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Overtreatment rate after immediate local excision of suspected cervical intraepithelial neoplasia: A prospective cohort study

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HIGHLIGHTS

- Select-and-treat resulted in lower overtreatment rate than LLETZ after HSIL biopsy.
- Immediate treatment of CIN does not increase overtreatment rate if current care guidelines are followed.
- If HPV 16/18 was positive, the overtreatment rate was lower after immediate treatment than treatment after HSIL biopsy.
- The overtreatment rate was rather high in both treatment groups for patients with type 3 transformation zone.

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ABSTRACT

Objective. The gold standard of cervical intraepithelial neoplasia (CIN) treatment is large loop excision of the transformation zone (LLETZ) after histopathological diagnosis from punch biopsies. In addition, treatment may be appropriate at initial colposcopy. Our objective was to study the applicability of immediate treatment strategy according to clinical parameters.

Methods. We conducted a prospective cohort study among patients referred to colposcopy at Helsinki University Hospital, Finland, between January 2014, and September 2018 (ISRCTN10933736). Patients treated with LLETZ, either after biopsies or immediately at initial colposcopy, were included. The main outcome measure was overtreatment (OT) rate defined as normal or low-grade histopathological findings in LLETZ specimen within both treatment groups.

Results. A total of 572 patients treated with LLETZ were included: 360 treated after biopsies and 212 treated immediately at initial colposcopy. When LLETZ was performed immediately after high-grade referral cytology and with colposcopic impression of high-grade disease, the overtreatment (OT) rate was 10.0% (95% CI 9.10 to 17.2), whereas when LLETZ was done after biopsy-confirmed high-grade lesions, the OT rate was 18.9% (95% CI 14.7 to 23.7), resulting in risk difference (RD) −8.91% (95% CI −16.0 to −1.82). Among HPV16/18 positive patients the OT rate was 8.22% (95% CI 3.08 to 17.0) for immediate treatment, resulting in RD of −10.7% (95% CI −18.3 to −3.04) compared to LLETZ after biopsies.

Conclusions. Immediate LLETZ does not result in overtreatment when applied on selected cases, especially after high-grade referral cytology and when high-grade lesion is also colposcopically suspected.

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1. Introduction

Organized cervical cancer screening programs have resulted in a marked decrease in cervical cancer incidence and mortality [1–3]. Unlike many other cancer screening programs cervical screening primarily aims to detect cancer precursors (cervical intraepithelial neoplasia; CIN) that can be locally treated before progression to invasive cancer [4]. The gold standard of treatment of histopathological high-grade squamous intraepithelial lesions (HSIL, or cervical intraepithelial neoplasia grade 2 or worse) is excision of the uterine cervical transformation zone after histological confirmation of (the presence of) HSIL by colposcopically directed punch biopsies. In current practice the excision procedure is predominantly done under local anesthesia as large loop excision of the transformation zone (LLETZ) in an outpatient setting.

However, treatment at initial colposcopy, when presence of high-grade lesion is suspected by the colposcopist, has also been advocated as a "see-and-treat" approach when performed regardless of cytology, and as a "select-and-treat" approach based on both high-grade referral cytology and respective colposcopic impression [5,6]. Colposcopy alone has high sensitivity but only moderate specificity for detecting high-grade cervical lesions [5]. Decision to treat based on colposcopy alone can lead to overtreatment, while high-grade lesions may remain undetected due to unrepresentative punch biopsies. The traditional two-step protocol of taking biopsies at first appointment and treating at second appointment consumes recourses, and patients may remain untreated due to missed appointments [6]. The immediate treatment approach can be more cost-effective with only one visit and histopathological specimen. Although the offered immediate treatment may be difficult to cope with for some patients, for others the option of not having to wait for histopathological diagnosis of the punch biopsies and for another appointment for the LLETZ may in fact reduce the experienced anxiety [6–8].

See-and-treat management, where a lesion is treated regardless of referral cytology if colposcopic impression is suggestive of high-grade lesion, has resulted in significant overtreatment [9–11]. For select-and-treat management, where the treatment is not performed at the first visit but is performed on a selected group of patients referred to colposcopy, the overtreatment rate has been lower, especially among patients with both high-grade cytology and impression of high-grade lesion at colposcopy [10]. In a systematic review and meta-analysis of 13 studies the overtreatment rate for see-and-treat approach varied between 29.3 and 72.9%, while it was about 12% for select-and-treat approach [12]. The results differed in relation to referral cytology and colposcopic impression, but the overtreatment rates were not compared to cohorts with traditional two-step approach of treatment after biopsies [12].

Our objective was to compare the performance of the immediate treatment approach with the gold standard approach of LLETZ after biopsies to explore whether clinical or colposcopic characteristics at initial colposcopy would predict the applicability of the immediate LLETZ approach. This would allow for further individualized treatment approaches taken for patients with suspected high-grade lesions at initial colposcopy.

2. Materials and methods

This study is part of a prospective cohort study of 1383 patients 18 years of age or older referred to Helsinki University Hospital's Outpatient Colposcopy Unit between January 2014 and March 2018 (ISRCTN10933736) [13,14]. All patients referred to colposcopy within the study period were offered participation in the study, and written informed consent was obtained from all participants. The patients in the cohort were examined and treated according to Finnish Current Care Guidelines (FCCG) [15]. Cervical swabs for HPV genotyping were obtained at all visits. HPV genotyping was performed for research purposes only. Endocervical sampling was performed at the discretion of the colposcopist. The protocol was approved by Helsinki University Hospital's Ethical Committee (130/13/03/03/2013).

Referral cytology and histopathology results were reported according to the Bethesda System. Colposcopic examination with 5% acetic acid with or without Lugol's iodine solution was performed by consultant colposcopists or by residents under supervision of the consultant. Colposcopic impression, Reid colposcopic index (RCI) [16], and type of transformation zone (TZ) were recorded. Punch biopsies were taken at the discretion of the colposcopist. LLETZ procedures were performed under local anesthesia and colposcopic guidance. Histological specimens were examined by gynecological histopathologists.

In Finnish Current Care Guidelines (FCCG) immediate treatment is currently accepted in three specific situations: 1) referral cytology is HSIL and the colposcopic impression is suggestive for high-grade disease; 2) referral cytology is HSIL or ASC-H (atypical squamous cells, cannot exclude HSIL) and the transformation zone is not fully visible (transformation zone type 3, TZ3); 3) referral cytology is AGC-FN (atypical glandular cells, favor neoplasia) [15]Throughout the study period immediate LLETZ was additionally performed at the first visit at the individual colposcopist's discretion, even when the Current Care Guidelines criteria were not met.

2.1. HPV genotyping

Cells collected with endocervical brush were transferred into specimen transport medium (STM, Qiagen GMBH, Hilden, Germany) and stored immediately at −20 °C. Later, the samples were divided into three aliquots without adding any medium and stored at −80 °C. One aliquot was sent frozen to the Karolinska Institute, Stockholm, Sweden, for HPV genotyping. DNA was extracted, and a modified GP5 +/6+ primer set was used for polymerase chain reaction (PCR) [17]. Genotyping was performed with the Bioplex 200 Luminex system (Bio-Rad, California).

HPV genotyping results were grouped for analysis. Genotypes HPV16 and HPV18 were reported separately. The group of "other high-risk HPV (hrHPV) types than HPV16 or 18" included HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. If none of these hrHPVs was detected, genotyping was reported hrHPV negative.

For statistical analysis the cervical histopathological diagnoses of punch biopsies or LLETZ cone were grouped as 1) ≥ HSIL: CIN2, CIN3, adenocarcinoma in situ (AIS), or squamous cell carcinoma and adenocarcinoma of the cervix, and 2) ≤ LSIL: negative for intraepithelial lesion or malignancy (NILM), histopathological low-grade squamous intraepithelial lesion (LSIL) and cervical intraepithelial neoplasia grade 1 (CIN1). Referral cytology results were grouped as 1) low-grade (LG): ASC-US (atypical squamous cells of undetermined significance), LSIL (low-grade squamous intraepithelial lesion) and AGC-NOS (atypical glandular cells not otherwise specified) and 2) high-grade (HG): ASC-H (atypical squamous cells, cannot exclude HSIL), HSIL (high-grade squamous intraepithelial lesion) and AGC-FN (atypical glandular cells, favor neoplasia). Other groups and abbreviations are explained in Table 1.

For statistical analysis the participants were divided into two main groups: 1) Immediate treatment group (treatment at the first colposcopy visit, without histopathological diagnosis) and 2) LLETZ after biopsies group, where histopathological diagnosis was based on punch biopsies taken at a previous colposcopy visit. Differences in background variables between the study groups were compared with chi-square and student's *t*-test, as appropriate.

The main outcome was overtreament rate (OT), defined as a percentage of LLETZ specimens where histopathological HSIL lesion was absent. Although LLETZ after HSIL biopsies is not considered overtreatment, the term overtreatment rate was used for both treatment groups for clarity.

Table 1
Characteristics of the immediate treatment group and LLETZ after biopsies group.

	Immediate treatment $n = 212$	LLETZ after biopsies $n = 360$	*P*-value
	n = (%)	n = (%)	
Age			
<30	18 (8.49)	94 (26.1)	<0.001
30–44.9	13 (6.13)	46 (12.8)	0.01
≥45	181 (85.4)	220 (61.1)	<0.001
Smoking status			
No	120 (56.6)	177 (49.2)	0.09
Quit	12 (5.66)	31 (8.61)	0.20
Smoking	65 (30.7)	129 (35.8)	0.21
Missing	15 (7.08)	23 (6.39)	0.75
Referral cytology			
Low-grade	37 (17.5)	110 (30.6)	0.001
High-grade	171 (80.7)	236 (65.6)	<0.001
Missing	4 (1.89)	14 (3.89)	0.19
TZ type			
TZ1	84 (39.6)	220 (61.1)	<0.001
TZ2	65 (30.7)	95 (26.4)	0.27
TZ3	58 (27.4)	40 (11.1)	<0.001
Missing	5 (2.36)	5 (1.39)	0.39
Colposcopic impression			
Normal	15 (7.08)	8 (2.22)	0.004
LSIL	41 (19.3)	132 (36.7)	<0.001
HSIL	128 (60.4)	193 (53.6)	0.12
Missing	28 (13.2)	27 (7.50)	0.03
RCI-Index			
1–2	10 (4.72)	50 (13.9)	0.001
3–4	80 (37.7)	192 (53.3)	<0.001
5–6	75 (35.4)	74 (20.6)	<0.001
Missing	47 (22.2)	44 (12.2)	0.002
HPV16+	61 (28.8)	154 (42.8)	0.001
HPV18+	13 (6.13)	24 (6.67)	0.80
Other hrHPV+	81 (38.2)	106 (29.4)	0.03
hrHPV negative	38 (17.9)	20 (5.56)	<0.001

TZ-type: TZ1 if the whole transformation zone is visible, TZ2 if the upper limit of the TZ is partly or fully in the canal but is completely visible around 360 degrees and TZ3 if part or the entire upper limit of the TZ cannot be seen in the canal.
Referral cytology: grouped into low grade: ASC-US (atypical squamous cells of undetermined significance), LSIL (low-grade squamous intraepithelial lesion) and AGC-NOS (atypical glandular cells not otherwise specified) and high grade: ASC-H (atypical squamous cells, cannot exclude HSIL), HSIL (high grade squamous intraepithelial lesion) and AGC-FN (atypical glandular cells, favor neoplasia).
Colposcopic impression: Determined by colposcopist and divided into normal, LSIL (low-grade squamous intraepithelial lesion).
including reactive changes, condyloma, HPV atypia, and CIN1 and HSIL (high-grade squamous intraepithelial lesion) including CIN2, CIN3, AIS and carcinoma.
RCI index = Reid colposcopic index.
hrHPV genotypes: grouped HPV16, HPV18, and other hrHPV (HPV31,33, 35, 39, 45, 51, 52,56, 58, 59, 66 and 68).

The risk difference (RD) and risk ratio (RR) estimates with 95% confidence intervals were calculated for overtreatment rates between the treatment groups. To further explore the clinical efficacy of the immediate treatment approach, the group was further divided into subgroups according to age, presence of HPV16 and/or 18 genotype, referral cytology, colposcopic impression, TZ type, smoking and RCI. Stratified overtreatment rates with corresponding RR and RD between groups were calculated both compared to the gold standard (LLETZ after HSIL biopsies), as well as to similar subgroup of patients where LLETZ was performed after biopsies. (Table 2 and Supplementary Table 1). All analyses were performed using STATA/SE 15 (StataCorp, College StationTX, USA).

3. Results

From all patients treated with LLETZ in the cohort ($n = 650$), we excluded the second treatment of those who underwent repeated LLETZ ($n = 70$), patients 30 years of age and younger whose CIN2 lesions were initially treated with active surveillance (n = 7), and one patient who had LLETZ because of unspecific finding in computed tomography ($n = 1$), resulting in a final study cohort of 572 patients. Of these, 212 were immediate treatments and 360 had LLETZ after punch biopsies.

Indications for treatment in the immediate treatment group, as defined by the colposcopist based on the electronic patient records, were colposcopic diagnosis and referral cytology ($n = 168$), referral cytology and TZ type ($n = 27$), referral cytology result alone ($n = 7$), colposcopic diagnosis alone ($n = 4$), discrepancy between cytology and colposcopic diagnosis (n = 2), postcoital bleeding (n = 2), persistent high-risk HPV positivity ($n = 1$), and the indication was missing (n = 1). In the LLETZ after biopsies group ($n = 360$), indications for treatment were presence of HSIL in preceding biopsies ($n = 312$), presence of persistent LSIL in preceding biopsies ($n = 26$), and discrepancy between two or more findings ($n = 16$). For 6 patients the indication was not available.

Compared to the patients treated after punch biopsies, the patients in the immediate treatment group were older and had more frequently TZ3, high-grade referral cytology, and higher RCI score. High-risk HPV other than HPV16 and/or 18 was more common than HPV16 and/or 18 in the immediate treatment group (Table 1).

The OT rate after immediate treatment overall was 30.2% (95% CI 24.1–36.9) and for LLETZ after biopsies 24.4% (95% CI 20.1–29.2), RD between the two groups 5.74% (95% CI −1.86 to 13.4, $p = 0.13$) (Table 2, Fig. 1, Supplementary Table 1). When LLETZ was performed immediately after high-grade cytology and colposcopic impression of high-grade disease, the OT rate was 10.0% (CI 95% 5.10 to 17.2) whereas when LLETZ was done after punch biopsies with histopathological HSIL, the gold standard for treatment, the overtreatment rate was 18.9% (95% CI 14.7 to 23.7), resulting in risk difference (RD) between OT rates of −8.91% (−16.0 to −1.82) and $p = 0.03$ (Table 2 and Fig. 1).

If FCCG criteria for immediate treatment were met, the OT rate was 20.6% (95% CI 14.0–28.6). In comparison to LLETZ after punch biopsies with HSIL (the gold standard) the RD was 1.70% (95% CI −6.48 to 9.88, $p = 0.68$). If referral cytology was high-grade, the OT rate in immediate treatment group regardless of colposcopic impression was 21.6% (95% CI 15.7–28.6), RD compared to the gold standard 2.73% (95% CI −4.82 to 10.3, $p = 0.47$). When the colposcopic impression indicated high-grade disease, the OT rate in immediate treatment group after any referral cytology was 15.6% (95% CI 9.81–23.1), RD compared to gold standard −3.29% (95% CI −10.9 to 4.36, $p = 0.41$). Also, if RCI was 5–6, corresponding to a high-grade lesion, the OT rate in immediate treatment group was 9.33% (95% CI 3.84 to 18.3), RD −9.58% (95% CI −17.5 to −1.69, $p = 0.05$) compared to gold standard. Among hrHPV 16/18 positive patients, the OT rate in immediate treatment group was 8.22% (95% CI 3.08 to 17.0), RD −10.7% (95% CI −18.3 to −3.04 $p = 0.03$) compared to gold standard. Among patients under 45 years of age the OT rate in immediate treatment group was 3.23% (95% CI 0.08–16.7), RD compared to gold standard −15.7% (95% CI −23.3 to −8.10, p = 0.03) (Table 2).

For patients referred to colposcopy due to high-grade cervical cytology and treated after HSIL biopsies with colposcopic impression of high-grade lesion at initial colposcopy, the OT rate was 12.5% (95% CI 7.45 to 19.3). Immediate treatment in a similar group, high-grade referral cytology with colposcopic impression of high-grade lesion, resulted in OT rate of 10% (RD between the two groups −2.50, 95% CI −10.4 to 5.39, $p = 0.54$). If colposcopic impression was high-grade in both immediate treatment and treatment after biopsies groups, regardless of referral cytology the RD between the OT rates was 0.95 (95% CI −7.15 to 9.06. $p = 0.82$). If referral cytology was high-grade, regardless of colposcopic diagnosis the RD between OT rates was 4.74 (95% CI −3.22 to 12.7, p. 0.24). After ASC-H cytology alone, regardless of colposcopic impression and other attributes, the OT rate was higher in immediate treatment than in treatment after biopsies group (25.4% vs 15.7%), while after HSIL cytology alone the OT rate was lower in

Table 2
Detection of histopathological HSIL in cones by study groups and subgroups, and overtreatment rates, risk ratios and risk differences between the groups and subgroups.

	Immediate treatment Histological HSIL/total	%	LLETZ after HSIL biopsy Histological HSIL/total	%	Immediate treatment OT% (95% CI)	LLETZ after HSIL biopsy OT% (95% CI)	RD for overtreatment rates*	RR for overtreatment rates	P-value
Immediate treatment	148/212	69.8	253/312	81.1	30.2 (24.1 to 36.9)	18.9 (14.7 to 23.7)	1.60 (1.17 to 2.17)	11.3 (3.72 to 18.8)	0.003
Ref. cytology HG & HSIL colposcopic impression	99/110	90.0	253/312	81.1	10.0 (5.10 to 17.2)	18.9 (14.7 to 23.7)	-8.91 (−16.0 to 1.82)	0.53 (0.29 to 0.97)	0.03
Select-and-treat according to FCCG	104/131	79.4	253/312	81.1	20.6 (14.0 to 28.6)	18.9 (14.7 to 23.7)	1.70 (−6.48 to 9.88)	1.09 (0.73 to 1.64)	0.68
Referral cytology HG (ASC—H, HSIL & AGC-FN)	134/171	78.4	253/312	81.1	21.6 (15.7 to 28.6)	18.9 (14.7 to 23.7)	2.73 (−4.82 to 10.3)	1.14 (−4.82 to 10.3)	0.47
Referral cytology ASC-H	47/63	74.6	253/312	81.1	25.4 (15.3 to 37.9)	18.9 (14.7 to 23.7)	6.49 (−5.11 to 18.1)	1.34 (0.83 to 2.17)	0.24
Referral cytology HSIL	75/85	88.2	253/312	81.1	11.8 (5.79 to 20.6)	18.9 (14.7 to 23.7)	-7.15 (−15.3 to 0.97)	0.62 (0.33 to 1.16)	0.12
Referral cytology AGC-FN	12/23	52.2	253/312	81.1	47.8 (26.8 to 69.4)	18.9 (14.7 to 23.7)	28.9 (8.04 to 49.8)	2.53 (1.56 to 4.11)	0.001
Referral cytology LG	11/37	29.7	253/312	81.1	70.3 (53.0 to 84.1)	18.9 (14.7 to 23.7)	51.4 (36.0 to 66.7)	3.72 (2.72 to 5.07)	<0.001
RCI 5–6	68/75	90.7	253/312	81.1	9.33 (3.84 to 18.3)	18.9 (14.7 to 23.7)	−9.58 (−17.5 to −1.69)	0.49 (0.24 to 1.04)	0.05
HPV16/18+	67/73	91.8	253/312	81.1	8.22 (3.08 to 17.0)	18.9 (14.7 to 23.7)	−10.7 (−18.3 to −3.04)	0.43 (0.20 to 0.97)	0.03
Other hrHPV+	68/81	84.0	253/312	81.1	16.0 (8.83 to 25.9)	18.9 (14.7 to 23.7)	−5.78 (−13.7 to 2.17)	0.69 (0.40 to 1.21)	0.19
hrHPV negative	7/38	18.4	253/312	81.1	81.6 (65.7 to 92.3)	18.9 (14.7 to 23.7)	62.7 (50.0 to 75.7)	4.31 (3.28 to 5.68)	<0.001
Age < 45	30/31	96.8	253/312	81.1	3.23 (0.08 to 16.7)	18.9 (14.7 to 23.7)	−15.7 (−23.3 to −8.10)	0.17 (0.02 to 1.20)	0.03
Colposcopic impression HSIL	108/128	84.4	253/312	81.1	15.6 (9.81 to 23.1)	18.9 (14.7 to 23.7)	−3.29 (−10.9 to 4.36)	0.83 (0.52 to 1.31)	0.41
Referral cytology HG & age < 45	27/27	100	253/312	81.1	0 (NP)	18.9 (14.7 to 23.7)	−18.9 (−23.3 to 14.6)	0 (NP)	0.01
Referral cytoloty High-grade & hrHPV pos	120/130	92.3	253/312	81.1	7.69 (3.75 to 13.7)	18.9 (14.7 to 23.7)	−11.2 (−17.5 to 4.90)	0.41 (0.21 to 0.77)	0.003
Referral cytology Low-grade & colposcopic impression HSIL	7/15	46.7	253/312	81.1	53.3 (26.6 to 78.7)	18.9 (14.7 to 23.7)	34.4 (8.81 to 60.0)	2.82 (1.67 to 4.77)	0.001

Definitions and abbreviations:
Immediate treatment = treatment done at the initial colposcopy.
HSIL = high-grade squamous intraepithelial lesion.
LLETZ after biopsy; two-step protocol, treatment done at the second appointment, punch biopsies taken at the initial colposcopy.
RD = risk difference; *(Negative value indicating lower overtreatment rate in Immediate treatment group).
RR = risk ratio.
CI 95% = confidence interval.
Referral cytology high-grade (HG = 1) ASC-H (atypical squamous cells, cannot exclude HSIL).
2) HSIL (high-grade squamous intraepithelial lesion).
3) AGC-FN (atypical glandular cells, favor neoplasia).
Ref. cyt = Referral cytology low-grade LG = 1) ASC-US (atypical squamous cells of undetermined significance).
2) LSIL (low-grade squamous intraepithelial lesion).
3) AGC-NOS (atypical glandular cells not otherwise specified).
Colp. imp = Colposcopic impression; Determined by colposcopist and divided into.
1) normal.
2) LSIL (low-grade squamous intraepithelial lesion) including reactive changes, condyloma, HPV-atypia, and CIN1.
3) HSIL (high-grade squamous intraepithelial lesion) including CIN2, CIN3, AIS and carcinoma.
FCCG = Finnish Current Care Guidelines; immediate treatment approach suitable in the following cases:
1) referral cytology is HSIL and colposcopic impression of HSIL.
2) referral cytology is HSIL or ASC-H (atypical squamous cells, cannot exclude HSIL) and the transformation zone is not fully visible (transformation zone type 3, TZ3).
3) referral cytology is AGC-FN (atypical glandular cells, favor neoplasia).
NP = not pertinent due to perfect correlation.
RCI: Reid colposcopic index.
Other hrHPV+: HPV 31/33/35/39/45/51/52/56/58/59/66/68 positive.

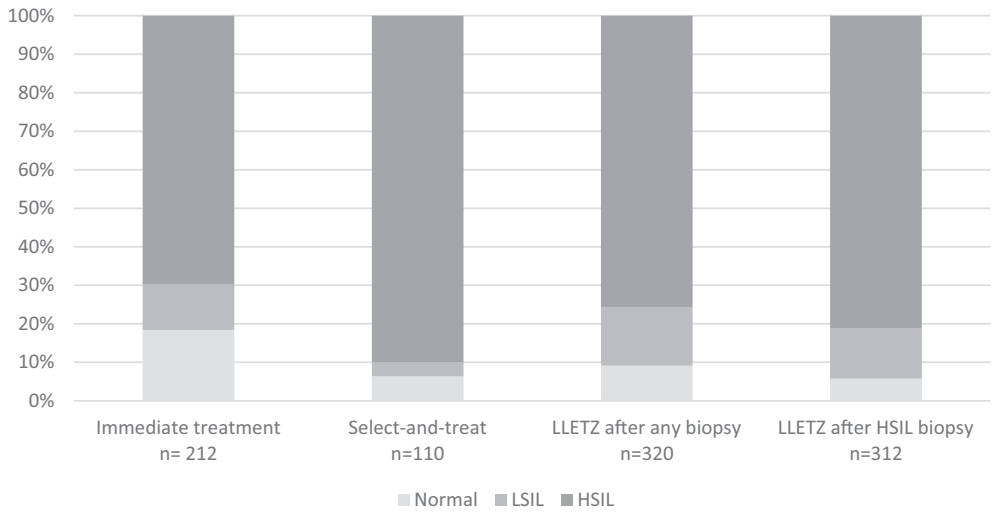

Fig. 1. LLETZ histology by treatment regimen.

immediate treatment group (11.8% vs 18.6%). Among patients under 45, regardless of other variables, the OT rate was lower in immediate treatment group, RD between groups −17.4 (95% CI −26.7 to −8.08, $p = 0.02$) (Supplementary Table 1). When immediate treatment was performed for hrHPV negative patients, the OT rate was high; 81.6% (95% CI 65.7 to 92.3), RD between groups 45.9% (95% CI 17.9 to 73.8, $p < 0.001$). For women positive for HPV 16 and/or 18 or other hrHPV, regardless of other attributes the OT rates were still slightly lower in immediate treatment than in treatment after biopsies groups (Supplementary Tables 1 and 2).

4. Discussion

The immediate treatment approach was associated with varying overtreatment rates, depending on to whom it was perfomed. The OT rate after immediate LLETZ at initial colposcopy for any reason was relatively high, 30.2%, whereas for treatment after biopsies due to any indication the OT rate was 24.4%. However, when LLETZ was performed at initial colposcopy after high-grade cytology and high-grade colposcopic impression, the OT rate was lower (10.0%) than when LLETZ was done after punch biopsies indicating the presence of HSIL (18.9%). Immediate treatment resulted more often in excision of HSIL lesion than the gold standard treatment after HSIL biopsy also if patients were younger than 45 years and if HPV 16 or 18 was present.

The American Society of Colposcopy and Cervical Pathology (ASCCP) emphasizes the possibility to perform immediate treatment as an alternative method in nonpregnant patients older than 25 years when the immediate risk of CIN 3+ is ≥60% and accepts it for those with risks between 25% and 60%. According to ASCCP immediate treatment is preferred among nonpregnant patients 25 years or older with high-grade referral cytology and positive for HPV 16 [18]. In the United Kingdom, the NHS (National Health Service) Cervical Screening Program only recommends that treatment at first visit should not be offered after referral of borderline or low-grade dyskaryosis [19], based on Tombola group studies on low-grade cervical cytology [9]. The criteria for immediate treatment approach and local excision techniques have also varied in previous studies, leading to reported overtreatment rates varying from 4% to 29% [9–12,20–23]. In the meta-analysis by Ebisch et al., the overtreatment rate in see-and-treat approach was 11.6% in cases with high-grade referral cytology and high-grade colposcopic impression, in line with our observations [12]. The meta-analyses [12] did not examine age, type of transformation zone, formal Reid Colposcopy Index or HPV genotype. In a population-based retrospective cohort study from the Netherlands the overall overtreatment rate was 28.4% in immediate treatment group, and immediate treatment after low-grade referral cytology resulted in higher overtreatment rate than treatment after biopsies as well [24].

Ebisch et al. concluded in their meta-analysis that if there was discrepancy between referral cytology and colposcopic impression, immediate treatment results in higher overtreatment rate in comparison to LLETZ after biopsies. Here however, if RCI score was 5–6, i.e., indicative of the presence of HSIL, immediate treatment regardless of referral cytology resulted in lower overtreatment rate than LLETZ after HSIL biopsies.

Our results should not be interpreted to suggest that a LLETZ with only low-grade histological findings after high-grade biopsies should be clinically considered overtreatment, as the gold standard indication for LLETZ treatment is a preceding high-grade biopsy finding. Still, comparing the performance of immediate treatment approach to gold standard in terms of overtreatment rate can be considered as a valid approach, as it estimates the proportion of LLETZ without high-grade histological findings in both groups. Even though the patients without HSIL in LLETZ specimen might well be different after these two approaches, the total number of LLETZ resulting in low-grade or normal histology between the population is comparable.

The LLETZ cone commonly shows more severe findings than preceding biopsies [25–27]. This may be partly explained by interobserver variation of colposcopic impression and difficulty of ensuring that biopsies are taken from the most severe areas. Here the apparent rate of overtreatment (less severe findings in the cone than in preceding biopsies) is somewhat worrying. Cervical excision can lead to complications such as infection, hemorrhage, or cervical stenosis, and may increase the risk of preterm delivery [6,28,29] and therefore careful consideration of treatment decisions are warranted, especially in young women. However, in the present study even among patients under 45 years with high-grade referral cytology or with hrHPV present the overtreatment rates after immediate treatment were not higher than when LLETZ was performed after high-grade biopsies. Furthermore, among patients younger than 30 years of age, up to 60% of cervical intraepithelial neoplasia grade 2 (CIN2) lesions spontaneously regress within 24 months [30]. The Finnish Current Care Guidelines allow active surveillance as management of CIN2-lesions harboring no more than two quadrants of the transformation zone among women under 30 years of age. This might have contributed to the observed low overtreatment rate among these women, as immediate treatment might be considered only for those women whose lesion covers a majority of the transformation zone. Still, histopathological diagnosis of CIN2 is challenging and may differ from histopathologist to another [31,32], which could

explain the finding of overtreatment after HSIL biopsies at least to some extent. Small lesions present at initial colposcopy may also become completely excised by punch biopsies, and biopsies themselves can provoke disease regression [33,34].

Previously, a higher risk of overtreatment in see-and-treat apporoach than if the treatment was done after punch biopsies has been reported both among hrHPV positive and among hrHPV negative patients [24]. To our knowledge, the effect of HPV genotypes present at initial colposcopy has not been studied with immediate treatment. Contrary to previous data, in our study when HPV genotype 16 or 18 was present, the overtreatment rate was lower in the immediate treatment group than when LLETZ was performed after HSIL biopsies. Among patients positive for other high-risk HPV than 16 or 18, the OT rates were somewhat similar between these groups. High-risk HPV negative patients, on the other hand, had a significantly higher OT rate in immediate treatment group compared to gold standard group. Colposcopic impression of lesions harboring HPV16 may suggest higher lesion grade [35,36], making colposcopical assessment and decision-making easier for the clinician. On the other hand, the healing potential of HPV16 lesions may be poorer, with the probability of CIN2 regression being smaller after biopsies in patients with HPV16 as compared to those with other hrHPVs [37], which again would not explain the finding of lower overtreatment rate in the immediate treatment group.

Our data consist of a cohort of patients referred to colposcopy according to standard indications. Consecutive patients were invited to participate in the study. Treatment approach was determined by individual clinical assessment although adherence to national and international guidelines and quality indicators was recommended. A senior colposcopist was present at every colposcopy, and LLETZ procedures and colposcopy findings were systematically recorded in the electronic patient database in structured form. Due to non-randomised setting, selection bias between treatment approaches may have occurred, for example, very young patients most likely were not considered ideal candidates for immediate treatment, even if the guideline criteria would have been met. Interobserver variability of colposcopy could also be considered as a potential source of bias. Further, patient selection may have had an influence on treatment strategy decisions. Still, even in comparison of cases where the Finnish Current Care Guidelines criteria were met in both groups, there were no differences in the overtreatment rates between the groups. The threshold to perform immediate treatment might well have been lower than that of taking biopsies at first visit in cases of suspected future non-compliance. Still, this selection bias would rather increase than decrease the overtreatment rate (of immediate treatment) and should therefore not compromise our current interpretation of the results.

Instant treatment is likely to reduce the costs and the required colposcopy resources and provides an adequate histological specimen as well. In a previous study, patients treated at the first appointment also had significantly less anxiety compared to a two-step protocol [7]. However, to avoid overtreatment, colposcopy expertise is crucial, and the use of scoring systems such as RCI or the Swede score is well advised [16,38]. Clinicians should refrain from immediate LLETZ in cases where HSIL is not likely, especially in young patients planning for future pregnancies. If there is uncertainty about the clinical colposcopic diagnosis, it is always acceptable to perform punch biopsies first to ensure the diagnosis before proceeding to LLETZ. It should be noted that clinical decision-making based on scoring systems such as Reid's colposcopy index or Swede score requires training and high-quality standards in colposcopy. In the current study patients with TZ3 had a high overtreatment rate in both immedite treatment and treatment after biopsies even when adhering to guideline criteria, for which TZ3 continues to be a challenge independent of the treatment approach taken.

Our results support immediate treatment after high-grade cytology and high-grade colposcopic impression (also called select-and-treat approach). In these cases, immediate treatment does not result in excess overtreatment compared to treatment after biopsies. Of note, adhering to treatment only after biopsies, i.e., treating only those with high grade histology results, would also lead to comparable rates of overtreatment. HPV genotyping could provide further aid in clinical decision-making during colposcopy, e.g., by giving reassurance for deciding upon instant treatment, especially if HPV16 or HPV18 is present.

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Credit authorship contribution statement

MKi, MJ, PN, IK contributed to conception and design of the study. MKi, IK performed the statistical analysis. MKi, AH, KA,PN and IK interpreted the data. MKi, AH, KA LK-T and IK drafted the manuscript and EA, PN, MKy, SV and (JD) critically revised it. IK and PN were responsible for the funding. All authors approved the final version for submission.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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