Recurrent disease after treatment for cervical intraepithelial neoplasia – the importance of a flawless definition of residual disease and length of follow-up

Running headline: Residual and recurrent disease after CIN treatment

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Abstract

Objective: To evaluate adherence to national guidelines for follow-up, and assess residual and recurrent disease after treatment for cervical intraepithelial neoplasia grade 2 or worse (CIN2+).

Study design: In a case-series design women aged 25-69 years treated for primary CIN2+ in 2006-2011 (n=752) were followed through August 9, 2019 for residual or recurrent disease, i.e., CIN2+ diagnosed before or after, respectively, two consecutive, normal post-treatment cytology results. We used the Chi-Square test to assess predictive factors of adherence to post-treatment follow-up and residual disease, and survival analyses to assess the cumulative incidence of residual and recurrent disease.

Results: Strict adherence to post-treatment follow-up was low (59%). However, 702 (95%) women attended at least one post-treatment follow-up visit within the suggested time window. Forty-two women (5.6%) were diagnosed with residual disease, 38 (91%) of whom were diagnosed within 2 years of treatment. Among the 637 (85%) women with two consecutive, normal post-treatment cytology results, cumulative incidence of recurrent disease was 1.0 (95% confidence interval [CI]: 0.2-1.8) and 2.5 (95% CI: 1.2-3.8) per 100 women-years within 42 and 78 months of treatment, respectively. Three women with residual and two with recurrent disease were diagnosed with cervical cancer within 78 months of treatment. Women with not-free resection margins at treatment had a significantly increased risk of residual and recurrent disease. Using a 2-year definition for residual disease would misclassify 3 of 5 cancer cases as recurrent disease when they were true cases of residual disease.

Conclusions: This study emphasizes the importance of properly distinguishing between residual and recurrent disease after treatment for CIN2+. Many women with residual disease could benefit from an earlier colposcopy, cervical biopsy, or diagnostic conization during

post-treatment follow-up in order to detect occult cervical cancer. The cumulative incidence of recurrent disease within 78 months of treatment was low.

Introduction

The organized cervical cancer screening program in Norway was initiated in 1995. The program covers women aged 25-69 years, who are recommended to undergo screening by cervical cytology every 3 years, with the intention to detect and treat precancerous lesions and thereby reduce cervical cancer incidence and mortality. For many years, the loop electrosurgical excision procedure has been the method of choice to treat precancerous lesions (1). As the risk of cervical cancer remains high up to 20 years after treatment (2-4), it is important to assess treatment effectiveness before sending women back to the regular screening program.

During the period covered in this study, Norwegian guidelines recommended different post-treatment follow-up algorithms based on resection margins: women with free margins and two consecutive, normal cytology results within 4-18 months of treatment can return to the regular screening program; women with non-free margins should have two consecutive, normal cytology results within 12 months, as well as one normal cytology result each year for 4 years before returning to the regular screening program (5). Women with abnormal cytology results during post-treatment follow-up are referred according to the follow-up algorithm of the regular screening program.

Most previous studies defined residual disease as cervical intraepithelial neoplasia grade 2 or worse (CIN2+) diagnosed within 2 years of treatment, and recurrent disease as CIN2+ diagnosed thereafter (6,7), or did not distinguish between residual and recurrent disease when assessing treatment effectiveness (8-11). Treated women with minor cytological abnormalities (atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions), or intermittent normal or unsatisfactory cytology results during post-treatment follow-up, could be under surveillance for years before residual or recurrent disease is detected or they are returned to the regular screening program. Using a threshold of 2 years

has inevitably introduced misclassification of residual and recurrent disease, which overestimates the recurrence rate and underestimates the real number of treatment failures. In the present study, we evaluated adherence to national guidelines for follow-up and assessed residual and recurrent disease after treatment for CIN2+ in the two northernmost counties in Norway (Troms and Finnmark) using a historical prospective case-series design.

Material and Methods

The Department of Pathology, University Hospital of North Norway, Tromsø, is the only laboratory that performs both cytological and histological assessments for the residents of Troms and Finnmark counties, thus its clinical database, SymPathy, captures all information on screening history, treatment, and follow-up. Using that database, we identified 852 women who received treatment for primary CIN2+ from January 1, 2006 through December 31, 2011. We excluded women outside the target age group of the screening program (66 women aged 17-24 years and 11 aged 70-89 years), women with a diagnosis of cervical cancer in biopsies/cone specimens (n=20) and women who had a direct hysterectomy within 6 months of treatment (n=3), leaving 752 women in the study sample.

We categorized age into three (25-39, 40-54, and 55-69 years) and time period into two groups (2006-08 and 2009-11). Histological diagnoses in biopsies and cone specimens were recorded as CIN1, CIN2, CIN3 (including adenocarcinoma *in situ*), and cervical cancer. Resection margins were categorized as free or not free, with the latter category including missing and inconclusive assessment.

We applied a pragmatic approach when analyzing adherence to post-treatment follow-up, without considering resection margins. In addition, we expanded the window for adherence to post-treatment follow-up from 4-18 months to 3-18 months, as many women attended their first follow-up visit 3-4 months after treatment. Adherence was defined attending two follow-

up visits within the expanded post-treatment follow-up window. Non-adherence was defined as attending only one follow-up visit or none at all. In addition, women who attended their first follow-up visit before or within the expanded post-treatment follow-up window but had subsequent visits thereafter (after 18 months) were categorized as non-adherent, as were those who had first and subsequent follow-up visits after 18 months. If a woman had a cytology sample and a biopsy collected at the same follow-up visit, the histological outcome was used.

We defined residual disease as histologically confirmed CIN2+ diagnosed before two consecutive, normal post-treatment cytology results. Women awaiting further follow-up for abnormal post-treatment cytology results were classified as having "incomplete follow-up" at study end. Recurrent disease was defined as histologically confirmed CIN2+ diagnosed after two consecutive, normal post-treatment cytology results. Post-treatment follow-up time was calculated as the time in months between treatment and a histological outcome of CIN2+ or date of last post-treatment follow-up visit.

All analyses were performed in SPSS version 24.0 with a Chi-square test, Fisher's exact test, and survival analyses. P-values <0.05 were considered statistically significant. Follow-up ended on August 9, 2019. We analyzed residual disease within 24 months of treatment, and residual and recurrent disease within 42 and 78 months of treatment. Seventy-eight month of follow-up resembles two screening rounds from treatment including a 6 month delay as practiced by NCR (36+36+6 months).

The Regional Committee for Medical and Health Research Ethics, North Norway, has evaluated the protocol as a quality assurance study fulfilling the requirements for data protection procedures within the department (2015/2479/REK Nord). The Patient Ombudsman, University Hospital of North Norway, Tromsø, approved study start.

Results

Mean age at treatment was 37 years (range 25-68 years), and the majority of women were treated for CIN grade 2 or 3 (97%). Resection margins were not free in one-third of cone specimens. There were no significant differences in distribution of age, most severe histology, or status of resection margins by time period (Table 1).

In total, 443 women (58.9%) were adherent to post-treatment follow-up. Among non-adherent women, eight (1.1%) attended no post-treatment follow-up visits, whereas 26 women (3.5%) had only one post-treatment follow-up visit (Table 2). Nearly 97% of the women attended at least one post-treatment follow-up visit during our extended post-treatment follow-up window. There was no significant association between age at treatment, most severe histology, status of resection margins and adherence to post-treatment follow-up.

Within 78 months of treatment, 42 women (CIN2=13, CIN3=26, cervical cancer=3) (5.6%) were diagnosed with residual disease (Table 3). In 38 (91%) of these women, the diagnoses occurred within 2 years of treatment. Among women with residual disease, resection margins were not free in 54% of women with residual CIN2 and in 73% of women with residual CIN3. The cumulative incidence of residual disease (CIN2+) increased from 10.4 to 11.9 per 100 women-months among women with not-free resection margins within 24 and 78 months of treatment, compared to an increase from 2.3 to 3.1 per 100 women-months among women with free resection margins ($p<0.001$). Three women were diagnosed with residual cervical cancer within 43-71 months of treatment (Table 4). At 78 months post-treatment, 9.7% of women remained unresolved due to incomplete follow-up (8.6%) or non-attendance to post-treatment follow-up visits (1.1%).

Eighty-five percent of the women (n=637) returned to the regular screening program within 78 months of treatment, most of whom had free margins at treatment (69%). The cumulative incidence of recurrent disease was 1.0 (95% confidence interval [CI]: 0.2-1.8) and

2.5 (95% CI: 1.2-3.8) per 100 women-months within 42 and 78 months of treatment, respectively. In total, 14 women developed recurrent disease (CIN2=10, CIN3=2, cervical cancer=2), all of whom were diagnosed more than 2 years after treatment. Women with not-free margins had a significantly increased risk of recurrent disease (p=0.01) despite a low cumulative incidence.

Among the five cervical cancer cases, four had been diagnosed with CIN3 at primary treatment. Both recurrent cases of cervical cancer were adherent to post-treatment follow-up. However, the residual cases of cervical cancer had a delay in their diagnosis due to late referral and/or incomplete colposcopies (Table 4).

Comment

The adherence to guidelines for post-treatment follow-up we observed was higher than that in most studies, but it was still not satisfactory. Our residual disease estimate of 5.6% is lower than that reported in most other studies on treatment failure (6-11), but it may be underestimated, as 8.6% of the women were awaiting further follow-up at study end. Among women who returned to the screening program, the cumulative incidence of recurrent disease within 78 months of treatment was low.

Few studies have reported adherence with guidelines for post-treatment follow-up. Barken et al. (12) followed 45 984 Danish women for 5 years and assessed adherence at 15-month intervals. Ninety percent of their study sample attended at least one visit within 15 months of treatment, but only 40% had yearly Pap smears as recommended in Danish guidelines. This is in line with results on 2-year follow-up in studies from the US (13), the Netherlands (14), and Italy (15). Another study (16) from the UK found that over 20% of women did not attend follow-up visits within the recommended 12 months. A recent study from Australia (17) evaluated adherence within 12 and 24 months of treatment and found that over half of those

who attended a first follow-up visit did not attend a second follow-up visit. In our study, 95% of the women attended at least one follow-up visit within the recommended time window. In agreement with a study from England by Soutter et al. (16), but in contrast to other studies (11, 13, 15), we had a low rate of loss to follow-up.

Residual/recurrent rates of CIN2+ assessed within 4-6 months (18-20), 12 months (21) or within 2 years of treatment (6, 7) have ranged from 1-10% (6, 7, 18-22). We observed residual disease in 5.6% of our study sample within 78 months of treatment, which is consistent with a previous study that used a similar definition of residual and recurrent disease (22), and non-significantly lower than the estimate from a meta-analysis of 24 studies with at least 18 months of post-treatment follow-up (6.6%, 95% CI: 4.9-8.4) (23).

As reported by others, we confirmed that women with not-free resection margins have higher rates of residual disease (9, 10, 18, 19, 22, 23) and a higher incidence of recurrent disease (22). Our study did not show that CIN3 or older age were predictors of residual/recurrent disease.

Follow-up of abnormal post-treatment cytology results and specimen collection for histologic evaluation takes time and may delay the diagnosis of residual disease for years. In our study 9% of cases of residual disease were diagnosed after 2 years of treatment, while 8.6% still had an incomplete follow-up at study end. Many of these women had adverse post-treatment cytology outcomes that should have led to an earlier biopsy, including the three cases of residual cervical cancer. We could not decide whether this was a patient delay, a doctor delay, or a combination of the two.

If we had used a 2-year cut-off for residual disease, the number of recurrent cases of CIN3 would increase from 2 to 3, while the number cervical cancer cases would increase from 2 to 5 cases. This misclassification of cervical cancer increased the incidence of recurrent cervical

cancer from 52 to 130 per 100 000 women-years within 78 months of treatment . This stress the importance of a flawless definition of post-treatment residual and recurrent disease

Follow-up after treatment for CIN2+ has been studied for years, but there is still no consensus on tests, intervals, or duration of follow-up. Previous studies used various follow-up algorithms, and in recent years several authors have recommended the use of human papillomavirus (HPV) testing, either alone or as a co-test with cytology (23-26). Persistent HPV infection after treatment for CIN2+ has been shown to be the most important predictor of residual/recurrent disease (23). A study from the Netherlands found that co-testing led to fewer unnecessary colposcopy referrals, as co-testing showed higher specificity for the detection of residual/recurrent CIN2+ compared to cytology alone, while no difference in sensitivity was observed (27). However, Strander et al. followed women for 14 years after treatment and found that HPV testing 6-12 months after treatment was of limited value in predicting residual/recurrent CIN2+, as many of the women who developed CIN2+ more than 2 years after treatment were HPV-negative at short-term post-treatment follow-up (28).

Clearance rates of HPV infection after treatment varied from 45-50% at 3-6 months to 1-8% at 24 months after treatment (8,29), indicating that clearance may take years. Many post-treatment HPV studies had only one follow-up visit, or a follow-up interval that was too short to determine the importance of HPV testing in treatment algorithms. Co-testing with HPV testing and a cytology remains uncontroversial when both tests are negative or positive. However, if samples are collected too close to treatment, co-testing will inevitably lead to unnecessary follow-up due to discordant HPV (positive) and cytology (normal) results. A positive HPV test may also be due to a re-infection from an HPV-positive partner. Postponing HPV testing to at least 6 months after treatment, and implementing reflex testing in all cases with positive cytology has proven to be cost-effective in follow-up after treatment for CIN (30).

Table 5 summarizes post-treatment follow-up guidelines in selected countries. The main difference across countries is the timing of the first post-treatment follow-up visit. Very few studies report cancer within the first post-treatment follow-up year (2). In our study (Table 4) and other studies (3), the first case of cervical cancer was diagnosed 2-3 years after treatment. The other issue with co-testing in post-treatment follow-up is the persistence of HPV infections. The shorter the time interval from treatment, the more likely it is that the HPV test will be positive. As HPV infections wane over time; a 12-month interval before a first post-treatment follow-up visit will reduce over-diagnosing and unnecessary follow-up due to a false-positive HPV test in the presence of normal cytology or minor cytological abnormalities. The timing of the second post-treatment follow-up visit varies across countries. In the US, Australia, and Finland, a 24-month visit is recommended, while the UK, Denmark, and Sweden recommend returning to screening when the first co-test is negative. As most studies on this topic are short-term, we need to await risk assessment evaluations of the new guidelines in prospective studies before a more global follow-up regimen can be agreed upon (31). Except for Denmark, information about resection margins was not a parameter for follow-up evaluation in updated post-treatment follow-up guidelines (Table 5), as a meta-analysis including 97 studies concluded that a positive HPV test result outweighed information on resection margins in the prediction of treatment failure (23). All new algorithms for follow-up make a clear distinction between residual and recurrent disease, as the timing of return to the regular screening program is determined by one, or two consecutive, negative co-tests, where the first co-test occurs within 6 or 12 months of treatment, the subsequent co-test occurs at 12 or 24 months (Table 5).

The strengths of the present study were the large, population-based sample size and the long-term follow-up after treatment. Furthermore, we used firm definitions for residual and

recurrent disease. Limitations include the retrospective study design and the lack of consistent HPV testing during follow-up.

Conclusion

Adherence to follow-up guidelines after treatment for CIN2+ was low. It is important to discriminate between residual and recurrent disease in post-treatment follow-up. Most women with the residual disease were diagnosed within 2 years; however, the three residual cancer cases were diagnosed at a later time point. Few women developed recurrent disease within 78 months of treatment.

Author contributions: FES/SWS designed the study. MSB did data collection. MSB/FES run consistency analysis, cleaned data, and analyzed data. MSB was lead author. MSB, SWS and FES interpreted the results, evaluated literature, and agreed upon the final manuscript for submission.

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Conflicts of interest: None

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369 Table 1: Characteristics of the study sample by time period

	Time period	
	2006-08 N=334 %	2009-11 N=418 %
Age at treatment for CIN2+ (years)	69.5	67.9
25-39	24.0	25.1
40-54	6.6	6.9
55-69		
Most severe histology		
Normal	0.6	
CIN 1	2.4	2.4
CIN 2	27.8	36.6
CIN 3	69.2	61.0
Status of resection margins		
Free	63.8	69.6
Not free	36.2	30.4

CIN2+: cervical intraepithelial neoplasia grade 2 or worse

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371 Table 2: Adherence to post-treatment follow-up guidelines by status of resection margins

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	Time since treatment		Status of resection margins		
Adherence to post-treatment follow-up guidelines	First follow-up visit	Second follow-up visit	Free	Not-free	Total
			N=504	N=248	N=752
			%	%	%
Non-adherent					
No follow-up			1.2	0.8	1.1
1 follow-up visit	1-2 mo.		0.8	0.4	0.7
	3-18 mo.		3.2	1.6	2.7
	≥19 mo.			0.4	0.1
≥2 follow-up visits	≥3 mo.	≥19 mo.	20.0	14.9	18.4
	1-2 mo.	≤18 mo.	14.9	17.7	15.8
	1-2 mo.	≥19 mo.	2.2	1.6	2.0
	≥19 mo.	≥19 mo.	0.6		0.4
Adherent ≥2 follow-up visits	≥3 mo.	≤18 mo.	57.1	62.5	58.9

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376 Table 3: Status within 24, 42, and 78 months of treatment

	24 months N=752 %	42 months N=752 %	78 months N=752 %
Non-attenders	1.1	1.1	1.1
Incomplete follow-up	23.7	14.	8.6
Residual disease			
CIN2	1.7	1.7	1.7
CIN3	3.3	3.5	3.5
Cervical cancer			0.4
Back to regular screening program	70.2	79.8	84.7
Total	100	100	100

377 CIN1: cervical intraepithelial neoplasia grade 1;

378 CIN2: cervical intraepithelial neoplasia grade 2;

379 CIN3: cervical intraepithelial neoplasia grade 3

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Table 4 Status at conization, adherence to follow-up, and histology/stage for the five cervical cancer cases.

At conization			Follow-up				Cervical cancer	
Age	Histo-logy	Resection margins	No. of follow-up visits	Adherence to follow-up	Diagnosed during	Months to diagnosis	Histology	Stage
37	CIN2	Free	12	Incomplete colposcopy/ biopsy	Residual disease	71	Squamous-cell-carcinoma	IB
54	CIN3	Not free	10	Incomplete colposcopy/ biopsy	Residual disease	43	Squamous-cell-carcinoma	IB
60	CIN3	Not free	8	Incomplete colposcopy/ biopsy	Residual disease	52	Squamous-cell-carcinoma	IA1
29	CIN3	Not free	7	Adherent	Recurrent disease	45	Squamous-cell-carcinoma	IB
45	CIN3	Not free	4	Adherent	Recurrent disease	34	Squamous-cell-carcinoma	IA2

CIN1: cervical intraepithelial neoplasia grade 1;

CIN2: cervical intraepithelial neoplasia grade 2;

CIN3: cervical intraepithelial neoplasia grade 3

393 Table 5: Algorithms for post-treatment surveillance from select countries.

Country	Year	Recommendation	Reference
USA (ASCCP)	2012	○ Co-test at 12 and 24 months. ○ If 12 and 24 months tests are negative, retesting in 3 years ○ If any test is abnormal, colposcopy with biopsy	L.S. Massad, M.H. Einstein, W.K. Huh et al. ASCCP Consensus Guidelines Conference. J Low Genital Tract Dis 2013;17:S1-S27
Denmark	2012	○ Co-test + assessment of resection margins at 6 months ○ If all normal, return to regular screening program ○ If any positive, co-test at 12 months	http://www.sst.dk/~/media/B1211EAFEDFB47C5822E883205F99B79.ashx
Norway	2015	○ Co-test at 6 and 12 months ○ If negative HPV and normal cytology, co-test at 12 months ○ Otherwise follow-up dependent upon outcome of tests	https://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/Veileder-gynekologisk-onkologi/Premaligne-lidelser-i-cervix-uteri/
UK	2016	○ Co-test at 6 months ○ If pap negative/borderline/low-grade and HPV-negative, return to regular screening program ○ If the HPV test is positive, referral to colposcopy. ○ If pap high-grade, referral to colposcopy. No high-risk HPV test is required	https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management
Australia	2016	○ Co-test at 12 months and annually thereafter, until two negative co-tests on consecutive visits - then return to regular, 5year screening program ○ Otherwise follow-up dependent upon outcome of tests	https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening
Sweden	2018	○ Co-test at 6 months ○ If negative HPV and normal cytology, return to screening ○ Otherwise follow-up dependent upon outcome of tests	https://www.cancercentrum.se/samverkan/vara-uppdrag/prevention-och-tidig-upptackt/gynekologisk-cellprovskontroll/vardprogram/gallande-vardprogram/17.-uppfoljning-efter-dysplasibehandling/

Finland	2019	○ When most severe histology CIN2+, co-test at 6 and 24 months ○ If negative HPV and normal cytology, follow-up 24 months ○ Otherwise follow-up dependent upon outcome of tests ○ When most severe histology ≤CIN1, co-test at 6 months ○ If negative HPV and normal cytology, return to regular 5-year screening ○ Otherwise follow-up dependent upon outcome of tests	http://www.kaypahoito.fi/web/kh/suositukset/suositus?id=hoi50049#K1

394 CIN1: cervical intraepithelial neoplasia grade 1; CIN2+: cervical intraepithelial neoplasia
395 grade 2 or worse; HPV: human papillomavirus

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