) | Ref. | Ref. |
| Positive, n (%)\* | 28 (20.3) | 10 (35.7) | 18 (64.3) | 1.800 (0.831-3.899) | 0.136 |

CI, confidence interval; ORodd ratio; IQR, interquartile range (25-75%); HR-HPV, high-risk human papilloma virus; LLETZ, large loop excision of the transformation zone; **\***row percentage; \*\*Column percentage**;** \*\*\* Log-likelihood ratio test p-value.