**UNIVERSIDADE ESTADUAL DE CAMPINAS**
**FACULDADE DE CIÊNCIAS MÉDICAS**

**JULIANA YOKO YONEDA**

# AVALIAÇÃO DOS RESULTADOS DE EXCISÕES DA ZONA DE TRANSFORMAÇÃO COM ALÇA EM MULHERES COM LESÕES PRECURSORAS DO CÂNCER DO COLO DO ÚTERO TRATADAS EM UM SERVIÇO DE REFERÊNCIA

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Tese apresentada à Faculdade de Ciências Médicas da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutora em Ciências da Saúde, na área de concentração Oncologia Ginecológica e Mamária

**ORIENTADORA**: PROF. DRA. DIAMA BHADRA ANDRADE PEIXOTO DO VALE
**CO-ORIENTADORA:** PROF. DRA. JOANA FRÓES DE BRAGANÇA BASTOS

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**JULIANA YOKO YONEDA**

ORIENTADORA: PROFA. DRA. DIAMA BHADRA ANDRADE PEIXOTO DO VALE

CO-ORIENTADORA: PROFA. DRA. JOANA FRÓES BRAGANÇA BASTOS

| **MEMBROS** |
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| 2. Profa. Dra. Cássia Raquel Teatin Juliato |
| 3. Prof. Dr. Luiz Franciso Cintra Baccaro |
| 4. Profa. Dra. Silvana Maria Quintana |
| 5. Prof. Dr. Fábio Bastos Russomano |

Programa de Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas.

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**Dedico este trabalho:**

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*...E o futuro é uma astronave*
*Que tentamos pilotar*
*Não tem tempo, nem piedade*
*Nem tem hora de chegar*
*Sem pedir licença*

*Muda a nossa vida*
*E depois convida*
*A rir ou chorar...*
*Nessa estrada não nos cabe*
*Conhecer ou ver o que virá*
*O fim dela ninguém sabe*
*Bem ao certo onde vai dar*
*Vamos todos*
*Numa linda passarela*
*De uma aquarela*
*Que um dia enfim*
*Descolorirá...*

*Toquinho*

**RESUMO**

Frente à importância da prevenção secundária no combate ao câncer do colo do útero (CCU), a identificação de fatores associados ao sucesso do tratamento de lesões precursoras pode auxiliar na elaboração de condutas mais adequadas. A identificação dos casos mais propensos a recidiva e progressão para CCU é fundamental para traçar protocolos de seguimento após tratamento. **Objetivos:** Avaliar os resultados associados ao tratamento das lesões precursoras do CCU em mulheres submetidas a excisão da zona de transformação com alça em um serviço de referência. Objetivos específicos foram 1) Avaliar fatores relacionados à obtenção de margem endocervical negativa; 2) Avaliar resultados de acordo com o tipo de zona de transformação nos diferentes tipos de excisão; 3) Avaliar resultados nas pacientes submetidas ao método rastrear-e-tratar; e 4) Avaliar resultados nas pacientes submetidas ao reforço endocervical complementar ao fragmento principal. **Métodos:** Estudo de coorte retrospectiva pela revisão de registros de prontuário de mulheres submetidas à excisão da zona de transformação por cirurgia de alta frequência por lesões precursoras do CCU no Hospital da Mulher Prof. Dr. José Aristodemo Pinotti, da Universidade Estadual de Campinas (CAISM/Unicamp), de 2017 a 2020. Mulheres com resultados de citologia e/ou biópsia anormais foram encaminhadas ao Ambulatório de Patologias do Trato Genital Inferior. Foram incluídas todas as 734 mulheres que realizaram o procedimento no período de estudo. Os critérios de exclusão variaram de acordo com os objetivos da análise, sendo o critério comum ter sido submetida anteriormente à procedimento excisional no colo. **Resultados principais** e **conclusões**: **Artigo 1:** A proporção de margem endocervical negativa foi de 78% na excisão do tipo I e 86% na excisão do tipo II. O início sexual tardio e a excisão do tipo II aumentaram a chance de ser alcançada uma margem endocervical negativa. Esse benefício marginal deve ser contrabalançado com os riscos associados ao procedimento: realizar um procedimento mais conservador parece seguro e reduz morbidades, especialmente em mulheres jovens. **Artigo 2:** O status da margem endocervical foi negativo em pelo menos três de cada quatro mulheres submetidas à excisão, independentemente se do tipo I ou II. A excisão do tipo I apresentou resultados satisfatórios em mulheres na pré-menopausa e zona de transformação dos tipos 1 ou 2. **Artigo 3:** O diagnóstico final negativo após a excisão não foi significativamente maior nas mulheres conduzidas pelo método rastrear-e-tratar. O método foi adequado para mulheres encaminhadas por citologia de alto grau e com

achados colposcópicos compatíveis. **Artigo 4:** O diagnóstico final das mulheres submetidas ao reforço endocervical não foi alterado e não foi observado impacto na recidiva. O procedimento deve ser evitado em mulheres em idade reprodutiva.

**Palavaras chave**: Colo do útero; Displasia do colo do útero; Conização; Colposcopia; Exame colpocitológico; Recidiva.

**ABSTRACT**

Given the importance of secondary prevention in the fight against cervical cancer (CC), the identification of factors associated with the success of the treatment of precursor lesions can help in developing more appropriate approaches. Identification of cases most prone to recurrence and progression to CC is essential for designing follow-up protocols after treatment. Objectives: To evaluate the results associated with the treatment of precursor lesions of CC in women undergoing excision of the transformation zone with a loop in a reference service. Specific objectives were 1) Evaluate factors related to obtaining a negative endocervical margin; 2) Evaluate results according to the type of transformation zone in different types of excision; 3) Evaluate results in patients undergoing the track-and-treat method; and 4) Evaluate results in patients undergoing endocervical reinforcement complementary to the main fragment. Methods: Retrospective cohort study by reviewing medical records of women who underwent excision of the transformation zone by high-frequency surgery for precursor lesions of CC at Hospital da Mulher Prof. Dr. José Aristodemo Pinotti, from the State University of Campinas (CAISM/Unicamp), from 2017 to 2020. Women with abnormal cytology and/or biopsy results were referred to the Lower Genital Tract Pathology Outpatient Clinic. All 734 women who underwent the procedure during the study period were included. The exclusion criteria varied according to the objectives of the analysis, with the common criterion being having previously undergone an excisional procedure on the cervix.

Main results and conclusions: Article 1: The proportion of negative endocervical margin was 78% in type I excision and 86% in type II excision. Late sexual onset and type II excision increased the chance of achieving a negative endocervical margin. This marginal benefit must be balanced against the risks associated with the procedure: performing a more conservative procedure appears

safe and reduces morbidities, especially in young women. Article 2: Endocervical margin status was negative in at least three of every four women undergoing excision, regardless of whether type I or II. Type I excision showed satisfactory results in premenopausal women and types 1 or 2 transformation zone. Article 3: The final negative diagnosis after excision was not significantly higher in women managed by the track-and-treat method. The method was suitable for women referred for high-grade cytology and with compatible colposcopic findings. Article 4: The final diagnosis of women undergoing endocervical reinforcement was not changed and no impact on recurrence was observed. The procedure should be avoided in women of reproductive age.

**Keywords**: Cervix Uteri; Uterine Cervical Displasia; Conization; Colposcopy; Papanicolaou Test; Recurrence.

**LISTA DE ABREVIATURAS E SIGLAS**

| | |
|---|---|
| % | Porcentagem |
| > | Maior |
| ≥ | Maior ou igual |
| < | Menor |
| ≤ | Menor ou igual |
| AGC | Células Glandulares Atípicas |
| AIDS | Síndrome da Imunodeficiência Adquirida |
| AIS | Adenocarcinoma in situ |
| ASCCP | American Society for Colposcopy and Cervical Pathology |
| ASC-H | Células Escamosas Atípicas não podendo excluir Lesão Intraepitelial de Alto Grau |
| ASCUS | Células Escamosas Atípicas de Significado Indeterminado, possivelmente não neoplásicas |
| CAF | Cirurgia de Alta Frequência |
| CAISM | Centro de Atenção Integral à Saúde da Mulher |
| CCU | Câncer do Colo do Útero |
| CEP | Comitê de Ética em Pesquisa |
| cm | Centímetros |
| DNA | Ácido Desoxirribonucleico |
| EZT | Excisão da Zona de Transformação |
| HIV | Human Immunodeficiency Virus |
| HPV | Papilomavírus Humano |
| HSIL | Lesão Intraepitelial Escamosa de Alto Grau |
| IC | Intervalo de Confiança |
| IDH | Índice de Desenvolvimento Humano |
| INCA | Instituto Nacional de Câncer |
| JEC | Junção Escamo-colunar |
| LEEP | Loop Electrosurgical Excision Procedure |
| LLETZ | Large Loop Excision of the Transformation Zone |
| LSIL | Lesão Intraepitelial Escamosa de Baixo Grau |
| mm | Milímetros |

| | |
|---|---|
| n | Frequência Absoluta |
| NIC | Neoplasia Intraepitelial Cervical |
| OMS | Organização Mundial da Saúde |
| OR | Odds Ratio |
| *p* | Nível de Significância Estatística |
| PNI | Programa Nacional de Imunização |
| R&T | Rastrear e Tratar |
| UNICAMP | Universidade Estadual de Campinas |
| ZT | Zona de Transformação |

**SUMÁRIO**

## 1. INTRODUÇÃO

O câncer do colo do útero (CCU) é um importante problema de saúde pública, e persiste como uma das principais causas de morte por câncer em mulheres, apesar dos avanços no diagnóstico, tratamento e da introdução da vacinação profilática contra o papilomavírus humano (HPV) (1). Estima-se que em 2020 tenham sido diagnosticados aproximadamente 604.000 casos novos no mundo e que tenham ocorrido 342.000 mortes por essa causa, configurando assim o quarto tipo de câncer mais comum entre mulheres, e a quarta causa de morte por câncer nessa população (2).

Calcula-se que mais de 85% dos casos ocorram em regiões com menor índice de desenvolvimento humano (IDH), onde contabilizam mais de 13% dos cânceres da população feminina, sendo a maioria dos casos encontrados na África Subsaariana, Melanésia, América do Sul e Sudeste Asiático (3). A maior taxa de incidência e de mortalidade do mundo acontece na África Subsaariana. A falha no sistema de rastreamento e detecção precoce do CCU nos países com baixo IDH se deve à falta de recursos e infraestrutura, além de sistemas de saúde de baixa resolutividade e dificuldade de conscientização da população (4).

No Brasil, a estimativa é de aproximadamente 17.010 casos novos para cada ano no triênio 2023-2025, com risco estimado de 15,38 casos para cada 100.000 mulheres, sendo o terceiro tipo de câncer mais comum na população feminina brasileira. A estimativa de mortalidade mais recente aponta 6.627 óbitos em 2020, com taxa bruta de mortalidade de 6,12 para cada 100.000 mulheres. Observa-se no Brasil diferenças regionais, diretamente associadas ao desenvolvimento socioeconômico de cada região, e da facilidade ao acesso aos serviços de saúde, sendo o segundo tipo de câncer mais incidente na região Norte e Nordeste, terceiro na região Centro-Oeste, quarto na região Sul, e quinto na região Sudeste (5).

A história natural do câncer do colo do útero se estende por um período longo e envolve a infecção pelo papilomavírus humano (HPV), persistência da infecção, progressão para lesão precursora e evolução dessa para carcinoma invasor (6). A infecção genital pelo HPV é a infecção sexualmente transmissível mais comum em todo o mundo, afetando 75 a 80% de homens e mulheres de todas as idades (7). No

Brasil, um estudo recente revelou a prevalência de 54,9% de infecção pelo HPV entre mulheres de 16 a 25 anos (8).

O HPV é uma família de DNA vírus que infecta a camada basal das células epiteliais, causando lesões benignas e malignas da pele e mucosa do trato ano genital e orofaringe, e são classificados como alto e baixo risco, de acordo com o seu potencial oncogênico (9), sendo atualmente 12 tipos de HPV classificados como oncogênicos (16, 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, 66), e o HPV 68 possivelmente oncogênico (10). Anualmente, aproximadamente 570.000 casos de câncer em mulheres e 60.000 casos de câncer em homens podem ser atribuídos à infecção pelo HPV, correspondendo à 8,6% e 0,8% dos casos de câncer, respectivamente (11).

A infecção pelo HPV é comum logo após o início de atividade sexual (12), mas a maioria das infecções é não é mais detectável em 12-24 meses (13). Em estudos clínicos e de coorte observacional, constatou-se que a maioria das lesões precursoras são precedidas por infecção persistente pelo HPV, permitindo concluir que o rastreamento através da detecção do DNA-HPV de alto risco é efetivo para prevenção efetiva do CCU (14). A persistência da infecção por HPV por tempo suficiente para causar lesão precursora é influenciada por fatores virais (genéticos e possivelmente epigenéticos); pela resposta imune do hospedeiro e coinfecção por HIV (15), e por fatores comportamentais (como multiparidade, tabagismo, uso prolongado de contraceptivos orais) (16).

Atualmente, o câncer do colo do útero é considerado passível de erradicação, devido à possibilidade de intervenção nas três esferas: primária, secundária e terciária (2). Prevenção primária por meio da vacinação profilática contra HPV, secundária pelo rastreamento e tratamento de lesões precursoras, e terciária pelo diagnóstico e tratamento precoce das lesões invasivas.

Em 2018, frente à baixa eficiência das políticas atuais, e crescente inequidades, o diretor geral da Organização Mundial da Saúde (OMS) fez um chamado para eliminação do CCU, objetivando a redução de incidência para abaixo de 4 casos para cada 100.000 mulheres no mundo, por meio de três metas para serem alcançadas até o ano de 2030: 1) vacinação de 90% de todas as meninas até a idade de 15 anos; 2) rastreamento de 70% das mulheres com teste de alta performance aos 35 e 45 anos; 3) tratamento de 90% das mulheres diagnosticadas

com lesões precursoras durante o rastreamento e manejo de 90% das mulheres com lesões invasoras (17). Estima-se que com a implementação dessa estratégia, serão evitados 74 milhões de casos e mais de 62 milhões de mortes no próximo século (18).

Existem atualmente três vacinas profiláticas para prevenção da infecção por HPV de alto risco: Bivalente (Cervarix® GSK), que confere proteção contra HPV 16 e 18, cuja comercialização no Brasil foi interrompida em 2021); Tetravalente (Gardasil®MSD), que confere proteção contra HPV 6, 11,1 6 e 18, e faz parte do calendário nacional de imunização desde o ano de 2014; e Nonavalente (Gardasil-9® GSK), que confere proteção contra HPV 6,11,16,18,31,33,45,52,58, licenciada no ano de 2017 e disponibilizada pela rede privada brasileira em 2023. O programa nacional de imunização (PNI) preconiza a vacinação de meninas e meninos entre 9 e 14 anos de idade (19), com duas doses da vacina quadrivalente (com intervalo de 6 meses) e pessoas com imunossupressão (convivendo com HIV/AIDS, transplantados de órgãos sólidos, medula óssea e pacientes oncológicos), sendo nesse grupo recomendada a realização do esquema de 3 doses (intervalo 0; 1 a 2 e 6 meses). Frente à recente disponibilização no Brasil da vacina nonavalente, embora ainda não seja disponível no Sistema Único de Saúde (SUS), sugere-se dar preferência à sua utilização para iniciar o esquema de vacinação, ou ainda de complementar o esquema de pacientes já vacinadas e com indicação de vacinação pelo calendário do PNI (20).

De acordo com as diretrizes nacionais, o rastreamento deve ser realizado a partir dos 25 anos, com exame citopatológico (intervalo anual entre os dois primeiros exames e após trienal se resultados normais), interrompendo-se aos 64 anos para mulheres sem história prévia de lesões precursoras, e com ao menos dois exames consecutivos negativos nos últimos cinco anos (21). A realização de rastreamento por detecção HPV apresenta maior sensibilidade para detecção de lesão de alto grau e câncer, além de maior valor preditivo negativo, quando comparado ao uso citologia, podendo representar uma alternativa eficaz para situações de rastreamento esporádico (21–23).

No Brasil, o rastreamento do câncer do colo do útero disponibilizado pelo Ministério da Saúde baseia-se no exame citopatológico (21), estando os métodos de detecção de HPV disponíveis na iniciativa privada, com recomendações de uso

publicadas recentemente (24). Quando utilizado teste de HPV, a coleta pode ser iniciada aos 25 anos (dando-se preferência ao uso de genotipagem para evitar sobrediagnóstico), e interrompida a partir dos 65 anos, quando tiver realizado rastreamento efetivo pelos últimos 10 anos. Quando houver história de tratamento de lesão precursora, o rastreamento deve continuar por toda a vida, ou ao menos por 25 anos após o tratamento (24).

Após a detecção de alteração no rastreamento, a paciente é encaminhada para a realização de colposcopia com biópsia dirigida e tratamento das lesões de alto grau (25). A omissão da realização de biópsia dirigida tem sido recomendada em países de baixa renda, onde as múltiplas etapas de tratamento aumentam o risco de perda de seguimento (26). O objetivo do método rastrear-e-tratar, é oferecer tratamento imediato ou muito próximo, e tem sido preconizado pela OMS e pelo INCA, no Brasil (21,27), sendo observado encurtamento do tempo para tratamento, menores perdas de seguimento, e pequena proporção de histologia final negativa (28,29). A preocupação associada ao método rastrear-e-tratar é o sobretratamento, mas quando realizada nas pacientes com diagnóstico citológico de lesão de alto grau, colposcopia adequada e compatível com achados maiores, lesão restrita ao colo e sem suspeita de invasão ou doença glandular, o risco de histologia final negativa é reduzido (30).

A modalidade de tratamento mais utilizada para o tratamento da lesão precursora é a excisão de zona de transformação - EZT (em inglês, LLETZ- large loop excision of the transformation zone ou LEEP- loop electrosurgical excision procedure) (31), podendo ser realizada também conização por bisturi a frio, ou laser. Os métodos ablativos incluem crioterapia, laser, eletro fulguração e cauterização química (32). A escolha da técnica a ser utilizada depende de critérios a serem avaliados pelo examinador, como idade da paciente, paridade, desejo reprodutivo, risco de perda de seguimento, habilidade do examinador e satisfatoriedade da colposcopia (33). Os métodos excisionais têm sido mais recomendados pois permitem avaliação histológica do espécime excisado, confirmam diagnóstico, permitem excluir a presença de neoplasia invasora oculta e avaliação das margens da excisão (32).

Visando a unificação dos termos utilizados para descrever os tipos de procedimentos excisionais e adequar o tratamento para garantir a excisão completa

da zona de transformação (ZT), minimizando os riscos de tratamento incompleto e recidiva de lesão, Prendiville propôs a realização de um tipo de excisão para cada tipo de zona de transformação (34). Assim para ZT tipo 1, completamente ectocervical e visível, visando tratar doença que não se estende por mais de 1 cm no canal endocervical, está indicada a excisão tipo 1. Para tratar doença na ZT tipo 2, é necessário retirar uma porção maior do canal endocervical, o suficiente para ultrapassar a JEC (junção escamo-colunar), sendo necessária retirada de profundidade entre 1,5 e 2,0 cm, que caracteriza a excisão tipo 2. Já para as ZT tipo 3, é necessária maior profundidade, sendo recomendada a retirada entre 2,0 e 2,5 cm do canal na excisão tipo 3.

O reforço endocervical é uma técnica que pode ser realizada para complementação das excisões e consiste em uma segunda passagem de alça para ressecção de maior profundidade do canal endocervical após a realização da excisão tradicional (35). A realização do reforço endocervical foi descrita para pacientes com ZT tipo 3 na colposcopia (36), visando avaliar lesões que se localizam mais profundamente no canal endocervical, ou ainda a detecção de lesões multifocais, mas seu papel prognóstico é controverso (37,38).

Uma particularidade de tratamento ocorre após a detecção de Adenocarcinoma *in situ* (AIS) no rastreamento. Essas mulheres devem ser encaminhadas para a realização de colposcopia e terão indicação de realização de excisão tipo 3, exceto se houver suspeita de invasão, quando deverá ser realizada biópsia de colo. Mulheres com idade superior a 35 anos tem indicação da realização de avaliação endometrial, e abaixo dessa idade, a indicação persiste nos casos de sangramento uterino anormal, e condições sugestivas de anovulação crônica. Após a confirmação do resultado de AIS no espécime de excisão, há indicação de histerectomia simples, exceto nos casos de prole indefinida, em que a excisão poderá ser considerada suficiente (21).

Após a realização da excisão nas lesões escamosas é recomendável que as pacientes permaneçam em seguimento para surpreender uma possível recidiva (39). A prevalência de doença residual e/ou recidiva da lesões escamosas de alto grau após tratamento excisional descritas na literatura variam entre 4 e 18% (40) e a maioria dos casos ocorrerá no período de 2 anos após o tratamento inicial (41). A persistência da infecção por HPV de alto risco oncogênico parece ser a melhor

preditora de risco (42). Outros fatores como antecedente de tabagismo, imunossupressão e multiparidade também tem sido associado à recidiva de NIC (43).

Diversos estudos descrevem a excisão incompleta da lesão, determinada pelo comprometimento de margens, particularmente a endocervical, como um dos principais fatores de risco para a recidiva de doença (42,43). Mulheres mais velhas aparentam ter maiores chances de margens comprometidas, e por consequência, aumento da chance de recidiva (44).

Existe atualmente uma crescente preocupação sobre os efeitos da excisão cervical na integridade da cérvix e especificamente na preservação da sua função durante a gestação (42). Metanálises demonstraram que a profundidade do espécime de excisão está associada com o risco de parto prematuro e que algumas técnicas estão associadas a maior chance de comprometimento dessa função (conização a frio mais que excisão com alça) (44,45). Tem sido proposto profundidade de excisão de 10 mm para mulheres com desejo gestacional, sendo essa profundidade adequada para tratamento, e com menor chance de implicações obstétricas (46). Uma recente revisão sistemática e metanálise recomenda tratamento mais agressivo em mulheres mais velhas, quando não houver mais desejo reprodutivo, e também para casos de suspeita de invasão, alterações glandulares ou colposcopia insatisfatória, aumentando a profundidade da excisão (42).

A adequação do tipo de excisão, determinado pela profundidade de tratamento, juntamente com a identificação de fatores associados à excisão incompleta da lesão e à recidiva de NIC, pode auxiliar na melhora do manejo e do seguimento das pacientes com lesões precursoras, permitindo a identificação de pacientes com maior risco de persistência de lesão ou recidiva, reduzindo o risco de novas lesões e de evolução para carcinoma invasor do colo uterino.

Para o seguimento das mulheres após tratamento, podem ser empregados a citologia, colposcopia e o teste de DNA-HPV (47). Entretanto, como o teste de DNA-HPV não está disponível no Sistema Único de Saúde (SUS), o seguimento recomendado pelas Diretrizes Brasileiras de Rastreamento do Câncer do colo do útero, é indicado de acordo com o status da margem: nos casos de margens livres, seguimento com citologia semestral por 12 meses, com colposcopia a critério do

serviço e citologia anual por 5 anos, e nos casos de margens comprometidas, citologia e colposcopia semestrais por 24 meses, seguidos de citologia anual por 5 anos. Em ambos os casos, após os 5 anos, a mulher deverá manter o rastreamento citopatológico trienal (21).

Quando disponível o seguimento com pesquisa de DNA- HPV, recomenda-se a realização deste com 6 meses, se normal, repetição anual durante 3 anos, e no caso de teste positivo, encaminhamento para colposcopia e biópsia se necessário. Após os primeiros 3 anos, rastreamento trienal até 25 anos pós tratamento (25).

Nos casos de adenocarcinoma *in situ*, as pacientes com prole incompleta deverão ser submetidas à citologia com 6 e 12 meses, após isso anualmente por 5 anos, e trienal a seguir, com indicação de colposcopia à critério do serviço. As pacientes histerectomizadas devem manter seguimento citológico anual por 5 anos e trienal a seguir.

Tendo em vista a importância da prevenção secundária no combate ao câncer do colo do útero, a identificação de fatores associados ao sucesso do tratamento de lesões precursoras, pode auxiliar na elaboração de condutas mais adequadas para o tratamento e seguimento dessas pacientes, através da identificação dos casos mais propensos à novas lesões e progressão para carcinoma invasor do colo do útero.

Este estudo pretendeu avaliar os resultados associados ao tratamento das lesões precursoras do câncer do colo do útero em pacientes submetidas à cirurgia de alta frequência em um serviço de referência. Inicialmente foram avaliados os fatores relacionados à obtenção de margem endocervical negativa. A seguir buscou-se investigar se a recomendação do tipo de excisão de acordo com o tipo de zona de transformação obteve resultados satisfatórios. Após foram avaliados os resultados nas pacientes submetidas ao método rastrear-e-tratar para verificar o risco de excesso de tratamento. Por fim, foi realizada uma avaliação dos resultados nas pacientes submetidas ao reforço endocervical na excisão. Os resultados deste estudo podem auxiliar o médico assistente na tomada de decisões e dar suporte às recomendações para o rastreamento do câncer do colo do útero.

# 2.OBJETIVOS

## 1. Objetivo geral:

Avaliar os resultados associados ao tratamento das lesões precursoras do câncer do colo do útero em pacientes submetidas à cirurgia de alta frequência em um serviço de referência

## 2. Objetivos específicos:

***Objetivo específico 1 (Artigo 1):*** Avaliar os fatores relacionados à obtenção de margem endocervical negativa.
***Objetivo específico 2 (Artigo 2):*** Avaliar os resultados de acordo com o tipo de zona de transformação nos diferentes tipos de excisão.
***Objetivo específico 3 (Artigo 3):*** Avaliar os resultados nas pacientes conduzidas pelo método rastrear-e-tratar.
***Objetivo específico 4 (Artigo 4):*** Avaliar os resultados nas pacientes submetidas ao reforço endocervical na excisão.

# 3. METODOLOGIA

## 3.1. Desenho do estudo

Esse foi um estudo de coorte retrospectivo que avaliou dados de registros de prontuário de mulheres que foram submetidas à excisão da zona de transformação por meio de cirurgia de alta frequência devido à lesão intraepitelial cervical de alto grau no Hospital da Mulher Prof. Dr. José Aristodemo Pinotti, da Universidade Estadual de Campinas (CAISM/Unicamp), entre os anos de 2017 e 2020.

## 3.2. Sujeitos do estudo

Os sujeitos foram todas as mulheres submetidas à tratamento com cirurgia de alta frequência no período do estudo. São mulheres de risco habitual que realizaram o rastreamento por meio da realização de citologia convencional nas Unidades Básicas de Saúde da região, conforme protocolo das Diretrizes de Rastreamento do Câncer do colo de útero do Ministério da Saúde (21).

Mulheres com resultados de citologia e/ou biópsia anormais foram encaminhadas ao Ambulatório de Patologia do Trato Genital Inferior - Colo do Hospital da Mulher José Aristodemo Pinotti – CAISM/Unicamp, na cidade de Campinas, estado de São Paulo. O CAISM é o serviço de referência para tratamento de mulheres da cidade de Campinas e municípios vizinhos, uma área densamente povoada no estado.

## 3.3. Amostra e critérios de inclusão e exclusão

A amostra foi selecionada por conveniência.

### 3.3.1. Critérios de inclusão

Foram incluídas todas as mulheres que realizaram excisão de zona de transformação com alça no período de estudo. As pacientes foram identificadas pela lista de procedimentos acessível no sistema de informação e gerenciamento de informações do CAISM, após aprovação do Comitê de Ética e Pesquisa da Unicamp. No período do estudo foram realizadas 734 excisões com alça em aparelho de alta frequência.

### 3.3.2. Critérios de exclusão

O critério de exclusão comum em todas as análises foi ter sido submetida anteriormente à procedimento excisional no colo. Para cada análise (objetivo específico/artigo), foram determinados os critérios de exclusão pertinentes, apresentados no quadro a seguir.

### 3.3.3. Amostra final

A amostra final das mulheres analisadas foi diferente para cada objetivo específico/artigo, em função dos critérios de exclusão empregados. No quadro são apresentados os critérios que foram atendidos de forma subsequente.

| **Quadro 1. Critérios de exclusão aplicados em sequência nos 734 procedimentos de cirurgia de alta frequência realizados no CAISM de 2017 a 2020, e amostra final para cada objetivo.** | |
|---|---|
| **Objetivos 1 e 2 (Margens e tipo de Zona de Transformação)** | |
| **Amostra final** | 610 casos |
| **Critérios de exclusão** | 59 casos com história de procedimento excisional anterior<br>28 casos com suspeita de micro-invasão ou invasão<br>20 casos cujo tipo de alça de excisão não foi registrado<br>6 casos cujo espécime principal foi fragmentado prejudicando a avaliação das margens<br>11 casos de excisão do tipo 3 |
| **Objetivo 3 (Rastrear-e-tratar)** | |
| **Amostra final** | 524 casos |
| **Critérios de exclusão** | 59 casos com história de procedimento excisional anterior<br>28 casos com suspeita de micro-invasão ou invasão<br>20 casos cujo tipo de alça de excisão não foi registrado<br>6 casos cujo espécime principal foi fragmentado prejudicando a avaliação das margens<br>97 casos encaminhados por citologia ASC-US ou LSIL persistentes |
| **Objetivo 4 (Reforço endocervical)** | |
| **Amostra final** | 440 casos |
| **Critérios de exclusão** | 59 casos com história de procedimento excisional anterior<br>28 casos com suspeita de micro-invasão ou invasão<br>20 casos cujo tipo de alça de excisão não foi registrado |

| | |
|---|---|
| | 6 casos cujo espécime principal foi fragmentado prejudicando a avaliação das margens<br>97 casos encaminhados por citologia ASC-US ou LSIL persistentes<br>48 casos cujo diagnóstico final foi doença micro-invasiva ou invasiva<br>36 casos cujo diagnóstico final foi cervicite no fragmento principal quando o reforço não foi realizado; e cervicite em ambos os fragmentos quando o reforço endocervical foi realizado |
| Legenda: ASC-US - Células escamosas atípicas de significado indeterminado, possivelmente não neoplásicas; LSIL - Lesão Intraepitelial Cervical de Baixo Grau. | |

### 3.4. Desfechos e Variáveis

#### 3.4.1. Desfechos principais

Artigos 1 e 2: Status da margem endocervical
Artigos 3 e 4: Resultado histopatológico

#### 3.4.2. Descrição das variáveis

a) ***Resultado da citologia:*** categorizado em células escamosas atípicas de significado indeterminado, possivelmente não neoplásicas *(ASC-US)* ou quando não se pode excluir lesão intraepitelial de alto grau (*ASC-H*), células glandulares atípicas (*AGC*), lesão intraepitelial escamosa de baixo grau (*LSIL*) ou de alto grau (*HSIL*), adenocarcinoma *in situ* (*AIS*), *câncer* ou *negativo*. Dado obtido da consulta de admissão.

b) ***Resultado histopatológico:*** diagnóstico mais severo no espécime oriundo do procedimento de excisão (cirurgia de alta frequência). Categorizado como neoplasia intraepitelial cervical graus 2 e 3 (*NIC2/NIC3*); lesão intraepitelial cervical de alto

grau ou mais severa (*HSIL+*); ou negativo ou lesão intraepitelial cervical de baixo grau (*negativo/LSIL*). Dado obtido do laudo do procedimento excisional.]

c) ***Status das margens endocervical e ectocervical:*** categorizados como *margem positiva* quando comprometida por HSIL; ou *margem negativa* ou *negativa/NIC1* quando negativas ou comprometidas por neoplasia intraepitelial cervical grau 1. Dado obtido do laudo anátomo-patológico do procedimento excisional.

d) ***Tipo da Zona de Transformação (ZT):*** categorizado em *ZT tipos 1, 2 ou 3*, segundo a "Terminologia IFCPC –Rio – 2011" (35). "ZT tipo 1 é completamente ectocervical e completamente visível, de pequena ou grande extensão. ZT tipo 2 tem componente endocervical completamente visível e pode ter componente ectocervical de pequena ou grande extensão. ZT tipo 3 tem componente endocervical que não é completamente visível e pode ter componente ectocervical de pequena ou grande extensão". Dado obtido do relatório cirúrgico do procedimento excisional ou de consulta até 3 meses antes quando estava ausente no relatório cirúrgico.

e) ***Tipo de Excisão:*** categorizado em *excisão dos tipos 1, 2 e 3*, segundo as "Diretrizes Brasileiras de Rastreamento do Câncer do colo do útero, 2016 (21). A excisão tipo 1 destinada a tratar doença ectocervical, ou que não se estende por mais de 1 cm no canal endocervical. Na excisão tipo 2 é necessário retirar maior porção do canal endocervical, suficiente para ultrapassar a JEC, usualmente obtido com profundidade de 1,5 a 2,0 cm. Na excisão tipo 3 é necessário retirar maior profundidade, sendo descrita a retirada entre 2,0 e 2,5cm do canal. Dado obtido do relatório cirúrgico do procedimento excisional.

f) **Profundidade**: categorizado como *≤10mm* ou *>10mm*. Dado obtido do laudo anátomo-patológico do procedimento excisional.

g) ***Impressão colposcópica:*** categorizada em *anormal* (sugestivo de HSIL+) ou *normal* (negativa, alterações metaplásicas ou sugestivo de LSIL grau). Dado obtido da consulta de admissão.

h) ***Recidiva:*** categorizada em *sim* ou *não*, referindo-se à nova detecção de lesão de alto grau (em resultado citológico e/ou biópsia) durante o período de seguimento após o tratamento inicial. Dado obtido da revisão das consultas de seguimento.

i) ***Método rastrear-e-tratar (R&T):*** categorizado em *sim* (se realizado) ou *não* (se não realizado), referindo-se à omissão da realização de biópsia previamente ao procedimento excisional. Dado obtido da consulta de admissão.

j) ***Reforço de canal:*** técnica que consiste em segunda passagem de alça no canal endocervical após a excisão do fragment principal no procedimento excisional, para amostragem mais profunda; categorizado em *sim* (realizado) ou *não* (não realizado). Dado obtido do relatório cirúrgico do procedimento excisional.

k) ***Idade:*** categorizada em *<40 anos* ou *≥40 anos*, referindo-se à idade da mulher na primeira consulta no serviço. Dado obtido da consulta de admissão.

l) ***Idade de início da atividade sexual:*** categorizada em *<18 anos* ou *≥18 anos*, referindo-se à idade relatada pela mulher na primeira relação sexual. Dado obtido da consulta de admissão.

m) ***Menopausa:*** categorizada em *sim* ou *não*, referindo-se ao relato de parada definitiva da menstruação na admissão no serviço de referência. Dado obtido da consulta de admissão.

n) ***Tabagismo:*** categorizado em *sim* ou *não*, referindo-se ao relato do hábito de fumar na admissão no serviço de referência. Dado obtido da consulta de admissão.

o) ***Uso de contraceptivo hormonal:*** categorizado em *sim* ou *não*, referindo-se ao relato de uso de método hormonal para fins de contracepção na admissão no serviço de referência. Dado obtido da consulta de admissão.

### 3.5. Procedimentos e técnicas:

**CONSULTA DE ADMISSÃO**

As mulheres são encaminhadas das unidades básicas de saúde após um resultado anormal nas citologias de rastreamento para lesões precursoras do colo do útero. Na consulta de admissão no Ambulatório de Patologia Cervical do Hospital da Mulher José Aristodemo Pinotti – CAISM/Unicamp, é realizada anamnese dirigida ginecológica, com avaliação de antecedentes pessoais e ginecológicos, comorbidades, hábitos e checagem de laudos de citologia e eventuais biópsias que constavam no encaminhamento. É realizado exame ginecológico incluindo inspeção, exame especular a olho nu e colposcopia.

**COLPOSCOPIA**

Realizada com colposcópio binocular, em sala adequada, na presença dos materiais necessários: espéculo, pinça Cheron, pinça de biópsia (saca bocado - Professor Medina), gaze ou algodão, ácido acético 3 a 5%. Aplica-se a solução de ácido acético de 3 a 5% por 1-2 minutos, seguida por avaliação de fundos de saco e paredes vaginais e suas pregas, depois realizado o exame do colo uterino dando atenção especial para identificação da junção escamo-colunar (JEC), da zona de transformação (ZT) e epitélios escamoso e colunar. Nesse momento pode ser necessária a realização da exploração de canal cervical, de biópsias, retiradas de pólipos, entre outros procedimentos correlatos.

O exame é realizado por médico residente do segundo ou terceiro ano do programa de residência em ginecologia e obstetrícia da Faculdade de Ciências Médicas da Unicamp, supervisionados por médico ou docente sênior. Após a realização do exame, foi realizado registro em prontuário conforme a Terminologia IFCPC –Rio – 2011 (35), com comentários, conclusões diagnósticas e recomendações terapêuticas.

Diante de citologia anormal e biópsia confirmando o diagnóstico de HSIL ou AIS a mulher é encaminhada para a excisão da zona de transformação (EZT) com alça, exceto se a colposcopia sugerir micro-invasão ou invasão. Quando a biópsia não é realizada previamente e a colposcopia apresentar achados anormais,

considera-se o encaminhamento para EZT, omitindo-se ou não a realização da biópsia (método rastrear e tratar – R&T). A biópsia é sempre realizada quando a mulher é encaminhada por ASC-US ou LSIL persistentes, diante da suspeita de micro-invasão ou invasão, ou em qualquer situação se a idade for inferior a 25 anos. Mais de um fragmento pode ser obtido em cada procedimento. Os casos com citologia anormal e colposcopia negativa são manejados individualmente avaliando os fatores de risco da mulher e seu acesso ao sistema de saúde. A EZT é realizada preferencialmente por cirurgia de alta frequência no centro cirúrgico ambulatorial com bloqueio cervical. Em alguns casos pode ser optado pela realização do procedimento com bisturi a frio (quando indicado- colo incorporado/raso) ou em centro cirúrgico sob analgesia quando a paciente não tolera o exame especular.

## EXCISÃO DA ZONA DE TRANSFORMAÇÃO COM ALÇA COM APARELHO DE ALTA FREQUÊNCIA

Previamente ao procedimento é realizada a checagem de prontuário e exames da paciente, confirmando a indicação da realização do procedimento, verificando também medicações em uso e condições clínicas para a realização do procedimento (aferição de pressão, checagem da data da última menstruação e realização de teste de gravidez se necessário).

O procedimento é realizado em centro cirúrgico ambulatorial, na presença de materiais necessários: colposcópio, seringa e anestésico local, algodão/gazes, swabs, espéculo isolante, frasco e mangueira de aspiração, aparelho de alta frequência com placa de dispersão, alças adequadas para cada tipo de excisão, eletrodos de hemostasia, gel hemostático, material de sutura (em caso de necessidade).

A excisão da zona de transformação por cirurgia de alta frequência é realizada por equipe treinada, geralmente um residente do terceiro ano do programa de residência em Ginecologia e Obstetrícia da Unicamp, sob supervisão de docente ou médico assistente sênior.

O procedimento é realizado sob visão colposcópica, e anestesia local, seguindo as técnicas padronizadas nas Diretrizes Brasileiras para o Rastreamento do Câncer do Colo do Útero, do Ministério da Saúde (21). A classificação dos tipos de excisão leva em conta os tipos de zona de transformação, sendo a excisão tipo 1

destinada a tratar doença ectocervical, ou que não se estende por mais de 1 cm no canal endocervical. Na excisão tipo 2 é necessário retirar maior porção do canal endocervical, suficiente para ultrapassar a JEC, usualmente obtido com profundidade de 1,5 a 2,0 cm. Na excisão tipo 3 é necessário retirar maior profundidade, sendo descrita a retirada entre 2,0 e 2,5 cm do canal.

**SEGUIMENTO**

Para as mulheres cujo diagnóstico final era Adenocarinoma in situ foi indicada a realização de histerectomia extra-fascicular, quando a prole era constituída. Os casos de micro-invasão ou invasão foram manejados segundo os protocolos vigentes da instituição.

O seguimento das pacientes com lesões escamosas após tratamento foi realizado com anamnese, exame ginecológico, coleta de citologia e colposcopia, com intervalo de 6 meses, por no mínimo 1 ano quando as margens do espécime cirúrgico eram negativas, e 2 anos quando positivas para HSIL. Na alta do serviço a mulher recebe um relatório de contra-referência para sua unidade de origem, com orientações para exame físico e coleta de citologia anual até completar 5 anos do procedimento, voltando para o rastreamento de rotina após.

No seguimento, frente a qualquer resultado anormal na colposcopia é indicada bióspia e o caso conduzido de acordo com o resultado encontrado. Quando o resultado citológico é anormal a paciente é convocada para nova colposcopia e decisão compartilhada do manejo, de acordo com a impressão colposcópica. De forma geral, qualquer resultado HSIL+, citológico com ou sem biópsia confirmatória, é indicada a realização de novo procedimento excisional.

### 3.6. Coleta de dados

Após a definição do período de abrangência do estudo, foram identificados os prontuários de todas as pacientes submetidas à cirurgia de alta frequência no período, e os dados foram coletados a partir da análise dos prontuários, em fichas numericamente catalogadas. O sistema de registro de prontuário é online e

interligado ao sistema de descrição de procedimento cirúrgico e de laudos de exames de anatomia patológica. Para manipulação e análise, os dados foram transcritos em planilhas desenhadas especificamente para o estudo, omitindo-se a identificação do nome da mulher. Os dados foram submetidos à análises frequentes de consistência.

### 3.7. Análise dos dados

Para descrever o perfil da amostra segundo as variáveis em estudo foram feitas tabelas de frequência das variáveis categóricas com valores de frequência absoluta (n) e percentual (%), e estatísticas descritivas das variáveis numéricas com valores de média, desvio padrão, valores mínimo e máximo, mediana e quartis, em função do estado das margens, da realização ou não de biópsia, e da realização ou não do reforço de canal.

Para comparação das variáveis categóricas entre grupos foram utilizados os testes Qui-Quadrado ou exato de Fisher (para valores esperados menores que 5). Para comparação das variáveis numéricas entre grupos foi utilizado o teste de Mann-Whitney (2 grupos) e o teste de Kruskal-Wallis (3 grupos), devido à ausência de distribuição normal das variáveis. Análise de regressão logística uni ou multivariada foi realizada para analisar fatores relacionados aos desfechos, e os riscos descritos por Razão de Chances (Odds Ratio – OR) e o intervalo de confiança (IC) de 95%. Para as análises multivariadas foi adotado o critério de Stepwise para seleção das variáveis.

A análise estatística foi realizada pelo serviço de estatística da instituição que utiliza o SAS System for Windows (Statistical Analysis System) versão 9.4, *SAS Institute INC, 2002-2012, Cary, NC, USA*. Foi adotado nível de significância estatística de 5% ($p<0.05$).

### 3.8. Aspectos Éticos

O projeto foi submetido à análise e aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da Universidade Estadual de Campinas (CEP-Unicamp) e aprovado com o registro CAAE 13034013.6.0000.5404, seguindo

os princípios éticos para pesquisas médicas com seres humanos contidos na Declaração de Helsinki.

Por se tratar de estudo retrospectivo baseado na análise de prontuários não houve riscos implicados aos sujeitos do estudo. Devido ao caráter retrospectivo do estudo, o CEP-Unicamp dispensou a aplicação do Termo de Consentimento Livre e Esclarecido.

Não houve riscos ou benefícios individuais para as mulheres sujeitos do estudo, uma vez que a coleta de dados foi realizada após as condutas adotas rotineiramente pela instituição. Os resultados das análises realizadas nesse estudo podem beneficiar indiretamente as mulheres portadoras de lesões precursoras do câncer do colo do útero, pela melhoria da assistência prestada à essas mulheres.

# 4. RESULTADOS

Os produtos desta tese foram 4 artigos versando aos objetivos específicos correspondentes.

**Artigo 1:**

**“The value of the endocervical margin status in LEEP: analysis of 610 cases.”**

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GYNECOLOGIC ONCOLOGY

# The value of the endocervical margin status in LEEP: analysis of 610 cases

**Camila Castelhano Mirandez[1] · Juliana Yoko Yoneda[1] · Larissa Nascimento Gertrudes[1] · Carla Fabrine Carvalho[1] · Sophie Derchain[1] · Julio Cesar Teixeira[1] · Diama Bhadra Vale[1]**

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## Abstract

**Purpose** To describe the results of 610 patients who underwent LEEP and evaluate factors related to a negative margin.

**Methods** A retrospective study of patients treated by LEEP at a colposcopy referral service in Campinas, Brazil, 2017–2019. Patients were referred to treat high-grade squamous intraepithelial lesion or adenocarcinoma in situ suspected by cytology and colposcopy (screen-and-treat) or by biopsy. Descriptive analysis was performed by frequencies as a function of the status of the margins (negative or positive). Factors associated with margin status were assessed by regression.

**Results** The endocervical, ectocervical or both margins were negative in 82.4%, 75.7% and 65.9%, respectively. Age, sexual debut, parity, menopause status, smoking and hormonal contraception showed no difference in the proportion of negative margins. Both margins were negative in 66.1% of patients with transformation zone type(TZ) 1, 73.1% of TZ 2, and 54.7% of TZ 3 ($p=0.015$). The endocervical negative margin was obtained in 78.0% of patients submitted to excision I (loop 10 mm) and 82.5% to excision II (loop 15 mm) ($p=0.016$). Having the sexual debut at 18 years or older or being submitted to an excision type II doubled the chance of negative endocervical margin (1.98;1.04–3.77 and 1.95; 1.18–3.21, respectively).

**Conclusion** The proportion of negative endocervical margin was 78% in excision I and 86% in excision II. Sexual onset and excision type II increased the chance of obtaining a negative endocervical margin.

**Keywords** Uterine cervical neoplasms · Cervical intraepithelial neoplasia · Colposcopy · Conization · Secondary prevention

## Introduction

The treatment of precursor lesions is an essential strategy in cervical cancer prevention. In its call for the global elimination of this cancer, the World Health Organization advocates that 90% of women with positive screening tests should be treated [1]. The issue is relevant because cervical cancer is one of the leading causes of death for women in low- and middle-income countries [2, 3].

Treatment can be destructive or excisional, with the latter being preferred due to the possibility of obtaining material for histopathologic analysis excluding invasive disease. The Loop Excision of the Transformation Zone (LEEP) is the excisional technique most used in countries with structured healthcare networks. It uses a metal loop to conduct electrical current and cut the tissue by fulguration. It can be performed in an outpatient clinic under local anaesthesia.

The objective of excision is to remove the lesion, preventing invasive disease development. The lesion is considered completely removed when the histopathological ectocervical and endocervical margins are negative. When it happens, the risk of intraepithelial disease recurrence is reduced [4–8]. In patients with one or both margins positive for precursor lesion (high-grade intraepithelial squamous lesion—HSIL, or adenocarcinoma in situ—AIS), this risk is higher but still very low [9]. In the risk assessment, the inner or endocervical margin is more relevant than the superficial or ectocervical margin [9–11].

This study aimed to describe the results of 610 patients who underwent LEEP for treating precursor lesions (HSIL or AIS) in a reference service of a large urban conglomerate in São Paulo state, Brazil, from 2017 to 2019. The factors

✉ Diama Bhadra Vale
dvale@unicamp.br

[1] Department of Obstetrics and Gynecology, University of Campinas, Rua Vital Brasil, 80 Cidade Universitária, Campinas, CEPSão Paulo 13083-888, Brazil

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related to obtaining a negative endocervical margin were verified. The results of this study can support the decision on the management of patients in the context of cervical cancer prevention.

## Methods

It is a retrospective study evaluating data obtained from medical records of patients with precursor lesions treated by LEEP at the colposcopy service of the University of Campinas Women's Hospital (CAISM/Unicamp). The service assists women from Campinas and surroundings, a highly populated region in São Paulo state, Brazil. The sample was selected by convenience, including all women that underwent LEEP from January 1, 2017, to July 31, 2020. The project was approved by the 'Ethics and Research Committee of Unicamp' under the number CAAE 13034013.6.0000.5404. The Committee waived the free and informed consent form as a retrospective study.

Patients were referred to treat HSIL or AIS suspected or confirmed at the public health program that uses cervical cytology screening tests at primary unit care facilities. At the admission, a colposcopy was performed. Women were referred to LEEP without a confirmatory biopsy when the colposcopy was suggestive of HSIL or AIS ('screen-and-treat approach'). Biopsies were taken when colposcopy was suggestive of low-grade squamous intraepithelial lesion (LSIL), suggestive of invasion, or if the women were younger than 25 years old. When this biopsy result was HSIL or AIS, women were referred for LEEP. LEEP was performed at the outpatient colposcopy unit under local anaesthesia by the standard technic.

In the period, 734 LEEPs were performed. We excluded cases with suspicious of micro-invasion or invasion (28 patients); when the margins could not be evaluated due to piece fragmentation (6 patients); when the size of the loop used was not recorded (20); or when the patient had a history of a previous excisional procedure (59 cases). To uniform the sample, we chose to exclude 11 patients that had undergone excision type III (loop of 20 mm). The final sample consisted of 610 patients that underwent excision types I and II (loops of 10 and 15 mm, respectively). AIS was suspected in only 11 of the included cases.

The dependent variable was the endocervical or ectocervical margin status, categorized as negative or positive, obtained from the anatomopathological report. The margin was positive when showing involvement of HSIL or more severe. When LSIL was at the margins, they were considered negative. Independent variables were age at onset of sexual activity, age, parity, use of hormonal contraceptives, smoking, menopausal status, type of transformation zone (TZ), and excision. All clinical variables were obtained from medical records and referred to the time when the procedure was performed.

The TZ was categorized into types 1, 2 or 3 (TZ 1, 2 or 3), according to the IFCPC 2011 colposcopic terminology [12]), obtained from the procedure description record. The type of excision was categorized according to the loop size: type I—10 mm loop, type II—15 mm loop and type III—loop larger than 15 mm (excision I, II or III), according to the Brazilian Guidelines on Screening for Cervical Cancer, based on the recommendation of the IFCPC 2011 [13].

For statistical analysis, descriptive analysis was performed by frequencies as a function of the status of the margins, using the Chi-square or Fisher's exact test. Uni and multivariate logistic regression was performed to assess factors associated with margin status by Odds Ratio and its 95% Confidence Interval (CI) estimation. A significance level of 5% ($p<0.05$) was adopted.

## Results

Table 1 shows the proportion of negative endocervical, ectocervical, and both margins concerning the analyzed variables. The endocervical, ectocervical or both margins were negative in 82.4%, 75.7% and 65.9%, respectively. The categories age, sexual debut, parity, menopause status, smoking and use of hormonal contraception showed no difference in obtaining negative margins. The TZ type was significantly associated with getting both endocervical and ectocervical negative margins: in TZ 1 both margins were negative in 66.1%, TZ 2 73.1%, and TZ 3 54.7% ($p=0.015$). The TZ type did not influence having a single negative endocervical or ectocervical margin ($p=0.141$ and $p=0159$, respectively). Regarding the excision type, excision I showed a significantly lower proportion of endocervical negative margin when compared to excision II (78.0% and 82.5%, respectively, $p=0.016$). It was not significantly different for obtaining an ectocervical negative margin or both negative margins ($p=0.661$ and $p=0.926$).

Table 2 presents the regression analysis results of obtaining a negative margin according to the variables studied. After controlling the other variables, we found two situations when the chance of having an endocervical margin was doubled: having the sexual debut at 18 years or older (1.98; 1.04–3.77); or being submitted to an excision type II (1.95; 1.18–3.21). No variable significantly increased the chance of having an ectocervical negative margin or having both margins negative.

## Discussion

In this cross-sectional study of 610 patients who underwent LEEP in the context of cervical cancer prevention, the endocervical, ectocervical or both margins were negative in

**Table 1** Margin status in 610 patients who underwent cervical excisional procedure for precursor lesion treatment

| Variables | Endocervical margin | | Ectocervical margin | | Both negative | |
|---|---|---|---|---|---|---|
| | Negative *n* (%) | *p* value | Negative *n* (%) | *p* value | Negative *n* (%) | *p* value |
| Total | 504 (82.4) | | 462 (75.7) | | 402 (65.9) | |
| Age | | | | | | |
| < 40 | 335 (81.5) | 0.297 | 312 (75.9) | 0.885 | 268 (65.2) | 0.603 |
| ≥ 40 | 169 (84.9) | | 150 (75.4) | | 134 (67.3) | |
| Sexual debut* | | | | | | |
| < 18 | 250 (78.9) | 0.068 | 243 (76.7) | 0.906 | 203 (64.0) | 0.339 |
| ≥ 18 | 98 (86.7) | | 86 (76.1) | | 78 (69.0) | |
| Parity* | | | | | | |
| 0 | 89 (81.7) | 0.751 | 82 (75.2) | 0.878 | 70 (64.2) | 0.686 |
| + 1 | 403 (82.9) | | 369 (75.9) | | 322 (66.3) | |
| Menopause* | | | | | | |
| No | 449 (82.7) | 0.896 | 413 (76.0) | 0.745 | 359 (66.1) | 0.876 |
| Yes | 55 (83.3) | | 49 (74.2) | | 43 (65.2) | |
| Smoking* | | | | | | |
| No | 379 (82.6) | 0.835 | 349 (76.0) | 0.737 | 302 (65.8) | 0.975 |
| Yes | 115 (83.3) | | 103 (74.6) | | 91 (65.9) | |
| HCO* | | | | | | |
| No | 273 (83.0) | 0.864 | 250 (76.0) | 0.823 | 218 (66.3) | 0.800 |
| Yes | 216 (82.4) | | 197 (75.2) | | 171 (65.3) | |
| ZT type | | | | | | |
| 1 | 311 (81.6) | 0.141 | 291 (76.4) | 0.159 | 252 (66.1) | **0.015** |
| 2 | 118 (88.1) | | 106 (79.1) | | 98 (73.1) | |
| 3 | 75 (78.9) | | 65 (68.4) | | 52 (54.7) | |
| Excision type | | | | | | |
| I | 184 (78.0) | **0.016** | 181 (76.7) | 0.661 | 155 (65.7) | 0.926 |
| II | 320 (85.6) | | 281 (75.1) | | 247 (66.0) | |

*Neg* negative, *p value* Chi-square or Fisher test, *HCO* hormonal contraception

*Some missing values

respectively 82.4%, 75.7% and 65.9%. Sexual activity onset after 18 years and excision type II were the only factors that independently increased the chance of obtaining a negative endocervical margin.

The acquired knowledge of the natural history of cervical cancer and its precursor lesions has enabled the adoption of more conservative approaches in recent years. The goal of treatment is to prevent the development of invasive disease. In this sense, excisional methods should remove the lesion and reduce the risk of residual disease or recurrence. In clinical practice, it is broadly accepted that the goal of the procedure should be to obtain negative margins.

In 2010, Ghaem-Maghami demonstrated in a retrospective analysis of 2455 patients that the risk of intraepithelial lesion recurrence stabilized in about 5% when both margins were negative, 10% when the ectocervical margin was positive, 15% when the endocervical margin was positive, and 20% when both margins were positive [5]. Thus, only one in five patients with both positive margins would experience recurrence. However, more recent evidence has shown that a negative margin is not the central aspect to be considered [4, 14]. Preterm labour is a significant morbidity associated with the procedure [15]. In this context, the concept that obtaining negative margins should be the objective of treatment has recently come to be questioned. The approaches are currently more conservative, as the benefits of a negative margin should be counterbalanced with the risks. The depth of excision should be the minimum necessary to remove the lesion, preserving the morphologic function of the cervix.

This shift in the paradigm was supported by results indicating that the positive margin rates were not consistent with the risk observed in clinical practice. Arbyn et al. in a meta-analysis found in LEEP 25.9% of positive margins, but only 6.7% residual/recurrent disease [4]. The rates of negative margins in this study are in line with the meta-analysis results. Indeed, following recent evidence, the clinical practice in the period studied (2017–2020) was already as conservative as possible regarding the excision depth.

**Table 2** Uni and multivariate analysis of predictor factors to obtain negative margins in 610 patients who underwent cervical excisional procedure for precursor lesion treatment

| Univariate analysis | | | | | | |
|---|---|---|---|---|---|---|
| | Endocervical | | Ectocervical | | Both negative | |
| Variable | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) |
| Age | | | | | | |
| < 40 | | 1.00 | | 1.00 | | 1.00 |
| ≥ 40 | 0.297 | 1.28 (0.81–2.03) | 0.885 | 0.97 (0.66–1.44) | 0.603 | 1.10 (0.77–1.58) |
| Sexual debut | | | | | | |
| < 18 | | 1.00 | | 1.00 | | 1.00 |
| ≥ 18 | 0.070 | 1.75 (0.96–3.21) | 0.905 | 0.97 (0.59–1.61) | 0.339 | 1.25 (0.79–1.98) |
| Parity | | | | | | |
| 0 | | 1.00 | | 1.00 | | 1.00 |
| + 1 | 0.751 | 1.09 (0.64–1.87) | 0.877 | 1.04 (0.64–1.68) | 0.686 | 1.09 (0.71–1.69) |
| Menopause | | | | | | |
| No | | 1.00 | | 1.00 | | 1.00 |
| Yes | 0.897 | 1.05 (0.53–2.07) | 0.745 | 0.91 (0.51–1.63) | 0.876 | 0.96 (0.56–1.64) |
| Smoking | | | | | | |
| No | | 1.00 | | 1.00 | | 1.00 |
| Yes | 0.835 | 1.06 (0.64–1.76) | 0.737 | 0.93 (0.60–1.44) | 0.975 | 1.01 (0.67–1.50) |
| HCO | | | | | | |
| No | | 1.00 | | 1.00 | | 1.00 |
| Yes | 0.864 | 0.96 (0.63–1.48) | 0.822 | 0.96 (0.66–1.40) | 0.800 | 0.96 (0.68–1.35) |
| ZT type | | | | | | |
| 1 | | 1.00 | | 1.00 | | 1.00 |
| 2 | 0.088 | 1.66 (0.93–2.97) | 0.519 | 1.17 (0.73–1.89) | 0.137 | 1.39 (0.90–2.16) |
| 3 | 0.551 | 0.84 (0.48–1.47) | 0.111 | 0.67 (0.41–1.10) | 0.039 | 0.62 (0.39–0.98) |
| Excision type | | | | | | |
| I | | 1.00 | | 1.00 | | 1.00 |
| II | 0.017 | 1.68 (1.10–2.55) | 0.661 | 0.92 (0.63–1.35) | 0.926 | 1.02 (0.72–1.43) |
| Multivariate analysis | | | | | | |
| Sexual debut | | | Not selected | | Not selected | |
| < 18 | | 1.00 | | | | |
| ≥ 18 | 0.038 | 1.98 (1.04–3.77) | | | | |
| Excision type | | | | | | |
| I | | 1.00 | | | | |
| II | 0.009 | 1.95 (1.18–3.21) | | | | |

*P p* value by logistic regression (Stepwise criteria), *OR* Odds Ratio, *CI* Confidence Interval, *HCO* hormonal contraception

The excision type did not influence the chance of obtaining a negative ectocervical margin. This result is expected since what differentiates the types of excision are the height sizes of the loops used, if 10, 15 or 20 mm. About the base, the 20-mm loop is conventionally used, which guarantees the excision of the periorificial transformation zone. Only very extensive lesions, occupying multiple quadrants, escape from excision with a 20-mm loop. Residual or recurrent disease risk is low when there is a positive ectocervical margin, around 10% [5]. By activating local cellular immunity, the role of the vaginal environment in post-LEEP ectocervical wound healing must be considered [16]. When the lesion persists or recurs, it can be more easily identified through cytology and colposcopy than when there is an endocervical residual lesion.

Excision II resulted in a more significant proportion of negative margins regarding the endocervical margin. When compared to excision I, undergoing excision type II increased the chance of a negative endocervical margin by twice (OR 1.95; 1.18- 3.21). It is an expected result since the 15-mm loop used in excision II gets more inner tissue than the 10-mm loop used in excision I. However, the clinical value of removing a more considerable amount of tissue is questionable, as the risk of treatment failure remains very low [4, 5, 17]. In this study, the proportion

of negative endocervical margin was 78% in excision I and 86% in excision II.

To translate these data to clinical practice, 100 excisions II would be required to benefit about eight women compared to excision I. Considering a 15% risk of residual disease or recurrence, only one of these eight women would benefit from recurrence in every 100 procedures performed. Performing excision I, therefore, seems quite safe. In women in their reproductive age, excision with a loop other than 10 mm should be restricted to special conditions that increase the risk of persistence or recurrence, such as suspected immunodeficiency or glandular lesions. In menopause women the surgeon should be more confident indicating a 10-mm loop [18]. In cases of positive margins, a DNA-HPV test would indicate an evaluation for a new procedure.

It is well documented that early onset of sexual activity is a risk factor for cervical cancer [19, 20]. The initiation of sexual activity at age 18 or older increased the chance of a woman having a negative endocervical margin by twice (OR 1.98;1.04–3.77). Young women are more vulnerable to HPV infection due to an immature immune response and a larger area of exposure of metaplastic epithelium (ectopia) [21]. HPV infections in this group persist for more extended periods than in older women [16, 22]. The hypothesis for our study's result is that women who have initiated sexual activity later would carry less oncogenic HPV types. Therefore, the lesions would have more potential for regression and less extensive lesions.

The main limitation of our study is that testing for high-risk HPV types was not available, which is the prevailing situation in most low- and middle-income countries. In this sense, clinical studies like this are relevant as the only available data to support management recommendations in these regions. The strength of this study is in the significant sample, enhanced by the detailed information recorded with quality. We believe that further analysis of this sample concerning follow-up may provide more information for critical analysis of the matter.

## Conclusion

Sexual onset and excision type II increased the chance of obtaining a negative endocervical margin. The proportion of negative endocervical margin was 78% in excision I and 86% in excision II. This marginal benefit should be counterbalanced with the risks associated with the procedure: performing a more conservative procedure seems safe and reduces morbidities, particularly in young women.

**Author contributions** CCM: protocol/project development, data collection or management, data analysis, manuscript writing; JYY: protocol/project development, manuscript writing; LNG: data collection or management, data analysis, manuscript writing; CFC: data collection or management, manuscript writing; SD: data collection or management, data analysis, manuscript writing; JCT: data analysis, manuscript writing; DBV: protocol/project development, data analysis, manuscript writing/editing.

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## Declarations

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval** This study was performed in line with the principles of the Declaration of Helsinki. The project was approved by the 'Ethics and Research Committee of Unicamp' under the number CAAE 13034013.6.0000.5404.

**Consent to participate** The Committee waived the free and informed consent form given the retrospective nature of the study.

**Consent to publish** Not applicable.

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**Artigo 2:**

**“Endocervical Margin Status in Excision for PreventiNg Cervical Cancer According to the Transformation Zone Type.”**

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# Endocervical Margins Status in Excision for Preventing Cervical Cancer According to the Transformation Zone Type

*Larissa Nascimento Gertrudes, MD, Juliana Yoko Yoneda, MD, MSc, Camila Castelhano Mirandez, MD, Carla Fabrine Carvalho, MSc, Sophie Derchain, MD, PhD, Julio Cesar Teixeira, MD, PhD, and Diama Bhadra Vale, MD, PhD*

**Objective:** The aim of this study is to assess the outcomes of 610 excision types I and II in a referral facility as a function of transformation zone (TZ) types.

**Methods:** This is a retrospective cohort study of women with cervical precursor lesions who underwent loop electrocautery excision procedure from 2017 to 2019 at the University of Campinas. The primary outcome was endocervical margin status, negative or positive. Other variables were excision type (I/II), TZ (1/2/3), age, menopausal status, hormonal contraceptives, smoking, and sexual debut. Tests used were chi-square or Fisher exact, Mann-Whitney, and simple and multiple logistic regression.

**Results:** The most frequent was TZ 1 (62.5%). Excision II was the most frequent: 54.1% in TZ 1, 67.2% in TZ 2, and 82.1% in TZ 3. A negative margin was observed in TZ 1, 76.0% when excision I and 86.4% when excision II ($p = .009$); TZ 2, 86.4% when excision I and 88.9% when excision II ($p = .672$); and TZ 3, 76.5% when excision I and 78.9% when excision II ($p = .672$). Multivariate analysis revealed in TZ 1 a 2.12 (1.23–3.65) higher risk of obtaining a negative margin in excision type II. In TZ 2 and 3, none of the variables predicted the chance of a negative margin.

**Conclusions:** The endocervical margin was negative in 3 in every 4 women who underwent loop electrocautery excision procedure, regardless of excision type. Age, menopausal status, smoking, and hormonal contraception did not predict margin status.

**Key Words:** cervical intraepithelial neoplasia, colposcopy, secondary prevention, uterine cervical neoplasms, cancer prevention

(*J Low Genit Tract Dis* 2022;00: 00–00)

Treatment of precursor lesions is one of the main strategies for eliminating cervical cancer. The World Health Organization has set a target that at least 90% of women with a positive screening test result should be treated.[1] When possible, excisional methods should be preferred because they allow analyzing histopathological material, avoiding occult invasive disease.

The International Federation of Cervical Pathology and Colposcopy (IFCPC) standardized in 2011 the nomenclature of excision methods. According to the transformation zone (TZ) type, they should be classified into 3 types, indicating the depth of the excision into the endocervical canal.[2] The Brazilian guideline for cervical cancer screening recommends excision type I (depth of excision up to 10 mm) in TZ 1 (TZ ectocervical); excision type II (depth of excision from 10 to 15 mm) in TZ 2 (TZ totally seen but with an endocervical part); and excision type III (depth of excision more than 15 mm) in TZ 3 (TZ not totally seen/in endocervical canal).[3] In clinical practice, the TZ would guide the loop size to be used.

Department of Obstetrics and Gynecology, University of Campinas, Campinas, Brazil

Reprint requests to: Diama Bhadra Vale, MD, PhD, Rua Vital Brazil, 80 – Cidade Universitária, CEP 13083-888, Campinas, Brazil. E-mail: dvale@unicamp.br

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This adjustment would be necessary to avoid procedures that are more extensive than necessary, ensuring that the lesion would be removed with the minimum tissue possible. This concern is justified by the abundant evidence in the literature that the depth of excised tissue is directly related to the risk of complications, particularly preterm labor,[4] a significant public health problem worldwide. In addition, recent studies demonstrate that a high-risk (hr)-HPV test at follow-up is more sensitive than margin status indicating women who will have persistence or recurrence of the disease. Although hr-HPV is not available in most low-income and middle-income countries, the histological results still have their value in managing these women.

It is known that the endocervical margin is more relevant than the ectocervical margin in risk assessment of treatment failure.[5–7] This study aimed to assess the outcomes of 610 excision types I and II in a referral university facility as a function of the TZs. The results can help perioperative decisions by gynecologists and support future recommendations.

## METHODS

This is a retrospective cohort study of women diagnosed with cervical precursor lesions who underwent excision of the TZ using the loop electrocautery excision procedure (LEEP) technique between 2017 and 2019 at the Lower Genital Tract Pathology outpatient clinic of the University of Campinas.

All LEEP procedures performed at the institution during the study period were evaluated. The inclusion criteria were women referred for treatment by cytology and/or biopsy suggestive of a precursor lesion (high-grade squamous intraepithelial lesion [HSIL] or adenocarcinoma in situ [AIS]). The exclusion criteria were invasive cancer suspected in cytology, biopsy or colposcopy impression, previous excisional treatment in the cervix, and unavailability of crucial information such as margin status, loop size, and TZ. During the period, only 11 excision type IIIs were performed. We chose to exclude these cases because it would not be possible to perform analyses with statistical significance.

A total of 734 women who underwent LEEP during the period were selected, and clinical and pathological data were accessed from their medical records. The final sample after applying the exclusion criteria consisted of 610 women. The cytology and/or biopsy suggestive of HSIL or AIS were collected in the context of screening in primary care units of the region. On admission, the women underwent colposcopy. If colposcopy confirmed the hypothesis of HSIL, the woman was referred to LEEP ("screen-and-treat strategy"). If colposcopy was divergent, a biopsy was performed, and LEEP indicated if the diagnosis of HSIL was confirmed. Loop electrocautery excision procedure is the excisional procedure routinely performed in the service, at the outpatient clinic, under local anesthesia. Cold conization is rarely indicated, reserved for cases with invasive lesions suspected that could not be confirmed by biopsy or because of technical difficulties in performing LEEP. During the procedure, the site of the margins of the specimen is not oriented by the surgeon. At the university pathology laboratory, the endocervical margin is defined as the one where

the glandular epithelium is observed. Gynecology pathologists review all cases.

The primary outcome analyzed was the status of the endocervical margin, identified by the pathologist as negative or positive. We classified it as "negative" when a low-grade squamous intraepithelial lesion was in the margin. The ectocervical margin was also the object of secondary analysis. The other variables evaluated were the excision type (types I or II) and the TZ of the woman at the time of the procedure or up to 3 months before (types 1, 2, or 3). The colposcopic nomenclature recommendation of the IFCPC Rio 2011[3] was used. The clinical variables evaluated were age and menopausal status on the day of the procedure; use of hormonal contraceptives and smoking within 6 months of the procedure date; and age at onset of sexual activity.

To study the relationship of factors associated with the negative endocervical margin, simple and multiple logistic regression analyses were performed using stepwise criteria for variable selection. To compare categorical variables, the chi-square or Fisher exact tests were used. The Mann-Whitney test was used to compare numerical variables because of the absence of normal distribution. The significance level adopted for the statistical tests was 5%, that is, $p < .05$. The project was approved by the Ethics and Research Committee of the University of Campinas, under the number CAAE 13034013.6.0000.5404 version 3, on September 24, 2018. The committee waived the informed consent term because of the retrospective nature of the research.

## RESULTS

A total of 734 women who underwent LEEP during the period were selected. We excluded 124 women, and the reasons are shown in Figure 1. The final sample consisted of 610 women. In 11 of the included cases, the glandular disease was suspected in the referral (3 AIS and 8 atypical glandular cells). In 10 of them, both margins were negative. The last woman, referred by a cytology HSIL plus a biopsy AIS, had both margins negative and a final diagnosis of HSIL. A new procedure was performed, showing residual HSIL and both margins negative.

The sample of 610 women was predominantly women aged younger than 40 years (80.5%). Only 9.2% of women were in the menopause period, and 22.6% had the habit of smoking on admission. The most frequent (62.5%) was TZ type 1. Women aged older than 40 frequently had more TZ type 3 than younger women (67.4% vs 32.6%) and underwent more excision type II than type I (41.2% vs 19.2%). Menopause status and smoking also influenced the frequency of TZ types and excision types. Women using contraceptives had a higher frequency of TZ type 1 than types 2 and 3: 51.6%, 36.2%, and 26.1%, respectively (Table 1).

Excision type II was the most frequently performed, regardless of the TZ type: 54.1% in TZ type 1, 67.2% in TZ type 2, and 82.1% in TZ type 3. Compared with women undergoing excision type I, type II presented less frequently in TZ type 1 (74.2% vs 55.1%) and more frequently in TZ type 2 (18.6% vs 24.1%). These differences were significant ($p < .001$) (Table 1).

In women with TZ type I, a negative endocervical margin was obtained in 76.0% of excision type I and 86.4% of type II ($p = .009$). In women with TZ type 2, the negative endocervical margin was observed in 86.4% of excision type I and 88.9% of type II ($p = .672$). In women with TZ type 3, it was observed in 76.5% of excision type I and 78.9% of type II ($p = .672$) (Table 2).

Univariate and multivariate analyses were performed to assess the risk of obtaining a negative endocervical margin as a function of the excision type and the TZ type (Table 3). Multivariate analysis revealed a 2.12 (1.23–3.65) higher risk of obtaining a negative endocervical margin in women with TZ type 1 undergoing excision type II. For women with TZ types 2 and 3, none of the

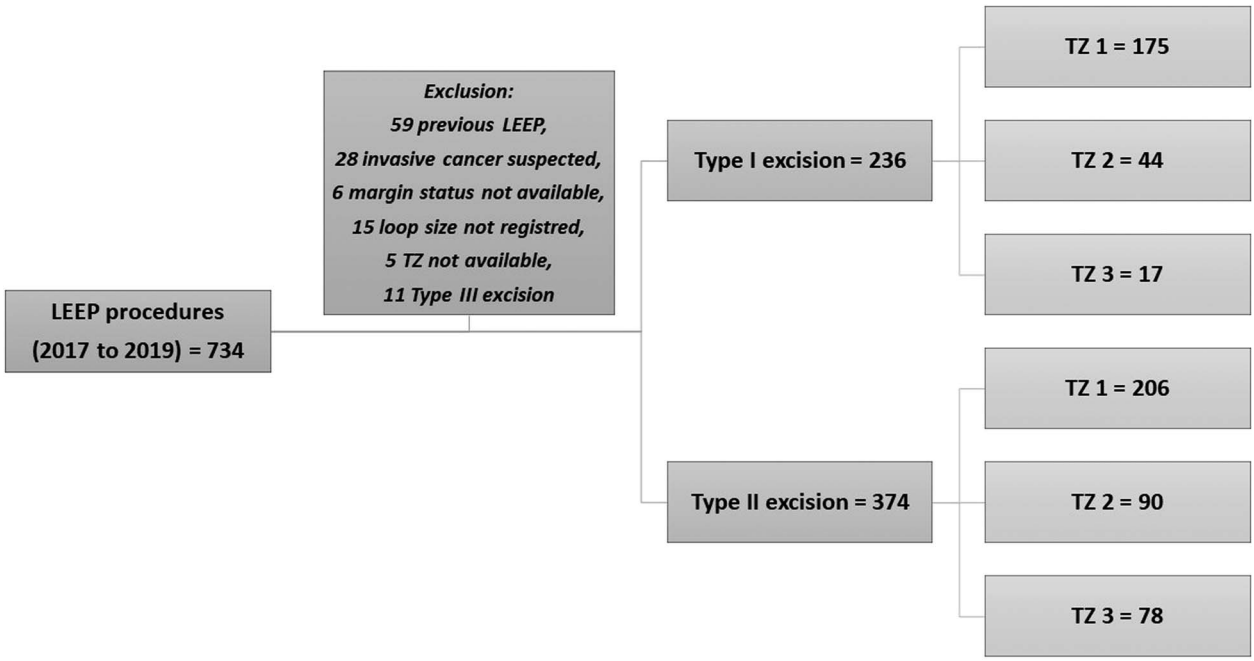


**FIGURE 1.** Flowchart of 734 women who underwent LEEP to treat cervical cancer precursor lesions between 2017 and 2019 at the Lower Genital Tract Pathology outpatient clinic of the University of Campinas. Of the 734 women, 124 were excluded: 59 by previous LEEP, 28 by suspicion of invasive cancer, 6 whose margin status were not available, 15 whose loop sizes were not registered, 5 whose TZ types were not available, and 11 who submitted to type III excision. Of the 610 women included, type I excision was performed in 236 women, 175 in TZ 1, 44 in TZ 2, and 17 in TZ 3; excision type II was performed in 374 women, 206 in TZ 1, 90 in TZ 2, and 78 in TZ 3.

**TABLE 1.** Descriptive Analysis of 610 Patients Who Underwent Cervical Excisional Procedure by LEEP

| | | TZ type | | | | Excision type | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | *p* | I | II | *p* |
| Total | N = 610 | 381 | 134 | 95 | | 236 | 374 | |
| Age | <40 y | 300 (78.7) | 80 (59.7) | 31 (32.6) | <0.001 | 191 (80.9) | 220 (58.8) | <0.001 |
| | ≥40 y | 81 (21.3) | 54 (40.3) | 64 (67.4) | | 45 (19.1) | 154 (41.2) | |
| Menopausal status[a] | No | 366 (96.1) | 116 (86.6) | 61 (64.9) | <0.001 | 218 (92.4) | 325 (87.1) | 0.043 |
| | Yes | 15 (3.9) | 18 (13.4) | 33 (35.1) | | 18 (7.6) | 48 (12.9) | |
| Smoking[a] | No | 300 (80.7) | 100 (74.6) | 59 (64.8) | 0.005 | 190 (82.3) | 269 (73.5) | 0.014 |
| | Yes | 72 (19.3) | 34 (25.4) | 32 (35.2) | | 41 (17.7) | 97 (26.5) | |
| Hormonal contraception[a] | No | 180 (48.4) | 81 (63.8) | 68 (73.9) | <0.001 | 118 (52.2) | 211 (57.8) | 0.183 |
| | Yes | 192 (51.6) | 46 (36.2) | 24 (26.1) | | 108 (47.8) | 154 (42.2) | |
| TZ | Type 1 | | | | | 175 (74.2) | 206 (55.1) | <0.001 |
| | Type 2 | | | | | 44 (18.6) | 90 (24.1) | |
| | Type 3 | | | | | 17 (7.2) | 78 (20.8) | |
| Excision | Type I | 175 (45.9) | 44 (32.8) | 17 (17.9) | <0.001 | | | |
| | Type II | 206 (54.1) | 90 (67.2) | 78 (82.1) | | | | |

*p* value by chi-square or Fisher test.

[a]There are some missing values not included in the analysis: 1 in menopausal status, 13 in smoking, and 19 in hormonal contraception.

variables evaluated was predictive of increasing the chance of obtaining a negative endocervical margin.

## DISCUSSION

In this study, which included 610 women who underwent excision of the TZ by LEEP to treat cervical cancer precursor lesion, excision type II was the most frequent, regardless of the TZ type. A negative endocervical margin was obtained in 4 of 5 women. No clinical variable evaluated predicted the chance of getting a negative endocervical margin.

In adolescents and young adults, the cervix is characterized by ectopia, where the columnar epithelium of the endocervix extends to the ectocervix (TZ 1). With advancing age, hormonal changes, and external agents, metaplasia guides the TZ to the endocervix (TZ 2 and 3).[8,9] In this study, the sample was predominantly young women.

**TABLE 2.** Endocervical Margin Status as a Function of Excision Types and TZ Types

| Excision | Negative | % | Positive | % | *p* |
|---|---|---|---|---|---|
| | | | **TZ 1** | | |
| Type I (10 mm) | 133 | 76.0 | 42 | 24.0 | *p* = .009 |
| Type II (15 mm) | 178 | 86.4 | 28 | 13.6 | |
| Total | 311 | 81.6 | 70 | 18.4 | |
| | | | **TZ 2** | | |
| Type I (10 mm) | 38 | 86.4 | 6 | 13.6 | *p* = .672 |
| Type II (15 mm) | 80 | 88.9 | 10 | 11.1 | |
| Total | 118 | 88.1 | 16 | 11.9 | |
| | | | **TZ 3** | | |
| Type I (10 mm) | 13 | 76.5 | 4 | 23.5 | *p* = .751 |
| Type II (15 mm) | 62 | 79.5 | 16 | 20.5 | |
| Total | 75 | 78.9 | 20 | 21.1 | |

*p* value by chi-square or Fisher test.

In addition to age, studies suggest that estrogen stimulates TZ 1. Squamous cells are sensitive to carcinogenesis by estrogen, increasing the expression of oncogenes, promoting the degradation of the suppressor tumor gene p53, and increasing the capacity of viral DNA to transform cells.[10,11] We found that TZ 1 was more frequent in hormonal contraceptive users, indicating that our sample was representative of the population that usually undergoes LEEP.

The Brazilian national guideline, based on the IFCPC, recommends that the type of excision should be indicated according to the type of TZ.[3,12] Even considering that 11 women that had undergone excision type III were excluded, excision type II was the most frequent regardless of the TZ type. These results suggest that surgeons did not adhere to the recommendation and chose to use the 15-mm loop probably because they felt more comfortable using it.

The recommendations are supported by the premise that, in the management of HSIL, the risks and benefits of treatment must be considered. The greater the depth of the excision, the greater the risk of preterm labor.[4,13] This risk seems particularly important in very young women when the cervical tissue is not yet fully formed.[14] Considering that these lesions usually affect reproductive age, the future obstetric risk is relevant. A cohort study has shown that in women younger than 35, the recurrence rate was similar between women at loop depths <10 mm compared with ≥10 mm.[15] Furthermore, clinical practice shows that perioperative bleeding is directly related to the volume of tissue excised.

The history of the treatment of intraepithelial lesions has always considered that for oncological safety, obtaining lesion-free surgical margins should be crucial.[5,16,17] Thus, the indication of the excision type by TZ is a strategy to guarantee the removal of a minor depth of tissue, ensuring oncological safety. However, the observation that negative margins would not exclude residual disease and that residual pathological disease would not mean clinical residual disease or recurrence are new elements indicating that other factors are involved in this issue.[5,18] A retrospective study of 3,582 women undergoing LEEP found 101 women with persistent HSIL after 6 months.[6] Circumference, width, and depth were not significantly different in those with or without persistence, but a positive endocervical margin was.[6] Another study with positive margins

**TABLE 3.** Analysis of Predictor Factors to Obtain Endocervical Margins According to the Type of TZ

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **Category** | ***p*** | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** |
| TZ Type 1 | | | | | | | |
| Age | <40 y | — | 1.00 | — | | Not selected | |
| | ≥40 y | 0.543 | 1.23 | 0.63–2.37 | | | |
| Menopausal status | No | — | 1.00 | — | | | |
| | Yes | 0.137 | 0.43 | 0.14–1.31 | | | |
| Smoking | No | — | 1.00 | — | | | |
| | Yes | 0.776 | 0.91 | 0.47–1.75 | | | |
| Hormonal contraception | No | — | 1.00 | — | | | |
| | Yes | 0.574 | 1.16 | 0.69–1.97 | | | |
| Excision type | Type I | — | 1.00 | — | — | 1.00 | — |
| | Type II | 0.010 | 2.01 | 1.18–3.41 | 0.007 | 2.12 | 1.23–3.65 |
| TZ Type 2 | | | | | | | |
| Age | <40 y | — | 1.00 | — | | None selected | |
| | ≥40 y | 0.192 | 2.21 | 0.67–7.24 | | | |
| Menopausal status | No | — | 1.00 | — | | | |
| | Yes | 0.907 | 1.10 | 0.23–5.29 | | | |
| Smoking | No | — | 1.00 | — | | | |
| | Yes | 0.566 | 0.72 | 0.23–2.24 | | | |
| Hormonal contraception | No | — | 1.00 | — | | | |
| | Yes | 0.504 | 0.70 | 0.24–2.01 | | | |
| Excision type | Type I | — | 1.00 | — | | | |
| | Type II | 0.673 | 1.26 | 0.43–3.73 | | | |
| TZ Type 3 | | | | | | | |
| Age | <40 y | — | 1.00 | — | | None selected | |
| | ≥40 y | 0.799 | 1.14 | 0.41–3.23 | | | |
| Menopausal status | No | — | 1.00 | — | | | |
| | Yes | 0.159 | 2.36 | 0.71–7.82 | | | |
| Smoking | No | — | 1.00 | — | | | |
| | Yes | 0.156 | 2.39 | 0.72–7.93 | | | |
| Hormonal contraception | No | — | 1.00 | — | | | |
| | Yes | 0.437 | 0.64 | 0.21–1.96 | | | |
| Excision type | Type I | — | 1.00 | — | | | |
| | Type II | 0.782 | 1.19 | 0.34–4.15 | | | |

OR indicates odds ratio.

observed the residual disease in only 22 of 41 women who underwent a second procedure within 3 months of the event.[7]

Few studies correlate the TZ type with excision type. Chen and Zhou,[19] studying 215 women, observed that TZ type 3 is more associated with positive margins, but they did not relate this finding to the excision type. Lara-Peñarada, studying 353 women, observed that excision type I was not associated with a positive endocervical margin risk. The 10-mm loop was enough to obtain a negative endocervical margin in 3 of 4 women in our study. This proportion increased to 4 of 5 women when the 15-mm loop was used. Although this difference was significant, it is necessary to consider the low risk of recurrence indicated in the literature, even when margins are positive.[20] Even in TZ types 2 and 3 women, none of the variables evaluated showed a predictor of increasing the chance of obtaining a negative endocervical margin. A meta-analysis on margins and excision showed that an hr-HPV test more accurately predicts the risk of residual or recurrent disease than the margin result.[18]

The originality of this study is to have related the TZ type with the excision type. The large sample and adequate information recording enabled analyses in subgroups by type. Here, we did not assess the follow-up of these women, which may provide additional information in the future. We also did not analyze the subgroup of women with glandular lesions because they were only 11 women. The HPV-DNA test is not available in public settings in Brazil, like in almost all middle-income and low-income countries. In this sense, we still depend on clinical variables to define adequate management for these women.

Even when margins are positive, the low risk of recurrence reported in the literature reinforces the hypothesis that the depth of excision is not as relevant in the management of these women. It is possible to indicate excision type I for all women with HSIL regardless of the TZ type and propose a follow-up algorithm that includes HPV genotyping in decision making in selected cases. Future research may indicate the feasibility of this recommendation.

The endocervical margin status was negative in at least 3 in every 4 women who underwent LEEP to treat cervical cancer precursor lesion, regardless of type I or II excision. Age, menopausal status, smoking, and hormonal contraception were not predictors of increasing the chance of obtaining a negative endocervical

margin. Considering the sample was predominantly of women younger than 40 years, excision type I showed satisfactory results in premenopausal women and TZ 1 or 2.

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**Artigo 3:**

**“Screen-and-treat approach in managing cervical cancer precursor lesions: An observational study with 524 women.”**

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# Screen-and-treat approach in managing cervical cancer precursor lesions: An observational study with 524 women☆

Juliana Y. Yoneda, Julio C. Teixeira, Sophie Derchain, Joana F. Bragança, Luiz C. Zeferino, Diama B. Vale *

*Department of Obstetrics and Gynecology, University of Campinas, Rua Vital Brazil, 80 – Cidade Universitária, CEP 13083-888 Campinas, Brazil*

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ABSTRACT

*Objective:* To detect factors related to overtreatment with the "Screen-and-treat" approach (S&T) in women with suspicious cervical precancerous lesions.
*Study design:* A retrospective observational study of 524 women with high-grade squamous intraepithelial lesions (HSIL) or more severe (HSIL+) in cytology, treated by the Large Loop Excision of the Transformation Zone (LLETZ): 161 without a previous biopsy (S&T group) and 363 with a previous biopsy (biopsy group) from January 2017 to July 2020. The main outcome was a diagnosis of LLETZ: negative (negative or low-grade squamous intraepithlelial lesion LSIL) or HSIL+. A negative diagnosis was interpreted as "overtreatment." Results were analyzed as a function of the S&T approach (whether previous biopsy or not). Variables were obtained from medical records, and were compared with Chi-square or Fisher's exact test (p, p-value), to estimate the chances of a logistic regression analysis (Odds Ratio, OR, or admitting a Confidence Interval (CI) of 95 %).
*Results:* No differences were observed in groups regarding menopausal status, smoking, hormonal contraceptive use, colposcopy findings, LLETZ diagnosis, and recurrence. Comparing biopsy vs S&T groups, the frequency of women over 40 years was 28.4 % vs 39.7 % ($p = 0.011$), and transformation zone type 3 was 12.2 vs 26.8 % ($p < 0.001$), respectively. In women managed by S&T, when compared to a LLETZ diagnosis, an HSIL+ result was more frequent in women presenting with TZ 1 (93.1 % TZ1 vs 78.5 % TZ2 vs 73.8 % TZ3, $p = 0.008$) and in women with abnormal colposcopy (92.9 % abnormal vs 38.1 % negative, $p < 0.001$). Multiple regression analysis found that women with negative colposcopic findings presented a higher risk for negative LLETZ diagnosis (LSIL/Negative final histology) (18.6; 6.18–56.02).
*Conclusions:* No difference was observed in the LLETZ diagnosis in women who did or did not use the S&T approach: it was adequate for women referred by cytological HSIL along with high-grade colposcopic findings.

## Introduction

Cervical cancer is still one of the leading causes of death among women from both low and middle-income countries [1,2]. The World Health Organization (WHO) called for the global elimination of cervical cancer, advocating full vaccination for 90 % of girls by the age of 15; screening with a high-performance test for 70 % of women by the ages of 35 to 45; treating 90 % of women with pre-cancer and 90 % of managed invasive cancer [3].

In cytology-based screening, women with abnormal results usually follow a 3-step conventional strategy requiring at least two follow-up visits: one for colposcopy and biopsies and at least one for treatment and/or follow-up. The expedited treatment or "Screen-and-treat" (S&T) approach involves diagnosis and treatment of precursor lesions in a single visit, reducing the costs, loss of follow-up, and patient anxiety [4–6]. Treatment with an excisional procedure, such as large loop excision of the transformation zone (LLETZ), is preferred if possible [7]. One concern is risk of overtreatment and adverse pregnancy outcomes, e.g., preterm births [8–10].

In Brazil, the National Guidelines for Cervical Cancer Screening recommends referring women older than 25 showing in cytology a high-grade squamous intra-epithelial lesion or more severe (HSIL+) for

☆ The project was approved by the "Ethics and Research Committee" of the University of Campinas, under the number CAAE 13034013.6.0000.5404 version 3, on September 24, 2018.

* Corresponding author.
*E-mail address:* dvale@unicamp.br (D.B. Vale).

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colposcopy. Given agreement between cytology and colposcopy, it is recommended to proceed with the S&T approach [11]. Brazil has a moderate cervical cancer incidence, with follow-up loss as a significant screening concern [12]. Many referral services adopt the S&T approach, using broader criteria to avoid such losses.

Recent guidelines tend to indicate the S&T approach, based on a women's risk profile, rather than using strict criteria. These guidelines consider the human papillomavirus (HPV) status [10,13,14]. In regions where the HPV test is not available, alternative recommendations should be tested. The objective of this study was to detect factors related to overtreatment in the S&T approach to help decisions to manage those with suspicious cervical precancerous lesions.

## Material and methods

This is a retrospective study of 524 women referred to a colposcopy service to treat precursor lesions by LLETZ, 161 without a previous biopsy (S&T group) and 363 with a previous biopsy (biopsy group) from January 2017 to July 2020. The women were relying on the public health system in the metropolitan region of Campinas, a densely populated urban area of São Paulo state, Brazil. Medical records of the Women's Hospital of the University of Campinas were reviewed. The sample was all women who underwent LLETZ during this period. The research project was approved by the 'Ethics and Research Committee of the University of Campinas' (CAAE 13034013.6.0000.5404).

The national guidelines for cervical cancer screening in Brazil recommends cytology every-three years in women from 25- to 64-years-old. Yet, it is possible that women not in this target group or for a shorter period would be screened. This occurs in the public health system occurs at primary health care (PHC) facilities, and a physician or nurse collects cervical samples. Atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL) are managed at a PHC. Any abnormal result is referred to a colposcopy service and evaluated by a specialized gynecologist: HSIL, atypical squamous cells suggestive of high-grade lesions (ASC-H), atypical glandular cells (AGC), adenocarcinoma in situ (AIS), or suggestive of invasive carcinoma.

The S&T approach is recommended for women over 25 years when the cytology is HSIL+, colposcopy is suggestive of a high-grade lesion, and the transformation zone (TZ) is type 1. This avoids losses due to difficulties in accessing facilities. However, in clinical practice, when losses are likely, it is possible to extend those criteria to women over 25 years of age, regardless of the colposcopy impression (except when suggestive of invasion) or TZ type.

In this study, women were referred by cytology and/or biopsies HSIL+ (ASC-H, HSIL, AGC, AIS). At admission, women underwent colposcopy. If the colposcopy impression was suggestive of microinvasive or invasive cancer, a direct biopsy was performed. When the colposcopy impression was abnormal (all cases suggestive of a high-grade lesion and some cases suggestive of a low-grade lesion), the woman was referred to LLETZ with or without a previous biopsy (non S&T or S&T), regardless of TZ. When the colposcopy was negative, a careful vaginal examination was performed. In the absence of suspected areas, the two approaches were proposed and discussed with the women: new cytology and careful follow-up, or immediate referral to LLETZ, considering its risks and benefits and highlighting obstetric morbidities post-LLETZ in women of reproductive age. LLETZ was performed at the outpatient colposcopy unit under local anesthesia by a standard technique on this or another visit.

In this period, 734 LEEP were performed. Were excluded cases with suspicious microinvasion or invasion (28 patients); when margins could not be evaluated due to piece fragmentation (6 patients); when loop size was not recorded (20); or when the patient had a history of a previous excisional procedure (59 cases). We excluded 97 cases with no cytology data or who were referred for cytology results other than HSIL. The final sample consisted of 524 patients who underwent LLETZ, 363 women with a previous biopsy, and 161 women without one. Average time from cytology to treatment was 7.9 months in the S&T group and 10.4 months for non S&T: in this group, average time from biopsy to treatment was 6.4 months.

The main outcome was diagnosis of LLETZ: negative (negative or cervical intraepithelial neoplasia grade 1 – CIN1) or CIN2+ (CIN 2 or 3, AIS, or more severe). A negative diagnosis was interpreted as "overtreatment." Results were analyzed as a function of the S&T approach (S&T group or biopsy group). Other variables were age, menstrual status, smoking, hormonal contraceptive use, TZ type, colposcopy findings, and recurrence. All clinical variables were obtained from medical records registered when the procedure was performed. TZ was categorized into types 1, 2, or 3 (TZ 1, 2, or 3), and colposcopic findings as negative or abnormal, according to the International Federation of Cervical Pathology and Colposcopy (IFCPC 2011) when using this terminology [10].

For statistical analysis, the description was performed by frequencies as a function of the S&T, using Chi-square or Fisher's exact test. Uni- and multivariate logistic regression were performed to assess factors linked to overtreatment (negative in the final diagnosis) by Odds Ratio and its 95 % Confidence Interval (CI) estimation. A significance level of 5 % ($p < 0.05$) was adopted. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., 2013, Cary, NC, USA).

## Results

Table 1 shows the distribution of the 524 women for analyzed variables and the S&T approach. The proportion of those in menopausal status, who smoked, used hormonal contraceptives, with colposcopy findings, histological diagnosis in LEETZ, and recurrence, showed no difference for patients in both groups. Older women (over 39 years) were frequently engaged in the S&T group (28.4 % in biopsy vs 39.7 % in S&T, $p = 0.011$). The TZ type 3 was more than twice as frequent in the

**Table 1**
Clinical and pathological features regarding S&T or conventional approach.

| | See-and-Treat (S&T) | | | | | |
|---|---|---|---|---|---|---|
| | No (Biopsy group) | | Yes (S&T group) | | | |
| | n | % | n | % | Total | P-value |
| **Age*** | | | | | | |
| <40 years | 259 | 71.6 | 97 | 60.3 | 356 | **0.011** |
| ≥40 years | 103 | 28.4 | 64 | 39.7 | 167 | |
| **Menopause** | | | | | | |
| No | 321 | 88.4 | 142 | 88.2 | 463 | 0.939 |
| Yes | 42 | 11.6 | 19 | 11.8 | 61 | |
| **Smoking*** | | | | | | |
| No | 273 | 75.8 | 125 | 78.6 | 398 | 0.489 |
| Yes | 87 | 24.2 | 34 | 21.4 | 121 | |
| **HCO*** | | | | | | |
| No | 197 | 55.5 | 94 | 58.8 | 291 | 0.490 |
| Yes | 158 | 44.5 | 66 | 41.2 | 224 | |
| **TZ*** | | | | | | |
| 1 | 232 | 64.5 | 87 | 55.4 | 319 | **<0.001** |
| 2 | 84 | 23.3 | 28 | 17.8 | 112 | |
| 3 | 44 | 12.2 | 42 | 26.8 | 86 | |
| **Colposcopy** | | | | | | |
| Negative | 49 | 13.5 | 21 | 13.0 | 70 | |
| Abnormal | 314 | 86.5 | 140 | 87.0 | 454 | 0.888 |
| **LLETZ diagnosis** | | | | | | |
| Negative/LSIL | 52 | 14.3 | 23 | 14.3 | 75 | 0.991 |
| HSIL+ | 311 | 85.7 | 138 | 85.7 | 449 | |
| **Relapse** | | | | | | |
| No | 347 | 95.6 | 155 | 96.3 | 502 | 0.720 |
| Yes | 16 | 4.4 | 6 | 3.7 | 22 | |

P-value by $x^2$ or Fisher exact test.
*Missing information.
Legend: HCO – Hormonal contraceptive; TZ – Transformation zone; LSIL – Low-grade intraepithelial lesion; HSIL+ - High-grade intraepithelial lesion or more severe.

S&T group (12.2 % in biopsy vs 26.8 % in S&T, $p < 0.001$).

Of 524 women, one was referred by a biopsy of adenocarcinoma in situ (AIS), as her diagnosis in LLETZ was CIN3, and she did not relapse. There were 15 women referred by AGC or AIS results in cytology; none confirmed glandular disease in biopsies at admission or in a LEETZ diagnosis. None showed relapse on follow-up. The diagnosis in LLETZ was AIS in 3, micro or invasive adenocarcinoma in 7, and micro or invasive squamous cell carcinoma in 34 (data not shown). All women were treated with the service as per national guidelines.

Table 2 shows a link between clinical features in women managed by S&T and LLETZ diagnosis: smoking and recurrence showed no difference in LLETZ diagnosis. A final negative diagnosis was more frequent in women older than 39 (21.9 % in ≥ 40 years vs 8.2 % <40 years, $p = 0.025$) or menopausal women (36.8 % menopause vs 11.3 % not in menopause, $p = 0.008$). A CIN2 + LLETZ diagnosis were more frequent in those on hormonal contraceptives (92.4 % yes vs 80.9 %, $p = 0.04$), women with TZ 1 (93.1 % TZ1 vs 78.5 % TZ2 vs 73.8 % TZ3, $p = 0.008$), and those with abnormal colposcopy (abnormal 92.9 % vs negative 38.1 %, $p < 0.001$).

Table 3 presents regression analysis results of overtreatment (negative final diagnosis) according to the variables studied. After controlling for others, we found these characteristics to have a greater chance of overtreatment: women over 40 (2.74;1.11–6.78); menopausal women (4.59; 1.58–13.36); those using hormonal contraception (2.89; 1.02–8.23), TZ 2 (3.68;10.08–12.54), TZ 3 (4.79;1.63–14.07), with negative findings at colposcopy (21.13; 7.10–62.87). Multiple regression analysis found that women with negative colposcopic findings presented a higher risk for overtreatment (negative final histology) (18.6; 6.18–56.02).

## Discussion

This study evaluated excision treatment results when the S&T approach was adopted in cervical cancer screening. Overtreatment, or a negative diagnosis in LLETZ, was not significantly higher in women who submitted to S&T. When a woman underwent S&T with a negative colposcopy, she had a chance 18 times higher of overtreatment. More women over 40 were submitted to S&T, which may indicate that gynecologists felt freer to offer it when obstetric morbidity was not a greater concern. These results might be seen in the context that the S&T is an important strategy to avoid loss to follow-up when cervical cancer is a public health problem.

The S&T approach has been debated since its beginning, due to risk of overtreatment, especially in young women. It was preferred for HSIL cytology management, as it requires fewer visits, increases patient compliance, and is more cost-effective than conventional management [5,15]. It appears to be psychologically beneficial and preferred by women with CIN2/3 [6]. From a public health perspective, providing patients with the most efficient and cost-effective strategy may reduce socioeconomic barriers in healthcare and any clinical consequences associated with delayed treatment of HSIL [16].

A systematic review and meta-analysis in 2016 supported evidence that S&T can be used to treat women referred for HSIL or with high-grade colposcopic impressions [17]. The Guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP) states that it is acceptable to treat women referred for high-grade smears, except in pregnancy or those between 21 and 24, without mentioning colposcopy findings [13]. Our findings suggest that avoiding loss is a relevant concern in clinical practice, as criteria were not consistently followed, favoring follow-up loss.

In the study, 31 % of women were managed by S&T. We found similar overtreatment rates for S&T and conventional strategies at 14.2 % and 14.3 %, respectively, comparable to the literature ranging from 11 % to 35 % [17]. A Brazilian study reviewing 616 women submitting to S&T from 1996 to 2017, excluded those with TZ type 3, and found 8.4 % of overtreatment [18]. A prospective finish cohort from 2014 to 2018 saw overtreatment at 10.0 % [19].

We found that older women and TZ type 3 were more frequently managed with S&T. A similarity in overtreatment can probably be explained by the high performance of cytology and an experienced colposcopy team [11]. A recent large population-based study in the Netherlands suggested a threshold of <15 % overtreatment for women under 40 [16]. As it is a high-income nation with organized vaccination and screening programs, it inspired us to achieve this goal.

A negative colposcopy was associated with an 18.6 higher risk of a negative final diagnosis in women who submitted to S&T. Several studies suggest that this approach will benefit women with high-grade cytology and consistent colposcopic findings [20,21]; this is crucial for young women when obstetric morbidities are a concern. However, it must be noted that S&T must be considered even without concordant colposcopy findings, in regions with moderate to high prevalence of cervical cancer where that adherence and follow-up were questionable [22,23]. Even S&T in younger women (ages 21–24) were discussed when access to care was a problem [24]. There is strong evidence that women with a history of cervical dysplasia have a higher risk of preterm delivery, regardless of previous LEEP history [25]. When referred by suspected cytology and negative colposcopy, follow-up loss may justify the S&T approach.

Strengths of our study are the number of patients with a colposcopy impression reported. The main limitations are its retrospective design, which may lead to heterogeneity in the selection criteria of both groups, and lack of HPV test results. In Brazil, like other middle- and low-income countries, the HPV test is unavailable in public settings. As such, we still depend on clinical variables to improve management for these women.

## Conclusions

Our findings suggest that S&T management is adequate for women referred by cytological HSIL and with high-grade colposcopic findings. The decision to proceed with S&T should be considered based on

**Table 2**
Clinical and pathological features in women managed by S&T and their relation to overtreatment (negative/LSIL final diagnosis).

| | S&T LLETZ Diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | Negative/LSIL | | HSIL+ | | | |
| | n | % | n | % | Total | P-value |
| **Age*** | | | | | | |
| <40 years | 9 | 8,2 | 88 | 91,8 | 97 | 0.025 |
| ≥40 years | 14 | 21,9 | 50 | 78,1 | 64 | |
| **Menopause** | | | | | | |
| No | 16 | 11,3 | 126 | 88,7 | 142 | 0.008 |
| Yes | 7 | 36,8 | 12 | 63,2 | 19 | |
| **Smoking*** | | | | | | |
| No | 17 | 13,6 | 108 | 86,4 | 125 | 1.000 |
| Yes | 5 | 14,7 | 29 | 85,3 | 34 | |
| **HCO** | | | | | | |
| No | 18 | 19,1 | 76 | 80,9 | 94 | 0.040 |
| Yes | 5 | 7,6 | 61 | 92,4 | 66 | |
| **TZ*** | | | | | | |
| 1 | 6 | 6,9 | 81 | 93,1 | 87 | 0.008 |
| 2 | 6 | 21,4 | 22 | 78,5 | 28 | |
| 3 | 11 | 26,1 | 31 | 73,8 | 42 | |
| **Colposcopy** | | | | | | |
| Negative | 13 | 61,9 | 8 | 38,1 | 21 | <0.001 |
| Abnormal | 10 | 7,1 | 130 | 92,9 | 140 | |
| **Relapse** | | | | | | |
| No | 23 | 14,8 | 132 | 85,2 | 155 | 0.595 |
| Yes | 0 | 0 | 6 | 100 | 6 | |

P-value by $x^2$ or Fisher exact test.
*Missing information.
Legend: HCO – Hormonal contraceptive; TZ – Transformation zone; LSIL – Low-grade intraepithelial lesion; HSIL+ – High-grade intraepithelial lesion or more severe.

**Table 3**
Uni and Multivariate analysis of predictive factors of overtreatment in the S&T group.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | p-value | OR | CI 95 % | p-value | OR | CI 95 % |
| **Age** | | | | | | |
| <40 years | – | 1.00 | – | | | |
| ≥40 years | 0.029 | 2.74 | 1.11–6.78 | | | |
| **Menopause** | | | | | | |
| No | – | 1.00 | – | | | |
| Yes | 0.005 | 4.59 | 1.58–13.36 | | | |
| **Smoking** | | | | | | |
| No | – | 1.00 | – | | | |
| Yes | 0.869 | 1.10 | 0.37–3.22 | | | |
| **HCO** | | | | | | |
| Yes | – | 1.00 | – | | | |
| No | 0.047 | 2.89 | 1.02–8.23 | | | |
| **TZ** | | | | | | |
| 1 | – | 1.00 | – | | | |
| 2 | 0.037 | 3.68 | 1.08–12.54 | | | |
| 3 | 0.004 | 4.79 | 1.63–14.07 | | | |
| **Colposcopy** | | | | | | |
| Abnormal | – | 1.00 | – | – | 1.00 | – |
| Negative | <0.001 | 21.13 | 7.10–62.87 | <0.001 | 18.60 | 6.18–56.02 |

Simple and multiple regression analysis. Multiple regression by Stepwise criteria.
Legend: OR – Odds Ratio; CI – Confidence Interval; HCO – Hormonal contraceptive; TZ – Transformation zone.

cervical cancer prevalence, patient adherence, access to screening, age, and risk of overtreatment repercussions.

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None to declare.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Artigo 4**:

**“The top-hat procedure does not impact the management of women treated by LEEP in cervical cancer screening.”**

Artigo submetido em revisão por pares em agosto de 2023 na revista **“Journal of Gynecology Oncology”**.

Journal of Gynecologic Oncology

# The top-hat procedure does not impact the management of women treated by LEEP in cervical cancer screening

--Manuscript Draft--

| | |
|---|---|
| **Manuscript Number:** | |
| **Full Title:** | The top-hat procedure does not impact the management of women treated by LEEP in cervical cancer screening |
| **Short Title:** | Top-hat does not impact women treated by LEEP |
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| **Corresponding Author:** | Diama Bhadra Vale<br>Universidade Estadual de Campinas<br>Campinas, BRAZIL |
| **Corresponding Author Secondary Information:** | |
| **Corresponding Author's Institution:** | Universidade Estadual de Campinas |
| **First Author:** | Juliana Yoneda, MD, MSc |
| **Order of Authors:** | Juliana Yoneda, MD, MSc |
| | Aline Santiago, MD, PhD |
| | Julio Teixeira, MD, PhD |
| | Helymar Machado, PhD |
| | Sophie Derchain, MD, PhD |
| | Milena Yanomine, Medical Student |
| | Diama Bhadra Vale |
| **Additional Information:** | |
| **Question** | **Response** |
| **Synopsis**<br>Original article, cooperative group report, and special report should include synopsis of the findings and strong points of the study in 3-4 sentences consisting of 10-15 words (total 350 characters in total). | Added |
| **Abstract:** | Aim<br>This study aimed to describe the Top-hat results and their association with margin status and disease relapse in a referral facility in Brazil.<br>Methods<br>A retrospective study of 440 women submitted to LEEP to treat HSIL, in which 80 cases were complemented immediately by the Top-hat procedure (Top-hat group - TH). TH group was compared to women not submitted to Top-hat (NTH). The sample by convenience included all women that underwent LEEP from January 2017 to July 2020. The main outcome was the histological result. Other variables were margins, age, transformation zone (TZ), depth, and relapse. The analysis used the Chi-square test and logistic regression.<br>Results |

| | |
|---|---|
| | The TH group was predominantly 40 and older (NTH 23.1% vs. TH 65.0%, p<0.001). No difference was found in having CIN2/CIN3 as the final diagnosis (NTH 17.0% vs. TH 21.3%, p=0.362), or in the prevalence of relapse (NTH 12.0% vs. TH 9.0%, p=0.482). Of the 80 patients submitted to Top-hat, in eight the histological result was CIN2/CIN3. A negative Top-hat result was related to negative endocervical margin in 83.3%. A CIN2/CIN3 Top-hat result was related to CIN2/CIN3 margin in 62.5% (p=0.009). The chance of obtaining a Top-Hat negative result was 22.4 times higher (2.4-211.0) when the endocervical margin was negative and 14.5 times higher (1.5-140.7) when the ectocervical margin was negative.<br>Conclusion<br>The top-Hat procedure did not alter the final diagnosis of LEEP. No impact on relapse was observed. The procedure should be avoided in women in reproductive ages. |
| **Suggested Reviewers:** | Yara Furtado<br>UFRJ: Universidade Federal do Rio de Janeiro<br>yarafurtadorj@terra.com.br |
| | Isabel Val<br>UFF: Universidade Federal Fluminense<br>isabeldoval1@gmail.com |
| **Opposed Reviewers:** | |
| **Author Comments:** | |
| **Order of Authors (with Contributor Roles):** | Juliana Yoneda, MD, MSc (Data curation; Formal analysis; Methodology; Validation; Writing – original draft; Writing – review & editing) |
| | Aline Santiago, MD, PhD (Formal analysis; Writing – original draft; Writing – review & editing) |
| | Julio Teixeira, MD, PhD (Conceptualization; Writing – review & editing) |
| | Helymar Machado, PhD (Formal analysis; Writing – original draft; Writing – review & editing) |
| | Sophie Derchain, MD, PhD (Conceptualization; Data curation; Writing – review & editing) |
| | Milena Yanomine, Medical Student (Data curation; Writing – original draft; Writing – review & editing) |
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UNIVERSIDADE ESTADUAL DE CAMPINAS
HOSPITAL DA MULHER PROF. DR. JOSÉ ARISTODEMO PINOTTI-CAISM
DIVISÃO DE ONCOLOGIA



**University of Campinas**
**School of Medical Sciences**
**Department of Obstetrics and Gynecology**

*Online submission*

May 28th 2023

Dear editor,

I am sharing the manuscript *'The top-hat procedure does not impact the management of women treated by LEEP in cervical cancer screening'* by Yoneda *et al*., which we wish to submit to *`Journal of Gynecology Oncology.`*

This manuscript is a retrospective analysis of 440 cases that aimed to describe Top-hat results in 80 cases and check its association with margin status and disease relapse compared to the non-Top hat group in a referral facility in Brazil. The Top-hat procedure did not alter the final diagnosis. No impact on relapse was observed. We concluded not recommending the procedure, especially in young women.

I guarantee that all authors have participated sufficiently in this work to take public responsibility, have reviewed the final version, and have approved it for publication. Neither this manuscript nor one with substantially similar content under our authorship has been published or is being considered for publication elsewhere. I confirm that neither my co-authors nor I have any personal, commercial, political, academic, or financial conflicts of interest.

We do hope that the manuscript can be considered suitable for publication in *`Journal of Gynecology Oncology.` We* look forward to hearing from you regarding our submission and will be pleased to answer any queries you or your reviewers may have.

Thank you, in advance, for your consideration,
Yours faithfully,

Assistant Prof. D. B. Vale, M.D., PhD
Corresponding author
dvale@unicamp.br; tel +551935219466.

# The top-hat procedure does not impact the management of women treated by LEEP in cervical cancer screening

**Authors**

Juliana Yoko Yoneda[1], ORCID 0000-0001-8312-6327

Aline Evangelista Santiago[2], ORCID 0000-0002-4562-3784

Julio Cesar Teixeira[1], ORCID 0000-0002-0979-376X

Helymar Costa Machado[1], ORCID 0000-0001-9800-2351

Sophie Derchain[1], ORCID 0000-0003-1029-9993

Milena Yonamine[1], ORCID 0000-0003-4727-0975

Diama Bhadra Vale[1], ORCID 0000-0003-2423-0225

*[1]Department of Obstetrics and Gynecology, University of Campinas. Rua Vital Brasil, 80. CEP 13083-888, Campinas, São Paulo, Brazil.*

*[2]Medicine School, University of Santo Amaro, Rua Professor Enéas de Siqueira Neto, 340, CEP 04829-300, São Paulo, São Paulo, Brazil.*

**Corresponding author**

Prof. Dr. Diama Bhadra Vale, MD, PhD

dvale@unicamp.br

Rua Vital Brazil, 80 – Cidade Universitária, CEP 13083-888, Campinas, Brazil

+551935219305

**Running Head**

The impact of Top-hat in LEEP

## Synopsis

- No difference was found in the final diagnosis or relapse in women submitted or not to Top-Hat.
- A higher chance of a Top-Hat negative result was observed when margins were negative.
- The top-Hat procedure should be avoided in women of reproductive age.

**Abstract**

**Aim**

This study aimed to describe the Top-hat results and their association with margin status and disease relapse in a referral facility in Brazil.

**Methods**

A retrospective study of 440 women submitted to LEEP to treat HSIL, in which 80 cases were complemented immediately by the Top-hat procedure (Top-hat group - TH). TH group was compared to women not submitted to Top-hat (NTH). The sample by convenience included all women that underwent LEEP from January 2017 to July 2020. The main outcome was the histological result. Other variables were margins, age, transformation zone (TZ), depth, and relapse. The analysis used the Chi-square test and logistic regression.

**Results**

The TH group was predominantly 40 and older (NTH 23.1% vs. TH 65.0%, p<0.001). No difference was found in having CIN2/CIN3 as the final diagnosis (NTH 17.0% vs. TH 21.3%, p=0.362), or in the prevalence of relapse (NTH 12.0% vs. TH 9.0%, p=0.482). Of the 80 patients submitted to Top-hat, in eight the histological result was CIN2/CIN3. A negative Top-hat result was related to negative endocervical margin in 83.3%. A CIN2/CIN3 Top-hat result was related to CIN2/CIN3 margin in 62.5% (p=0.009). The chance of obtaining a Top-Hat negative result was 22.4 times higher (2.4-211.0) when the endocervical margin was negative and 14.5 times higher (1.5-140.7) when the ectocervical margin was negative.

**Conclusion**

The top-Hat procedure did not alter the final diagnosis of LEEP. No impact on relapse was observed. The procedure should be avoided in women in reproductive ages.

**Key-words**

Uterine Cervical Neoplasms; Cervical Intraepithelial Neoplasia; Colposcopy; Conization; Top-Hat

## Introduction

Treatment of precursor lesions is a major strategy for cervical cancer prevention. The World Health Organization (WHO) made a global call to eliminate cervical cancer and advocates that 90% of women with positive screening tests should receive treatment (1). Despite the advances in screening and treatment, cervical cancer remains one of the leading causes of death among women in low- and middle-income countries (2,3).

Loop electrosurgical excision procedure (LEEP) is a widespread treatment of cervical intraepithelial neoplasia (CIN) since its first description in 1989 (4). The main focus of excision is to remove the entire lesion, preventing the development of invasive disease. Meanwhile, it provides the most reliable biopsy specimens and can exclude invasive disease (5). Incomplete excision and high-risk HPV infection persistence are the most important predictors of recurrence risk (5).

The Top-hat procedure is a technique of type 3 excision of the cervix, consisting of a second pass of a deeper resection into the endocervical canal with a small square loop immediately after a traditional LEEP. It aims to reduce incomplete excision and residual disease (6,7).

This study aimed to describe the Top-hat procedure's results and association with margin status and disease relapse in a referral facility in Brazil. The results of this study can support the decision on the management of patients in the context of cervical cancer prevention.

## Material and Methods

This is a retrospective study of 440 women submitted to LEEP to treat precursor lesions from January 2017 to July 2020 in the context of cervical cancer screening. In 80 cases, an additional endocervical fragment was obtained after the conventional LEEP procedure (Top-hat group - TH).

The subjects were women relying on the public health system living in the metropolitan region of Campinas, a heavily populated urban area in São Paulo state, Brazil. They were referred to the University of Campinas Women's Hospital, where medical records were reviewed. The sample was selected by convenience, including all women that underwent LEEP in the period.

Women were referred by cytology and/or biopsies showing high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), atypical glandular cells (AGC) or adenocarcinoma *in situ* (AIS) – HSIL+; or by the persistence of atypical squamous cells of undetermined significate (ASC-US) or low grade squamous intraepithelial lesion (LSIL). At admission, women were submitted to colposcopy and referred to LEEP when there was no suspicion of micro-invasive or invasive cancer. LEEP is performed in the outpatient clinic under local anesthesia by colposcopy vision. Top Hat is performed when there is a subjective impression of positive margins in the main fragment, avoiding it in women in their reproductive ages.

In the selected period, 734 LEEP were performed. The exclusion criteria were cases referred by persistent ASC-US or LSIL (97 cases); micro-invasive or invasive lesions suspected on cytology or colposcopy (28 cases); history of a previous excisional procedure (59 cases); LEEP margins not evaluated due to piece fragmentation (6 cases); when the size of the loop used was not recorded (20 cases); and when the final diagnosis in LEEP was micro-invasive or invasive neoplasia (48 cases) or negative (in the main and Top-hat fragment when applied - 36 cases). The final sample consisted of 440 patients.

The final histological diagnosis in the main LEEP fragment, the Top-hat fragment, or the endocervical/ectocervical margins was categorized as: negative (negative or LSIL/cervical intraepithelial neoplasia grade 1 – CIN 1) or positive (CIN 2 or 3, AIS or more severe). Age was categorized as younger or older than 40 (<40 or ≥40). The transformation zone was classified into types 1, 2, or 3 (TZ 1, 2, or 3), according to IFCPC 2011 colposcopic terminology, and obtained from the procedure form (6). The depth of the main fragment was categorized as 10mm or lower or greater than 10mm (≤10 or >10mm). A re-excision was performed in 48 cases when relapse was suspected by cytology, colposcopy and/or biopsy. In some cases, a re-excision was performed when margins were positive to avoid loss in follow-up in a vulnerable woman. The average time from LEEP to re-excision was 14.9 months, 16.0 in the Top-hat group, and 14.6 in the non-Top-hat group. Relapse was determined during follow-up by a positive cytology or biopsy/re-excision result showing HSIL+.

For statistical analysis, the description was performed by frequencies using the Chi-square or Fisher's exact test; and uni and multivariate logistic regression to estimate Odds Ratio

and its 95% Confidence Interval (CI). A significance level of 5% ($p<0.05$) was adopted. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc. 2013. Cary, NC, USA).

The project was approved by the "Ethics and Research Committee" of the University of Campinas, under the number CAAE 13034013.6.0000.5404 version 3, on September 24, 2018. The Committee waived the need for informed consent.

**Results**

The Top-hat procedure was performed in 80 of the 440 cases analyzed (18.8%). When compared to women not submitted to Top-hat (NTH), those who had the complementation were predominantly 40 years and older (NTH 23.1% vs. TH 65.0%, $p<0.001$), and presented more TZ type 3 (NTH 10.0% vs. TH 37.2%, $p<0.001$). Having CIN 2 or CIN 3 as the final diagnosis was not significantly different when performing or not the Top-hat (NTH 17.0% vs. TH 21.3%, $p=0.362$). Indeed, no difference was found in the prevalence of relapse (NTH 12.0% vs. TH 9.0%, $p=0.482$) (table 1).

Of 80 patients submitted to Top-hat, in eight (10%), the pathological result of this specimen was CIN 2 or 3. No case had an invasive result in the Top Hat fragment. Table 2 shows differences observed in cases regarding the Top-hat result. The only significant difference was related to the result of the endocervical margin in the main specimen: a negative Top-hat result was associated with a negative endocervical margin for CIN 2 or CIN 3 in 83.3% of cases, and when the Top-hat result was CIN 2 or CIN 3, it shared the same endocervical margin status in 62.5% of cases ($p=0.009$).

Looking at the chance of having a Top-Hat negative pathology result, the regression analysis showed that only margin status of the main fragment would predict the result. The multivariate analysis revealed a chance of obtaining a Top-Hat negative result 22.36 times higher (95% CI 2.37-211.02) when the endocervical margin was negative and 14.50 times higher (95% CI 1.50-140.68) when the ectocervical margin was negative (table 3).

**Discussion**

In this retrospective study of 440 women submitted to LEEP for HSIL treatment, the Top-hat procedure was performed in 80. Top-hat cases were majorly women older than 40 and, as expected, presented more TZ type 3. CIN 2 or CIN 3 as the final or more severe diagnosis

120 was not significantly different when performing Top-hat or not. The procedure showed no impact
121 on relapse.

122 The role of the additional procedure after LEEP by Top-hat or endocervical sampling is
123 still unclear. Cejtin *et al*. found that additional procedures for endocervix sampling had no
124 prognostic insight (8). At the same time, Cui *et al.* concluded that endocervical sampling had a
125 higher predictive value than margins to predict residual or persistent disease (9). Chen *et al.*
126 found that a positive Top-hat specimen was associated with short-term treatment failure (10).

127 Of the 80 cases submitted to the Top-hat procedure, only eight (10%) showed CIN2 or
128 CIN 3 on the pathological analysis. A negative Top-hat result was associated with a negative
129 endocervical margin in the main fragment in 83.3% of cases, and when the Top-hat result was
130 CIN 2 or CIN 3, the endocervical margin in the main fragment was positive in 62.5% of cases.
131 The chance of having a negative Top-hat result was 22 times higher when the endocervical
132 margin was negative and 15 times higher when the ectocervical margin was negative.

133 The role of endocervical margin in predicting relapse is well reported (11–14). A balance
134 between oncologic safety and obstetrics morbidities can be expected when relating the type of
135 excision with the TZ type (6,15–18). In three cases submitted to the Top-Hat these specimens
136 showed residual HSIL+, and the endocervical margin of the main fragment was negative.
137 However, the role of residual disease is controversial in predicting relapse. The healing
138 provocated by the scar is probably the mechanism for justifying the dissipation of the residual
139 lesion during follow-up. Important to note that residual disease or relapse should be a weak
140 argument for deeper incisions in young women because, even when margins are positive, the
141 relapse rate is low (5,12–14).

142 Top-hat was performed in 28 of 305 (8%) women younger than 40. In fact, 17% of
143 women with negative endocervical margin were submitted to Top Hat. Considering the lack of
144 evidence to support the benefits of the Top-hat procedures, those women were mistakenly
145 submitted to the potential risks of adverse obstetrics outcomes. The literature shows that
146 women with CIN have a higher risk for prematurity and that excisional treatment can increase
147 that risk, directly related to the deepness of the excisions (19). Top-hat should not be
148 recommended to women in their reproductive ages.

Older women are at a higher risk for recurrence (5,18) and may have some benefit in two situations: when the glandular disease is suspected or when TZ is type 3. In both situations, the Top-hat should be evaluated if the first loop is lower than 15mm (excision types 1 or 2), or when the first pass could not technically reach 10-15mm of deepness. The Top-hat procedure in this situation may prevent excessive bleeding or infection risk due to a lower stroma removal when compared to a loop of 20 or 25mm high.

The strength of this study is that it reinforces the value of clinical findings and provides quality information for colposcopists to improve the treatment of cervical intraepithelial neoplasia. The main limitation is its retrospective nature - we did not perform the Top-hat procedure randomly or follow subjective criteria for its election. There was a potential selection bias since the Top-hat procedure has been performed on older women at our institution. Another limitation is the lack of HPV testing information, which is prevailing in most low-and-middle-income countries. Further prospective studies could analyze the prognostic value of the Top-hat procedure. However, considering the obstetrics risks, there is a lack of support in the literature if the design includes young women.

In this retrospective evaluation of the top-Hat procedure, we observed that a second pass after LEEP did not alter the final diagnosis. No impact on relapse was observed. The procedure should be avoided in women in their reproductive ages. Considering the obstetrics morbidities and the value of the HPV status on follow-up (5,15), we believe there is no support to design a prospective study.

**Conflict of Interest Statement**

Authors declare no Conflict of Interests for this article.

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**Table 1. Description of variables related to LEEP, according to the complementation or not of an immediate second deeper procedure (Top-Hat).**

| | Top-Hat No | | Top-Hat Yes | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | P |
| | 360 | 100 | 80 | 100 | 440 | |
| **Age** | | | | | | |
| <40 | 277 | **76.94** | 28 | 35.00 | 305 | **<0.001** |
| ≥40 | 83 | 23.06 | 52 | **65.00** | 135 | |
| **Transformation Zone†** | | | | | | |
| Type 1 | 242 | **67.79** | 27 | 34.62 | 269 | **<0.001** |
| Type 2 | 76 | 21.29 | 22 | **28.21** | 98 | |
| Type 3 | 39 | 10.92 | 29 | **37.18** | 68 | |
| **Final Diagnosis** | | | | | | |
| Negative/CIN1 | 29 | 8.06 | 5 | 6.25 | 34 | 0.584 |
| CIN2/CIN3 | 331 | 91.94 | 75 | 93.75 | 406 | |
| **Deepness (Main Fragment)** | | | | | | |
| ≤10mm | 195 | 54.17 | 39 | 48.75 | 234 | 0.380 |
| >10mm | 165 | 45.83 | 41 | 51.25 | 206 | |
| **Endocervical Margin** | | | | | | |
| Negative | 299 | 83.06 | 63 | 78.75 | 362 | |
| Positive | 61 | 16.94 | 17 | 21.25 | 78 | 0.362 |
| **Ectocervical Margin** | | | | | | |
| Negative | 271 | 75.28 | 63 | 78.75 | 334 | 0.511 |
| Positive | 89 | 24.72 | 17 | 21.25 | 106 | |
| **Re-Excision Result** | | | | | | |
| Negative | 13 | 33.33 | 5 | 55.56 | 18 | 0.529 |
| HSIL+ | 24 | 61.54 | 4 | 44.44 | 28 | |
| SCC | 2 | 5.13 | 0 | 0.00 | 2 | |
| **Relapse†** | | | | | | |
| No | 272 | 88.03 | 61 | 91.04 | 333 | 0.482 |
| Yes | 37 | 11.97 | 6 | 8.96 | 43 | |

Median time to relapse: Top-Hat No 757.66 months (SD 380.36); Top Hat Yes 742.22 (SD 337.80); p=0.915

†Missing information in some cases.

*Legend: P – P-value; <40 – women younger than 40; ≥40 – women 40 or older; HSIL+ – cervical intraepithelial neoplasia grade 2 or more severe; SCC – squamous cell carcinoma; SD: standard deviation.*

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**Table 2. Relation of variables and pathological result of the immediate second deeper procedure (Top-Hat) in women who have undergone LEEP.**

| | Top-Hat Result | | | | | P |
|---|---|---|---|---|---|---|
| | Negative | | CIN 2 or CIN 3 | | Total | |
| | n | % | n | % | n | |
| | 72 | 100 | 8 | 100 | 80 | |
| **Age** | | | | | | |
| <40 | 27 | 37.50 | 1 | 12.50 | 28 | 0.250 |
| ≥40 | 45 | 62.50 | 7 | 87.50 | 52 | |
| **Transformation Zone†** | | | | | | |
| Type 1 | 24 | 34.29 | 3 | 37.50 | 27 | 0.203 |
| Type 2 | 18 | 25.71 | 4 | 50.00 | 22 | |
| Type 3 | 28 | 40.00 | 1 | 12.50 | 29 | |
| **Final Diagnosis** | | | | | | |
| Negative | 5 | 6.94 | 0 | 0.00 | 5 | 1.000 |
| CIN 2 or CIN 3 | 67 | 93.06 | 8 | 100.00 | 75 | |
| **Deepness (Main Fragment)** | | | | | | |
| ≤10mm | 33 | 45.83 | 6 | 75.00 | 39 | 0.150 |
| >10mm | 39 | 54.17 | 2 | 25.00 | 41 | |
| **Endocervical Margin** | | | | | | |
| Negative | 60 | 83.33 | 3 | 37.50 | 63 | **0.009** |
| Positive | 12 | 16.67 | 5 | 62.50 | 17 | |
| **Ectocervical Margin** | | | | | | |
| Negative | 59 | 81.94 | 4 | 50.00 | 63 | 0.058 |
| Positive | 13 | 18.06 | 4 | 50.00 | 17 | |
| **Re-Excision Result** | | | | | | |
| Negative/CIN1 | 4 | 66.67 | 1 | 33.33 | 5 | 0.524 |
| CIN2/CIN3 | 2 | 33.33 | 2 | 66.67 | 4 | |
| **Relapse†** | | | | | | |
| No | 56 | 93.33 | 5 | 71.43 | 61 | 0.115 |
| Yes | 4 | 6.67 | 2 | 28.57 | 6 | |

Median time to relapse: Negative/CIN1 752.43 (SD 327.86); CIN2/CIN3 654.71 (SD 433.84); p=0.448

†Missing information in some cases.

*Legend: P – P-value; <40 – women younger than 40; ≥40 – women 40 or older; CIN – cervical intraepithelial neoplasia; SD: standard deviation.*

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**Table 3. Factor related with the chance of having a negative pathology result of the immediate second deeper procedure (Top-Hat) in 72 women who have undergone LEEP.**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | **P** | **OR** | **95% CI** | **P** | **OR** | **95% CI** |
| **Age** | | | | | | |
| <40 | --- | 1.00 | --- | | | |
| ≥40 | 0.191 | 0.24 | 0.03 – 2.04 | | | |
| **Transformation Zone** | | | | | | |
| Type 1 | --- | 1.00 | --- | | | |
| Type 2 | 0.486 | 0.56 | 0.11 – 2.83 | | | |
| Type 3 | 0.292 | 3.50 | 0.34 – 35.90 | | | |
| **Final Diagnosis** | | | | | | |
| Negative | --- | 1.00 | --- | | | |
| CIN 2 or CIN 3 | 0.444 | 1.39 | 0.07 – 27.32 | | | |
| **Deepness (Main Fragment)** | | | | | | |
| ≤10mm | --- | 1.00 | --- | | | |
| >10mm | 0.137 | 3.55 | 0.67 – 18.76 | | | |
| **Endocervical Margin** | | | | | | |
| Positive | --- | 1.00 | --- | --- | 1.00 | --- |
| Negative | **0.008** | 8.33 | 1.75 – 39.65 | **0.007** | 22.36 | 2.37 – 211.02 |
| **Ectocervical Margin** | | | | | | |
| Positive | --- | 1.00 | --- | --- | 1.00 | --- |
| Negative | **0.049** | 4.54 | 1.01 – 20.55 | **0.021** | 14.50 | 1.50 – 140.68 |

Analysis by Logistic Regression with Stepwise criteria.

*Legend: P – P-value; <40 – women younger than 40; ≥40 – women 40 or older; CIN – cervical intraepithelial neoplasia; SD: standard deviation.*

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## 5. DISCUSSÃO

Este estudo avaliou os fatores associados ao tratamento das lesões precursoras do CCU em pacientes submetidas à excisão de zona de transformação com alça em aparelho de alta frequência em um serviço de referência. É sabido que o objetivo do tratamento dessas lesões é prevenir o desenvolvimento da doença invasiva. O conhecimento adquirido sobre a história natural do CCU tem permitido a adoção de abordagens mais conservadoras durante a últimas décadas (25). Os achados mais relevantes que contribuíram para essa tendência de mudança nas práticas clínicas são o reconhecimento de que essas lesões apresentam chances razoáveis de regressão espontânea, acometem muitas pacientes jovens, e que o impacto no futuro reprodutivo é significativo (48).

Os métodos excisionais devem remover a lesão e reduzir o risco de doença residual ou recorrência. Na prática clínica atual, é amplamente aceito que o objetivo do procedimento seja a obtenção de margens negativas, essencialmente as margens endocervicais. Uma análise retrospectiva de 2010 com 2.455 pacientes mostrou que o risco de recorrência da lesão escamosa intraepitelial foi de cerca de 5% quando ambas as margens são negativas, e de 20% quando ambas as margens foram positivas (49). Assim, apenas 1 em cada 5 pacientes com ambas as margens positivas apresentariam recorrência. O trabalho de parto prematuro é uma morbidade significativa associada ao procedimento, e é maior quanto maior a profundidade da excisão (50,51). Esse risco parece particularmente importante em mulheres muito jovens, quando o tecido cervical ainda não está totalmente formado (52). Um estudo de coorte mostrou que em mulheres com menos de 35 anos, a taxa de recorrência foi semelhante entre mulheres com profundidade de alça <10 mm em comparação com ≥10 mm (46). Além disso, a prática clínica mostra que o sangramento perioperatório está diretamente relacionado ao volume de tecido excisado.

Essas evidências sugerem que os esforços para a obtenção de margens negativas devam ser questionados, especialmente em mulheres jovens, em função dos riscos e benefícios (42,53). A profundidade da excisão deve ser a mínima necessária para remover a lesão, preservando a função morfológica do colo uterino. Essa mudança de paradigma foi sustentada por resultados que indicam que as taxas

de margens positivas não condizem com um risco significativamente elevado de recorrência. Uma meta-análise encontrou em pacientes submetidas à conização por alta frequência 25,9% de margens positivas, mas apenas 6,7% de doença residual/recorrente (42). Também mostrou que um teste de DNA-HPV de alto risco prediz com mais precisão o risco de doença residual ou recorrente do que o resultado de margem (42). Nessa tese demonstramos que as taxas de margens positivas em nossa amostra estão de acordo com os resultados observados na literatura. Importante dizer que no período do estudo já se praticava em nossa instituição condutas baseadas em abordagens mais conservadoras, como a utilização de alças com altura menores em mulheres jovens.

Para que o balanço entre riscos e benefícios seja considerado, a Sociedade Americana de Colposcopia e Patologia Cervical (ASCCP), recomendou que a indicação do tipo de excisão por tipo da zona de transformação (ZT) seria uma estratégia para atingir a remoção de uma menor profundidade de tecido, garantindo a segurança oncológica (21,25). Nesta tese, a proporção de margem endocervical negativa foi de 78% na excisão do tipo I e de 86% na excisão do tipo II. Considerando um risco de doença residual ou recorrência baixo, a realização da excisão do tipo I, portanto, nos parece bastante segura. Em mulheres em idade reprodutiva, a excisão com alças maiores de 10 mm deve ser restrita a condições especiais que aumentam o risco de persistência ou recorrência, como suspeita de imunodeficiência ou lesões glandulares. Um algoritmo de seguimento deve incluir a genotipagem do HPV na tomada de decisão em casos selecionados. Pesquisas futuras podem indicar a viabilidade dessa recomendação.

Na perspectiva de dar suporte às recomendações de condutas mais conservadoras no manejo das lesões precursoras, nos propusemos a avaliar o papel da obtenção do controverso fragmento adicional imediatamente após a exérese do fragmento principal, prática conhecida como “reforço endocervical” ou “segunda passada” ou “Top-hat” na língua inglesa. Nesta análise o “Top-hat” foi realizado em 8% de mulheres com menos de 40 anos. Considerando a falta de evidências para apoiar os benefícios do procedimento adicional, especulamos que essas mulheres foram submetidas aos riscos potenciais de resultados obstétricos adversos desnecessariamente - supertratamento. Além disso, no total das mulheres

submetidas ao procedimento adicional, 17% apresentaram margem endocervical negativa no resultado anátomo-patológico do fragmento principal.

Não observamos alteração do diagnóstico final das mulheres que foram submetidas ao procedimento adicional quando comparadas às que não o fizeram. Também não observamos impactos nas taxas de recidiva. Nas mulheres mais velhas o risco obstétrico não deve ser uma preocupação, além disso, essas mulheres apresentam maior risco de recorrência (42,49). Essas mulheres podem se beneficiar do procedimento adicional nas seguintes situações: quando a primeira passagem não atingir tecnicamente 10-15mm de profundidade, e houver a suspeita de doença glandular ou quando a ZT for do tipo 3. Nesta situação, o procedimento adicional ao invés de se realizar uma excisão do tipo 3 pode evitar um sangramento excessivo ou risco de infecção, devido a uma menor remoção do estroma quando comparado a uma alça de 20 ou 25mm de altura.

Essa discussão avançada sobre detalhes do manejo das lesões precursoras acontece em cenários onde o rastreamento é eficiente, e consequentemente, as taxas de câncer do colo do útero são moderadas a baixas. Entretanto, existe um grupo de mulheres vulneráveis que apresenta dificuldades em acessar os processos do rastreamento. As barreiras socioeconômicas e a fragilidade das redes de saúde onde essas mulheres vivem implicam em taxas de câncer do colo do útero mais elevadas. Para este grupo, a necessidade de reduzir essas barreiras se impõe.

Desta forma, o método rastrear-e-tratar (R&T), é recomendado em países ou regiões de moderada prevalência de CCU, como o Brasil, como estratégia para atingir esse grupo de mulheres vulneráveis. O método ver-e-tratar fica reservado para os países ou regiões que não apresentam infraestrutura de saúde para executar o rastreamento com citologia ou teste de HPV. O método R&T requer menos visitas, aumenta a adesão da mulher, e é mais econômico do que o manejo convencional com múltiplas etapas para o diagnóstico (30,54). Além disso, parece ser psicologicamente benéfico e preferido por mulheres com CIN2/3 (55). Uma revisão sistemática e meta-análise em 2016 apoiou evidências de que pode ser usado para tratar mulheres encaminhadas por lesões de alto grau ou com impressões colposcópicas de alto grau (56). As Diretrizes brasileiras afirmam que é aceitável tratar mulheres encaminhadas por citologias de alto grau, exceto na

gravidez ou entre 21 e 24 anos, sem mencionar a colposcopia como etapa intermediária (21).

O método R&T tem seu uso discutido pelo risco de supertratamento, especialmente em mulheres jovens. Nesta tese, observamos que a obtenção de um diagnóstico negativo após a excisão não foi significativamente maior em mulheres que se submeteram ao método R&T. Quando uma mulher foi submetida a R&T com colposcopia negativa, ela teve uma chance 18 vezes maior de supertratamento. Mais mulheres acima de 40 anos foram submetidas à R&T, o que pode indicar que os ginecologistas se sentiram mais confiantes para oferecê-lo quando a morbidade obstétrica não era uma preocupação. Assim, o método R&T não pareceu aumentar significativamente o risco de supertratamento, mas deve ser evitado em mulheres jovens com colposcopia negativa. Entretanto, é preciso ponderar os riscos de perda de seguimento deste grupo de mulheres em algumas situações.

A força deste estudo está no tamanho da amostra, potencializada pelo grau de detalhamento e da qualidade das informações registradas. Acreditamos que ele reforça o valor das informações clínicas e fornece informações de qualidade para ampliar o conhecimento dos colposcopistas, aprimorando assim o tratamento das lesões precursoras do colo do útero.

A principal limitação do nosso estudo é que o teste para a detecção do DNA-HPV de alto risco não estava disponível, situação predominante na maioria dos países de baixa e média renda. Nesse sentido, estudos clínicos como esse são relevantes por serem os únicos dados disponíveis para subsidiar recomendações de manejo nessas regiões. Além disso, trata-se de desenho retrospectivo, que pode levar à heterogeneidade nos critérios de seleção dos grupos.

## 6. CONCLUSÕES

**Artigo 1:** A proporção de margem endocervical negativa foi de 78% na excisão do tipo I e 86% na excisão do tipo II. O início sexual tardio e a excisão do tipo II aumentaram a chance de ser alcançada uma margem endocervical negativa. Esse benefício marginal deve ser contrabalançado com os riscos associados ao procedimento: realizar um procedimento mais conservador parece seguro e reduz morbidades, especialmente em mulheres jovens.

**Artigo 2:** O status da margem endocervical foi negativo em pelo menos três de cada quatro mulheres submetidas à excisão, independentemente se do tipo I ou II. A excisão do tipo I apresentou resultados satisfatórios em mulheres na pré-menopausa e zona de transformação dos tipos 1 ou 2.

**Artigo 3:** O diagnóstico final negativo após a excisão não foi significativamente maior nas mulheres conduzidas pelo método rastrear-e-tratar. O método foi adequado para mulheres encaminhadas por citologia de alto grau e com achados colposcópicos compatíveis.

**Artigo 4:** O diagnóstico final das mulheres submetidas ao reforço endocervical não foi alterado e não foi observado impacto na recidiva. O procedimento deve ser evitado em mulheres em idade reprodutiva.

## 7. REFERÊNCIAS

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# 8. ANEXOS

**Anexo 1: Aprovação do Comitê de ética em Pesquisa (CEP) da Unicamp:**

## PARECER CONSUBSTANCIADO DO CEP

**DADOS DA EMENDA**

**Título da Pesquisa:** Avaliação dos fatores determinantes de recidiva de lesão intra-epitelial cervical nas pacientes submetidas à conização com alça diatérmica

**Pesquisador:** Joana Fróes Bragança Bastos

**Área Temática:**

**Versão:** 3

**CAAE:** 13034013.6.0000.5404

**Instituição Proponente:** Hospital da Mulher Prof. Dr. José Aristodemo Pinotti - CAISM

**Patrocinador Principal:** Financiamento Próprio

**DADOS DO PARECER**

**Número do Parecer:** 2.913.889

**Apresentação do Projeto:**

Solicitasção de emenda 2 ao projeto original.

Justificativa da Emenda:

A emenda ao projeto original pretende avaliar transversalmente casos de conização realizadas em pacientes com diagnóstico de lesões precursoras (LIEAG e AIS) em 2017 e 2018. Não serão obtidos dados de seguimento. O objetivo principal da emenda é testar a relação dos achados colposcópicos com as variáveis obtidas na peça de conização. Os objetivos da emenda estão contidos no projeto original, o que nos levou a entender que seria desnecessário submissão de novo projeto para apreciação.

**Objetivo da Pesquisa:**

Nada é alterado do projeto original.

O projeto original já considerava como objetivos secundários do trabalho:

- Testar a associação de achados colposcópicos e da profundidade da excisão com comprometimento das margens cirúrgicas da peça operatória.
- Testar a associação de achados colposcópicos e da profundidade da excisão com recidiva da lesão.

**Avaliação dos Riscos e Benefícios:**

Nada é alterado do projeto original.

**Comentários e Considerações sobre a Pesquisa:**

Projeto originalmente aprovado em 13 de Março de 2013 Número do Parecer 217.724.

O projeto original previa : "Serão incluídas no estudo pacientes com diagnóstico de NIC 2 e NIC3, submetidas à conização com alça diatérmica no CAISM- Unicamp, que apresentem tempo de seguimento mínimo de 2 anos. Portanto o ano limite para realização de tratamento será o ano de 2010." Agora solicita uma nova coleta de dados de prontuário de mulheres que realizaram o procedimento em 2017 e 2018.

**Considerações sobre os Termos de apresentação obrigatória:**

- PB_INFORMAÇÕES_BÁSICAS_1201463_E2.pdf 09/09/2018: com a justificativa da emenda.
- ProjetoConeYonedaEmenda.pdf 09/09/2018: projeto completo com destaque nas alterações da emenda.

- Oficio_185_2018_alteracao_pesquisador_PB_Juliana_Yoko_Yoneda.pdf 05/09/2018 : ofício do CEP transferindo a responsabilidade do projeto de Juliana Yoko Yoneda ( mestranda no trabalho oroginal) para Joana Fróes Bragança Bastos.

**Recomendações:**

Um Relatório parcial de acompanhamento do projeto, em formulário adequado, deve ser encaminhado como notificação ao CEP para que a presente emenda seja adequadamente apreciada.

**Conclusões ou Pendências e Lista de Inadequações:**

- A emenda propõe "análise secundária em pacientes submetidas ao procedimento nos anos de 2017 a 2018". Assim sendo essas mulheres podem ainda estar em acompanhamento no serviço do CAISM devendo portanto conceder anuência para sua participação na pesquisa. Assim sendo,para essas, não é dispensado o TCLE.

Deve apresentar um TCLE para apreciação deste CEP para ser aplicado as mulheres que ainda estejam em acompanhamento devido ao procedimento em questão.

Um Relatório parcial de acompanhamento do projeto, em formulário adequado, deve ser

encaminhado como notificação ao CEP para que a presente emenda seja adequadamente apreciada.

**Considerações Finais a critério do CEP:**

Conforme compromisso assumido pelo mesmo com o cumprimento da resolução 466/2012, item IX.1 letra a. Quando for submeter respostas às pendências, verificar se o cronograma de realização da pesquisa, descrito na plataforma Brasil e no projeto anexado, está contemplando o início da coleta de dados APÓS a liberação do projeto pelo CEP.

Apresentar carta resposta ao CEP declarando quais as informações alteradas, quais as respostas as pendências apresentadas destacando-as no documento pertinente.

**Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

| Tipo Documento | Arquivo | Postagem | Autor | Situação |
|---|---|---|---|---|
| Informações Básicas do Projeto | PB_INFORMAÇÕES_BÁSICAS_1201463_E2.pdf | 09/09/2018 22:50:16 | | Aceito |
| Projeto Detalhado / Brochura Investigador | ProjetoConeYonedaEmenda.pdf | 09/09/2018 22:47:37 | Joana Fróes Bragança Bastos | Aceito |
| Outros | Oficio_185_2018_alteracao_pesquisador_PB_Juliana_Yoko_Yoneda.pdf | 05/09/2018 10:07:58 | Rodrigo Caetano Alves | Aceito |
| Outros | Documento.pdf | 24/08/2018 20:39:24 | JULIANA YOKO YONEDA | Aceito |
| Projeto Detalhado / Brochura Investigador | PROJETO CORRIGIDO JAN 2013.docx | 06/02/2013 14:17:38 | | Aceito |
| Folha de Rosto | document2013-02-06-132946 (1).pdf | 06/02/2013 14:15:20 | | Aceito |

**Situação do Parecer:**

Pendente

**Necessita Apreciação da CONEP:**

Não

CAMPINAS, 24 de Setembro de 2018

**Assinado por:**
**Maria Fernanda Ribeiro Bittar**
**(Coordenador(a))**

**Endereço:** Rua Tessália Vieira de Camargo, 126
**Bairro:** Barão Geraldo **CEP:** 13.083-887
**UF:** SP **Município:** CAMPINAS
**Telefone:** (19)3521-8936 **Fax:** (19)3521-7187 **E-mail:** cep@fcm.unicamp.br

**Anexo 2: Ficha de coleta de dados**

**Ficha de coleta de dados**

*"Segurança da profundidade do tecido excisado na EZT de acordo com a recomendação da IFCPC"*

| | | | |
|---|---|---|---|
| **Identificação** | | | **Ficha n.** |
| **HC** | | | **Iniciais** |
| **Data de nascimento** | | | **Data da coleta** |
| **Antecedentes** | | | |
| **Coitarca (anos)** | **Paridade** G P A C | | |
| **Status menstrual** | ( ) Menacme ( ) Menopausa, idade anos | | |
| **Tabagismo** | ( ) Sim ( ) Não | | |
| **Imunodepressão** | ( ) Não ( ) Sim, tipo | | |
| **Morbidades** | | | |
| **Procedimento no colo** | ( ) Não ( ) EZT ( ) Cone a frio ( ) Outro | | |
| **Citologia do encaminhamento** | **Data** | | **( ) NR** |
| ( ) Normal/ACI ( ) ASC-US ( ) ASC-H ( ) AGC ( ) LIEBG/NIC1 ( ) LIEAG/NIC2 ( ) LIEAG/NIC3 ( ) LIEAG ( ) AIS ( ) suspeita micro invasão ( ) CEC ( ) Adenocarcinoma ( ) Outros | | | |
| **Biópsia do encaminhamento** | **Data** | | **( ) NR** |
| ( ) Cervicite ( ) LIEBG/NIC1 ( ) LIEAG/NIC2 ( ) LIEAG/NIC3 ( ) LIEAG ( ) AIS ( ) CEC ( ) Adenocarcinoma ( ) Outros | | | |
| **EZT** | **Data** | | |
| **MAC** | **( ) Sem ( ) DIU cobre ( ) DIU Mirena ( ) Laqueadura ( ) Condon ( ) Oral Combinado ( ) Minipílula ( ) Injet. Mensal ( ) Injet. Trimestral** | | |
| **Colposcopia (Rio 2011)** | | | |
| Adequada | ( ) Sim ( ) Não | | |
| Zona de Transformação | ( ) ZT 1 ( ) ZT 2 ( ) ZT 3 ( ) Sem informação | | |
| Achados anormais | ( ) Sim ( ) Não | | |
| Suspeita de invasão ou micro invasão | ( ) Sim ( ) Não | | |
| Outros | | | |
| **Anátomo Patológico** | | | |
| ( ) Cervicite ( ) LIEBG/NIC1 ( ) LIEAG/NIC2 ( ) LIEAG/NIC3 ( ) LIEAG ( ) AIS ( ) CEC microinvasor ( ) CEC invasor ( ) Adenocarcinoma ( ) Outros | | | |
| Fragmento 1 | Base (cm) | Altura (cm) | Resultado |
| Fragmento 2 | Base (cm) | Altura (cm) | Resultado |
| Fragmento 3 | Base (cm) | Altura (cm) | Resultado |
| Invasão | ( ) Não ( ) Sim, profundidade (mm) | | |
| Margem endocervical | ( ) Negativa ( ) Positiva, resultado | | |
| Margem ectocervical | ( ) Negativa ( ) Positiva, resultado | | |
| Reforço de canal | ( ) Não realizado ( ) Negativo ( ) Positivo, resultado | | |
| **Re-cone** | Data | Resultado | |
| **Cirurgia** | Data ( ) HTA ( ) WM | Doença residual ( ) Não ( ) Sim, resultado | |
| **Citologias Seguimento** | | | |
| Data | Resultado ( ) Normal/ACI ( ) Outros, | | |
| Data | Resultado ( ) Normal/ACI ( ) Outros, | | |
| Data | Resultado ( ) Normal/ACI ( ) Outros, | | |
| Data | Resultado ( ) Normal/ACI ( ) Outros, | | |

**Anexo 3: Permissão para inclusão de Artigos**

Gmail **Juliana Yoko Yoneda <juyoko@gmail.com>**

# Permission to re-use Paper in PhD Thesis

**Diama Vale** <diamavale@gmail.com> Mon, Mar 6, 2023 at 12:31 PM
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Diama Bhadra Vale, MD, PhD

diamavale@gmail.com
dvale@unicamp.br

*Assistant Professor MS-3.2*
*Department of Obstetrics and Gynecology, Oncology Section*
*School of Medical Sciences, University of Campinas (Unicamp)*
*Campinas, Brazil*

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Best regards,

Diama Bhadra Vale, MD, PhD



diamavale@gmail.com

dvale@unicamp.br

*Assistant Professor MS-3.2*

*Department of Obstetrics and Gynecology, Oncology Section*
*School of Medical Sciences, University of Campinas (Unicamp)*
*Campinas, Brazil*

Gmail

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Diama Bhadra Vale, MD, PhD

diamavale@gmail.com
dvale@unicamp.br

*Assistant Professor MS-3.2*
*Department of Obstetrics and Gynecology, Oncology Section*
*School of Medical Sciences, University of Campinas (Unicamp)*
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