ASCCP Colposcopy Standards; WG2: Risk-based colposcopy-biopsy practice

Draft recommendations and supporting evidence

Recommendation #1:

Colposcopy-biopsy practice may be modified based on the risk level (which can be viewed as the probability of finding precancer/cancer at the time of the procedure) based on reason for referral and colposcopy impression.

Rationale and supporting evidence:

Women referred to colposcopy because of abnormal cervical cancer screening results have a wide range of underlying risk of cervical precancer. The risk can be estimated from screening and triage tests (e.g. cytology and HPV with HPV16/18 genotyping), and the colposcopic impression at the colposcopy visit. Risk markers can be combined to stratify the population in groups with very different risk. Depending on the underlying risk, colposcopy-biopsy practice could be usefully modified. For example, when the risk of precancer is very high, immediate treatment may be recommended. Conversely, if the risk is very low, more expectant management may be warranted. For intermediate risks, multiple biopsies of acetowhite lesions lead to increased detection of precancer.

Recommendation #2:

Multiple biopsies targeting all areas with acetowhitening, metaplasia or higher abnormalities are recommended. Usually, at least two and up to four targeted biopsies from distinct acetowhite lesions should be taken.

Rationale and supporting evidence:

Many studies have shown that taking a single biopsy targeting the worst appearing lesion may miss up to a third of prevalent precancers (Table 1). In all studies, there was a substantial increase moving from one to two targeted biopsies. In the NCI Biopsy Study, which used a very low threshold of colposcopic abnormality (any acetowhitening), the yield of precancer increased substantially from the first to second and second to third biopsies. A fourth targeted biopsy, or an additional non-targeted biopsy (random biopsy) only provided a minimal increase in disease yield.

Table 1: Increased detection of cervical precancer with increasing number of biopsies

Study	Population	Endpoints	1 biopsy	2 biopsies	3 biopsies	4 biopsies
Gage et al. Obstet Gynecol 2006	ALTS trial, multiple centers in the USA	2-year CIN3+	142/208 (68.3%)	108/132 (81.8%)	35/42 (83.3%)	NA
Pretorius et al. J Low Genit Tract Dis 2011	SPOCCS, China	Cross-sectional, CIN3+	141/222 (63.5%)			198/222 (89%)
Van der Marel et al. Gynecol Oncol 2014	EVAH study, Netherlands and Spain	Cross-sectional, CIN2+	136/263 (51.7%)	159/263 (60.4%)		
Wentzensen et al. J Clin Oncol 2015	Biopsy Study, USA	Cross-sectional, HSIL+	157/252 (60.6%)	222/252 (85.6%)	246/252 (95.6%)	252/252 (100%)

Recommendation #3:

Random biopsies are not recommended for women with less than HSIL cytology, negative for HPV16/18, and who have a completely normal colposcopic impression (i.e. no acetowhitening, metaplasia, or other visible abnormality).

Rationale and supporting evidence:

Multiple studies have shown that women with a low prior risk and a completely normal colposcopy impression (<acetowhitening) have a very low risk of prevalent precancer (Table 2). A prospective study from the UK showed that women with normal colposcopy impression and borderline-mild cytology findings have a very low risk of precancer in the following years (Table 3).

Table 2: Risk of cervical precancer in women with normal colposcopy and low prior risk

Low-risk group: <HSIL, HPV 16/18-, normal colposcopy

Study	Manuscript	N	CIN2+	CIN3+	Proportion CIN2+	Proportion CIN3+
ATHENA	Huh et al. Obstet Gynecol 2014	1225	8	2	0.0065	0.0016
ALTS	in preparation	373	4	2	0.0107	0.0054
BD	in preparation	1572	25	11	0.0159	0.0070
Biopsy	Wentzensen et al. J Clin Oncol 2015	19	0	0	0.0000	0.0000
Total		3189	37	15	0.0116	0.0047

Table 3: Prospective UK data (Kelly et al. BJOG 2012)

Cumulative disease at 1, 2, 3, >3 years after negative colposcopy in women with low-grade cytology

Years since negative colposcopy	Negative	Abnormal cytology	CIN1	CIN2	CIN3	Total
1	912 (95.4%)	10 (1.0%)	18 (1.9%)	6 (0.6%)	10 (1.0%)	956
2	869 (90.9%)	19 (2.0%)	33 (3.5%)	16 (1.7%)	19 (2.0%)	956
3	851 (89.0%)	25 (2.6%)	38 (4.0%)	19 (2.0%)	23 (2.4%)	956
>3	826 (86.4%)	30 (3.1%)	49 (5.1%)	23 (2.4%)	28 (2.9%)	956

Recommendation #4:

In non-pregnant women age 25 and older with very high risk of precancer (at least two of the following: HSIL cytology, HPV16 and/or HPV18 positive, high-grade colposcopy impression), both immediate treatment without biopsy confirmation or colposcopy with multiple targeted biopsies are acceptable. Endocervical sampling should be conducted according to the 2012 ASCCP management guidelines. If biopsies are taken and do not show precancer, surveillance according to the 2012 ASCCP management guidelines is recommended.

Rationale and supporting evidence:

A large systematic review of see-and-treat management strategies for women with HSIL cytology found that 89% of all women with HSIL had CIN2+, while some clinical trials have shown somewhat lower risk. Currently, 2012 ASCCP management guidelines give the option of immediate treatment for women with HSIL cytology. Table 4 shows that in each study, the risk of precancer in women with HSIL and high grade colposcopy impression or HPV16 and high grade colposcopy impression substantially exceeds the current HSIL risk threshold at which immediate treatment is acceptable suggesting that immediate treatment can be recommended particularly for these women. If biopsies show no precancer despite the high prior risk, increased surveillance is recommended.

Table 4: Risk of CIN2+ or HSIL+ in women with high prior risk strata

Strata	Study	Reference	Population	N	CIN2+	CIN3+	HSIL+	Proportion CIN2+	Proportion HSIL+
HSIL only (reference)	Syst. review	Ebisch et al. BJOG 2016	HSIL	3777	3351			0.89	
	ALTS	in preparation	ASCUS/LSIL	314	177			0.56	
	BD	in preparation	HPV+	133	65	34		0.49	
	Biopsy	Wentzensen et al. J Clin Oncol 2015	ASCUS+	236	--	--	125		0.61
	Total			4460	3593	34	125	0.85	0.53
High-grade colpo + HSIL +	Syst. review	Ebisch et al. BJOG 2016		3403	3077			0.90	
	ALTS	in preparation		103	80			0.78	
	BD	in preparation		17	13	10		0.76	
	Biopsy	Wentzensen et al. J Clin Oncol 2015		109	--	--	77		0.71
	Total			3632	3170	10	78	0.90	0.71
High-grade colpo + HPV16/18+	DSI trial	Zaal et al. BJOG 2012	BMD twice	18	17	14		0.94	
	ALTS	in preparation		101	76			0.75	
	BD	in preparation		31	19	13		0.61	
	Biopsy	Wentzensen et al. J Clin Oncol 2015		84	--	--	65		0.77
	Total			234	112	27	65	0.75	0.77
HSIL + HPV16/18+	ALTS	in preparation		153	103			0.67	
	BD	in preparation		46	31	20		0.67	
	Biopsy	Wentzensen et al. J Clin Oncol 2015		83	--	--	65		0.78
	Total			282	134	20	65	0.67	0.78
High-grade colpo + HSIL + HPV16/18+	ALTS	in preparation		55	47			0.85	
	BD	in preparation		9	8	6		0.89	
	Biopsy	Wentzensen et al. J Clin Oncol 2015		58	--	--	45		0.78
	Total			122	55	6	45	0.86	0.78