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Use of Pathology Data to Improve High-Value Treatment of Cervical Neoplasia

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Abstract

We investigated the influence of pathology data to improve patient outcomes in the treatment of high-grade cervical neoplasia in a joint pathology and gynecology collaboration. Two of us (B.S.D. and M.D.) reviewed all cytology, colposcopy and surgical pathology results, patient history, and pregnancy outcomes from all patients with loop electrosurgical excision procedure specimens for a 33-month period (January 2011-September 2013). We used this to determine compliance to 2006 consensus guidelines for the performance of loop electrosurgical excision procedure and shared this information in 2 interprofessional and interdisciplinary educational interventions with Obstetrics/Gynecology and Pathology faculty at the end of September 2013. We simultaneously emphasized the new 2013 guidelines. During the postintervention period, we continued to provide follow-up using the parameters previously collected. Our postintervention data include 90 cases from a 27-month period (October 2013-December 2015).

Our preintervention data include 331 cases in 33 months (average 10.0 per month) with 76% adherence to guidelines. Postintervention, there were 90 cases in 27 months (average 3.4 per month) and 96% adherence to the 2013 (more conservative) guidelines ($P < .0001$, χ^2 test). Preintervention, the rate of high-grade squamous intraepithelial lesion in loop electrosurgical excision procedures was 44%, whereas postintervention, there was a 60% high-grade squamous intraepithelial lesion rate on loop electrosurgical excision procedure ($P < .0087$ by 2-tailed Fisher exact test). The duration between diagnosis of low-grade squamous intraepithelial lesion and loop electrosurgical excision procedure also increased significantly from a median 25.5 months preintervention to 54 months postintervention ($P < .0073$; Wilcoxon Kruskal-Wallis test). Postintervention, there was a marked decrease of loop electrosurgical excision procedure cases as well as better patient outcomes. We infer improved patient safety, and higher value can be achieved by providing performance-based pathologic data.

Keywords

American Society for Colposcopy and Cervical Pathology, cervical neoplasia, guidelines, high-grade squamous intraepithelial lesion, indications, intervention, loop electrosurgical excision procedure

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Introduction

Loop electrosurgical excision procedure (LEEP) for the removal of the transformation zone in preinvasive cervical disease has many advantages over a cold knife cone biopsy, including performance in an office setting (rather than ambulatory surgery), less blood loss, better postprocedure viewing of the squamocolumnar junction, and smaller but evaluable specimens for pathology.[1] For these reasons, LEEP has become the dominant means of initial intervention in cervical cancer prevention.[2-4] However, there is a corresponding concern that this intervention for prevention of cervical cancer is over utilized, subjecting some patients to unjustified costs and risks.[1] Although LEEP has a favorable complication profile compared to other secondary interventions for cervical cancer prevention, it does not eliminate the costs and potential risks of conization.[1,5,6] Potentially unjustified LEEP intervention is particularly troubling for patients of reproductive age as LEEP has been associated with adverse pregnancy outcomes, most notably preterm delivery, although this is not universally accepted.[7-17]

Guidelines direct the application of LEEP.[18,19] In 2013 during discussion about the new American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, one of us noted a high number of LEEPs without high-grade squamous intraepithelial lesion (HSIL; cervical intraepithelial lesion [CIN] grade 2 or 3) compared to published expectations. We therefore discussed a joint quality assurance and patient safety project among the Departments of Pathology and Obstetrics and Gynecology and the School of Public Health. Our explanatory hypothesis was that clinicians were not strictly following guideline indications, which led to unjustified procedures with lower yields and potentially unjustified risk. We hypothesized that by reviewing cases in a collaborative fashion for indications and outcomes and then using these data in an educational manner with continued follow-up, we could improve high-value treatment of cervical intraepithelial neoplasia. Therefore, we analyzed our indications and outcomes for almost 3 years prior to our intervention (January 1, 2011), conducted educational interventions in September 2013, and continued ongoing review for 27 subsequent months (October 2013-December 2015).

Materials and Methods

Under our institutional review board # 1306049573, we reviewed 421 sequential LEEPs performed at our institution over a 5-year period (January 01, 2011-December 31, 2015) in our Anatomic Pathology Laboratory Information System.[a] The cases from January 2011 through September 2013 were classified as preintervention. The cases from October 2013 through December 2015 were classified as postintervention. We reviewed each LEEP result and determined the presence or absence of HSIL. We also reviewed the indication for each LEEP using pathology/cytology results and chart review and then compared the indications to the current published guideline. During the chart review for the preintervention group, we also reviewed for pregnancy outcomes. We used the 2006 ASCCP guidelines for our preintervention period and the 2013 guidelines for our postintervention period. The main outcome measure was the presence or absence of HSIL including CIN 2 or 3. The goal of these comparisons was to provide data that could motivate clinician behavioral change, if needed.

Table 1. Indications for LEEP Coded as Nonguideline Adherent.

Nonguideline adherent reasons for LEEP
Colposcopy
Unsatisfactory colposcopy only (without a HSIL biopsy or Pap test)
Extension of a lesion into the endocervical canal with negative ECC or cytobrush
Discrepancy with positive colposcopy and negative biopsy
Endocervical curettings with LSIL only
Cytology
ASC-H without biopsy findings
AGC NOS without findings on ECCs
Atypical endometrial cells only
Duration of LSIL less than 2 years
Patient findings
Patient preference (patients without other specific guideline indications who requested a LEEP)
Patient risk factors for progression for dysplasia
Diabetes
Smoking
Multiple sexual partners
Remote history of cervical dysplasia
Rheumatoid arthritis
Remote history of breast cancer
Morbid obesity with polycystic ovarian syndrome
History of Lyme disease
Noncompliant patients or detainees in prison or not using condoms

Abbreviations: AGC NOS, atypical glandular cells not otherwise specified; ASC-H, atypical squamous cells cannot exclude HSIL; ECC, endocervical curettings; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesion.

Summarized, the 2006 consensus guideline indications for LEEP included the following—CIN 2-3 with adequate colposcopy; inadequate colposcopy; recurrent CIN 2-3; endocervical curettings (ECC) with CIN 2-3; and 2 (or more) years of low-grade squamous intraepithelial lesion (LSIL) persistence.[18] Since the pathologic diagnosis of CIN 1-2 was unclear, our review coded it per the gynecologists' interpretation of CIN 2 because the gynecology interpretation initiates the procedure. Another possible indication that we accepted as guideline adherent was HSIL on Pap test with negative subsequent biopsy (cytology and biopsies would ideally be reviewed prior to intervention in this circumstance). Colposcopy was considered guideline adherent if the colposcopy and ECC were both unsatisfactory. The reasons given by clinicians considered as nonguideline adherent are summarized in Table 1.

The 2013 consensus guidelines are more complicated and more conservative.[19] They feature immediate LEEP for patients aged 25 years and older with HSIL on biopsy,

Table 2. Indications and Outcomes for LEEPs From the Preintervention Period January 1, 2011 to September 30, 2013.*

Indication for LEEP	≥CIN 2 on LEEP (%)	<CIN 2 on LEEP (%)	Total
Biopsy with HSIL	138 (64)	79 (36)	217
HSIL Pap	4 (24)	13 (76)	17
Persistent LSIL ≥ 24 months	4 (25)	12 (75)	16
LSIL < 24 months	0	6	6
Indefinite biopsy (CIN 1-2 or cannot rule out HSIL)	0	8	8
ECC with LSIL	0	8	8
Colposcopy	0	14	14
ASC-H Pap (15) or AGC NOS Pap (2)	0	17	17
Atypical endometrial cells on Pap	0	2	2
Patient preference	0	2	2
Risk factors	0	24	24
Total	146 (44)	185 (56)	331

Abbreviations: AGC NOS, atypical glandular cells not otherwise specified; ASC-H, atypical squamous cells cannot exclude HSIL; CIN, cervical intraepithelial lesion; ECC, endocervical curettings; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesion.
*These were the data used for the educational intervention.

persistent HSIL or atypical squamous cells, cannot rule out HSIL (ASC-H) Pap tests of ≥12-month duration, and duration of LSIL of ≥24 months. For women aged 21 to 24 years, the guidelines are even more restrictive with immediate LEEP recommended for these younger women with CIN 3 and observation preferred for CIN 2. Using the 2013 consensus guidelines, we also determined whether the LEEP was guideline adherent for the postintervention group.

Statistical comparisons were made using 2-tailed Fisher exact test (as there were many cross tabulations with small cell counts) or χ^2 test. Statistical analyses were performed using JMP version 11.0.[b]

The intervention started with a meeting by the pathologists (B.D., M.F., and M.D.) and public health specialist (A.D.) with the gynecologists (M.H. and P.C.), who were considered clinical experts in the treatment of cervical neoplasia. We presented our findings and asked for their advice. These leaders critiqued our analysis and reviewed the charts on patients with LEEPs the pathologists considered nonguideline adherent. For example, Pathology had considered LEEPs for CIN 1-2 as nonguideline adherent; however, the gynecologists explained that they interpreted such equivocal cases as "HSIL." Based on the information they provided, we conducted further analysis. After consensus agreement on the data analysis and its interpretation, the group set up 2 meetings.

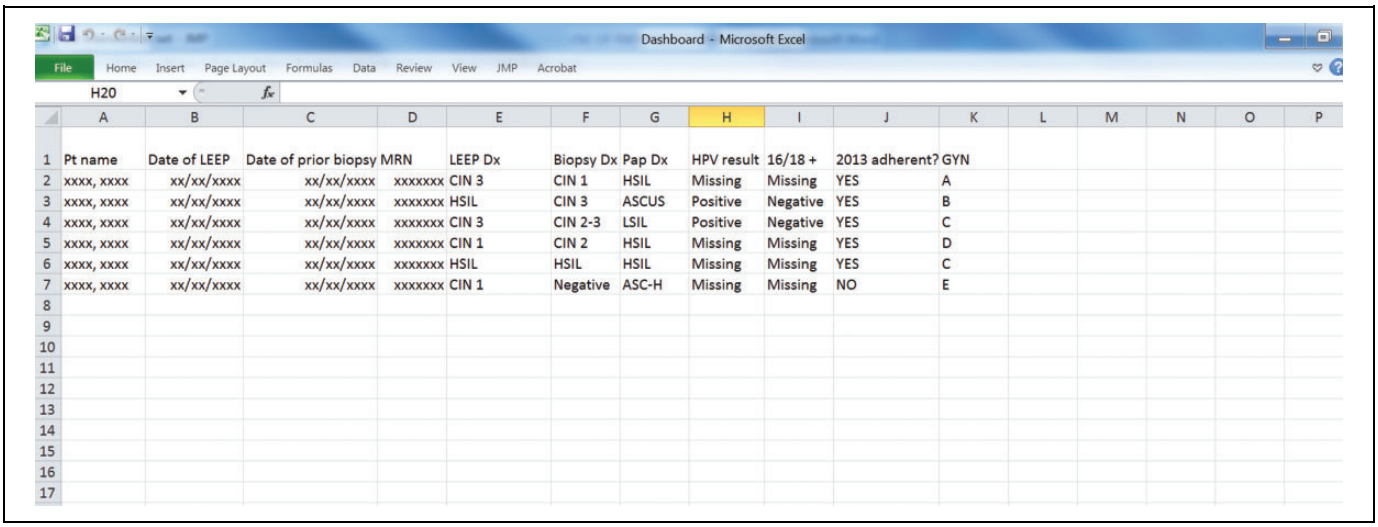
First, we met with the entire faculty of Pathology on September 25, 2013 and then with Obstetrics/Gynecology (OB/GYN) on September 26, 2013. Both groups received the same presentations—first, the 2013 guidelines were reviewed, and the results of the study to that date (Table 2) were presented, and then the 2006 guidelines and data on LEEPs were reviewed. We deliberately left ample time for questions—for Pathology 45 minutes and >1 hour for OB/GYN. In the Pathology meeting, only the faculty members were present; in contrast, both faculty and residents participated in the OB/GYN intervention. Since the Pathology issue was equivocal diagnoses, the Pathology faculty agreed for a second review for any biopsy with a diagnosis that might be interpreted as a high-grade dysplasia (such as CIN 1-2).

As we anticipated, OB/GYN clinicians expressed concerns about compromised patient safety attendant to more strictly following guidelines and framed this concern in terms of "missing a case of cervical cancer or high-grade dysplasia," particularly in the context of their practice in a tertiary care referral center with high-acuity and complex cases. This patient-oriented concern was addressed with specific performance data as noted in Table 2. We acknowledged that in any particular patient, there might be good reasons to recommend a LEEP that was not entirely guideline adherent; however, we were also able to illustrate that the outcome results supported national standards that it is safe to wait. The data also showed that the chances of missing HSIL in the group of patients were small. The percentage of LEEPs without HSIL was of concern to the gynecologists, and they agreed that they should adopt more stringent guidelines.

Our data and concerns were endorsed by our gynecology authors. We also discussed that we would be reviewing individual dashboard data on a quarterly basis using a spreadsheet (Figure 1). The dashboard is generated by pathology. A pathologist reviews relevant data and decides, based solely upon pathology data, whether they consider the LEEP to be guideline adherent. The list is sent to the gynecology clinical leadership who reviews additional clinical and colposcopy findings and follows up when necessary with individual clinicians. The follow-up is ongoing; however, a more broad-based tissue committee was instituted early in 2016, and possible cases that are nonguideline adherent are now referred to the formal tissue committee and reviewed in coordination with Gynecology.

Results

There were 421 total patients with 331 LEEP procedures from the 33-month preintervention period and 90 LEEP procedures



Dashboard - Microsoft Excel

File Home Insert Page Layout Formulas Data Review View JMP Acrobat

H20

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	Pt name	Date of LEEP	Date of prior biopsy	MRN	LEEP Dx	Biopsy Dx	Pap Dx	HPV result	16/18 +	2013 adherent?	GYN					
2	xxxx, xxxx	xx/xx/xxxx	xx/xx/xxxx	xxxxxxx	CIN 3	CIN 1	HSIL	Missing	Missing	YES	A					
3	xxxx, xxxx	xx/xx/xxxx	xx/xx/xxxx	xxxxxxx	HSIL	CIN 3	ASCUS	Positive	Negative	YES	B					
4	xxxx, xxxx	xx/xx/xxxx	xx/xx/xxxx	xxxxxxx	CIN 3	CIN 2-3	LSIL	Positive	Negative	YES	C					
5	xxxx, xxxx	xx/xx/xxxx	xx/xx/xxxx	xxxxxxx	CIN 1	CIN 2	HSIL	Missing	Missing	YES	D					
6	xxxx, xxxx	xx/xx/xxxx	xx/xx/xxxx	xxxxxxx	HSIL	HSIL	HSIL	Missing	Missing	YES	C					
7	xxxx, xxxx	xx/xx/xxxx	xx/xx/xxxx	xxxxxxx	CIN 1	Negative	ASC-H	Missing	Missing	NO	E					
8																
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Figure 1. Example of quarterly dashboard sent to the Department of Obstetrics/Gynecology (OB/GYN; all identifiers were removed).

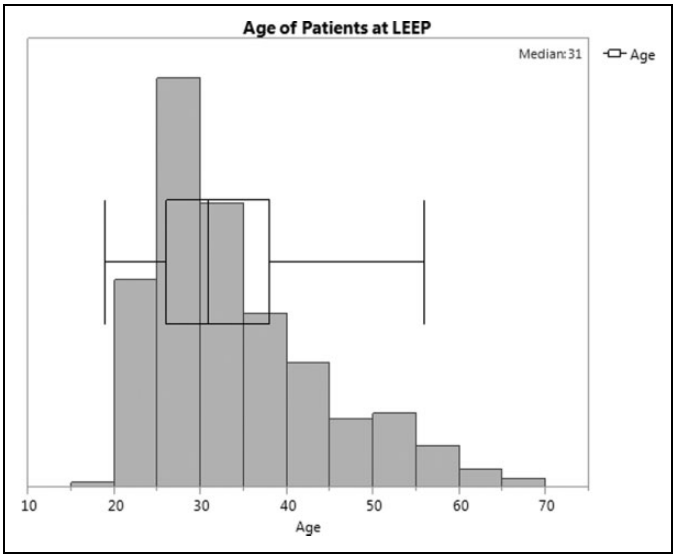

Figure 2. Histogram with box plot of patient age for all patients in our study. The median age at loop electrosurgical excision procedure (LEEP) was 31.1 years with 75% of patients <38 years.

subsequently. The age range of our patients was 19 to 67 years (overall mean: 33.3 years, median: 31 years) and is shown in a histogram (Figure 2) with superimposed box plot. Mean age of our patients in the preintervention group was 33.1 years (median: 33, range: 19-65), whereas the postintervention group was slightly, but not significantly, older with a mean of 34.4 years (median: 31, range: 22-67). Of importance to the clinical audience, 75% of our patients were aged $\leq$38 years, highly relevant for adverse pregnancy outcomes. Among our initial group of 81 preintervention patients who did not have guideline adherent indications for LEEP, 2 patients were categorized as "LEEP of cervix complicating pregnancy," and a third patient had preterm labor, albeit with multiple risk factor comorbidities.

Table 2 compares preintervention indications for LEEP with the presence of detected HSIL. The strongest indication for LEEP was a previous biopsy with HSIL; the majority (64%) of such cases demonstrated CIN 2 or above on the LEEP specimen. In contrast, when HSIL was noted on the Pap test only (ie, biopsy was discordant and did not have HSIL) or the indication was persistent LSIL, a much smaller percentage of cases showed HSIL on the LEEP specimen. In addition, no case of HSIL was found following less conservative indications.

Table 3 summarizes the results of our intervention. The number of LEEPs fell dramatically from an average of 10 per month in the preintervention period to an average of 3.4 per month in the postintervention period. The percentage of cases adherent to guidelines rose from an overall rate of 76% to 96% of cases, respectively. These results were highly statistically significant. When we further analyzed the cases per year, it appears that the number of LEEPs was already falling; however, there was no improvement trend for the percentage of cases that were guideline adherent during the preintervention period. We cannot explain why the number of LEEPs fell prior to the intervention. Over time, the dramatic initial decrease in the number of LEEPs has reversed slightly, possibly because it takes time to accumulate cases that are guideline adherent by persistence of LSIL findings. Importantly, the improved percentage of guideline adherent cases has remained relatively stable. Our purpose was to decrease the number of nonguideline adherent LEEPs, and every such case receives scrutiny from our Gynecology colleagues. We understand that there may be rare reasons for performing LEEPs that are nonguideline adherent (such as a patient who has a long history of noncompliance with screening guidelines). However, if the number of nonguideline adherent LEEPs continues to rise, the authors plan to discuss this with the specific clinicians responsible.

For those cases with the guideline adherent indication of persistent LSIL, the duration prior to LEEP doubled from a median of 25.5 months (mean: 28.6 months) preintervention

Table 3. Number and Percentage of Guideline Adherent and Nonguideline Adherent LEEPs and Number of LEEPs Per Year.*,†

Year	Guideline Adherent LEEPs (%)	Nonguideline Adherent LEEPs or Indeterminate Pathology (%)	Total	Average LEEPs Per Month
2011	126 (82)	29 (17)	155	12.9
2012	73 (68)	35 (32)	108	9
2013: preintervention (9 months)	51 (75)	17 (25)	68	7.5
Total preintervention (33 months)	250 (76)	81 (24)	331	10.0
2013: postintervention (3 months)	8 (100)	0 (0)	8	2.7
2014	38 (97)	1 (3)	39	3.3
2015	41 (95)	2 (5)	43	3.6
Total postintervention (27 months)	87 (96)	3 (4)	90	3.4

Abbreviation: LEEPs, loop electrosurgical excision procedures.
*Data from both the preintervention and postintervention periods are compared.
†$P < .0001$; χ^2 test.

Table 4. The Percentage of LEEPs Adherent to Guidelines Pre- and Postintervention by Clinician.

	% of Guideline Adherent LEEPs	
Clinician	Preintervention, %	Postintervention, %
A	100	100
B	64	96
C	88	100
D	83	100
E	83	90
F	80	100
G	100	100
H	92	92
I	67	100

Abbreviation: LEEPs, loop electrosurgical excision procedures.

Table 5. Outcomes for LEEPs Preintervention and Postintervention.*

Count (%)	HSIL Present	HSIL Absent	Total
Preintervention, January 2011 to September 2013	146 (44%)	185 (56%)	331
Postintervention, October 2013 to December 2016	54 (60%)	36 (40%)	90
Total	200	221	421

Abbreviations: HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure.
*$P < .0087$, 2-tailed Fisher Exact test.

to 54 months (mean: 55.4 months) postintervention which was highly statistically significant ($P < .0073$; Wilcoxon Kruskal-Wallis test). In addition, there were no cases postintervention in which the indication for the LEEP was risk factors, patient preferences, atypical endometrial or endocervical cells on Pap test, ECC with LSIL, or inconclusive biopsies. There were only 3 nonguideline adherent cases in the post-intervention period—inappropriate duration (LSIL of less than 24 months duration), ASC-H Pap test without a confirmatory biopsy, and colposcopy findings only without confirmatory Pap test or biopsy.

The individual percentage of guideline-adherent LEEPs by gynecologist for both preintervention and postintervention are shown in Table 4. This table only includes those clinicians for whom data were available preintervention and postintervention and shows a dramatic drop for most individuals. New faculty hired postintervention were all 100% compliant. Although there were statistically significant differences in practice patterns before the intervention ($P < .0001$; χ^2 test), postintervention, these differences were not significant. Results of histology on our LEEP cases preintervention and postintervention are compared in Table 5. During the preintervention period, HSIL was found on only 44% of our cases, whereas after the intervention, HSIL was found in 60% of cases (a 16% rate improvement). These results were highly statistically significant ($P < .0087$; 2-tailed Fisher exact test).

Discussion

The educational and peer-leader dashboard intervention prompted a swift and persistent change in behavior in gynecologists, women's health nurse–practitioners, and pathologists. The number of LEEPs fell from approximately 10 per month to 3 to 4 per month with corresponding increase in adherence to guidelines. Furthermore, the percentage of cases with the desired outcome rose from 44% to 60%. Our intervention definitely improved outcomes. Although we cannot prove that we decreased complications and future adverse pregnancy outcomes, this would appear to be likely. The national birth registry of Finland provides an evidence basis for the number needed to harm calculation of 1 additional premature birth for every 38.5 preceding LEEP procedures.[11] Based on our data preintervention and postintervention, we model that intervention spared unneeded LEEPs in approximately 92 patients of whom about 75% (71) would theoretically be of reproductive age.

We recognized that some of these patients will eventually require LEEP, especially among those with LSIL duration of less than 24 months at the time of the LEEP. In fact, only a quarter of the patients with LSIL duration >24 months had

subsequent HSIL on LEEP; therefore, continued close follow-up of patients with LSIL who have not yet reached 24 months should detect these cases. The duration of follow-up for this indication also increased in the postintervention period. It may be useful for larger-scale studies to investigate whether longer periods of follow-up can further improve safety. This question is consistent with the general movement in the field of cervical cancer prevention. The 2013 guidelines for the prevention of cervical cancer are more conservative in the recommendations for screening and management than the 2006 guidelines.[18-20] Our findings appear to support this more conservative approach.

The critical parts of the intervention were the collaborative, interdisciplinary, and interprofessional review and presentation of the preintervention data and the continuing collaborative postintervention review. Clinicians need compelling reasons to change behaviors that consistently favor additional intervention. The human bias that accepts current practice as justified and reasonable likely means that data will often be important when the goal is to address deviations from standard practice.[21] We anticipated that clinical staff, including physicians and nurse practitioners, would question the safety of abandoning nonguideline practices that favored early intervention. Our data revealed clearly that patients received no additional diagnostic benefit from more aggressive nonguideline interventions and strongly suggested that there were instead probably risks that had not been considered by participating clinicians, including unneeded procedures, premature procedures that may or may not have been needed at a later time, and possibly, increased risk of premature delivery in the patients who were still in their reproductive years.

Even when there are strong guidelines, our experience suggests an important role for local data when there are questions about current practice.[22,23] Based on our experience, change requires addressing clinician concerns with reference to data.[23] Clinicians justifiably seek to avoid missing a detectable case of advanced cervical cancer. The mistaken idea that more is always better is an accepted cause of overtreatment.[24,25] However, this assumption in the treatment of HSIL was not supported by our data. Instead, our data suggest no additional value and probable risk.

The specific case of CIN 1-2 revealed a nomenclature etiology for nonguideline behavior that is worth discussing because it suggests a need for pathologists to change behavior. Most pathologists in our institution considered CIN 1-2 to be closer to "LSIL" than "HSIL" and believed there is a communication benefit to expressing the potential presence of an intermediate finding. In contrast, gynecologists felt they must react to a CIN 1-2 in the report no differently than to a CIN 2 or high-grade lesion. This is understandable in terms of the goal of screening, the preventability of this disease, and the differential medical-legal consequences of overtreatment compared to undertreatment. Thus, pathologists need to understand that the terminology used in a report has implications for treatment. Following the intervention, we required a second pathologic review for CIN 1-2 diagnoses in our institution, and to date, we have eliminated the equivocal biopsy result as an indication for LEEP in our patients.

Our data have some important limitations. This study is limited to a single institution and its outreach network; however, a large-scale review of treatment of carcinoma in situ (CIN 3, HSIL) at the Michigan Cancer Surveillance Program noted wide variation in the treatment of HSIL with more aggressive treatment, such as LEEP and cone, favored over less aggressive treatment.[2] In addition, we deliberately did not consider cost implications (either direct costs of the procedure or indirect costs of adverse pregnancy outcomes) as part of the study because the goal was improved care and not cost savings. However, we definitively decreased the number of procedures and probably decreased risk for adverse pregnancy outcomes, so theoretically we should have also decreased costs, thus achieving Berwick's Triple Aim.[26]

Summary and Conclusion

Significant data reside on pathology AP LIS systems that can be used to improve high-value care. In 1 example, we used pathology data to change practice patterns for both pathologists and gynecologists in order to decrease unnecessary LEEPs for treatment of cervical neoplasia. Pathologists reduced equivocal HSIL cases by requiring a second review while gynecologists improved adherence to guidelines. This process improved patient outcomes and theoretically reduced complications and costs. We advocate that pathologists use such data in interdisciplinary and interprofessional interventions to improve value.

Authors' Note

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Sources and Manufacturers

[a]Copath; Cerner Corporation, Waltham, Massachusetts.
[b]Copyright 2012 SAS Institute Inc, Cary, North Carolina.

Declaration of Conflicting Interests

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