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Editorial

The role of human papillomavirus testing after treatment for high-grade cervical dysplasia

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▸ See the article "A human papillomavirus (HPV)-16 or HPV-18 genotype is a reliable predictor of residual disease in a subsequent hysterectomy following a loop electrosurgical excision procedure for cervical intraepithelial neoplasia 3" in volume 27, e2.
▸ See the article "Posttreatment human papillomavirus testing for residual or recurrent high-grade cervical intraepithelial neoplasia: a pooled analysis" in volume 27, e3.

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The introduction of human papillomavirus (HPV) testing into cervical cancer screening programs has significantly improved the detection of premalignant lesions and continues to improve the detection and prevention of invasive cervical cancer. The results of 4 large trials successfully demonstrated higher detection rates of cervical intraepithelial neoplasia (CIN) 3 with HPV-based screening compared to cervical cytology [1-5], and a recent meta-analysis of long term follow up in those trials demonstrated 60% to 70% greater protection against invasive cancer compared to cytology screening [6]. While the role of HPV screening is well established with well-conducted randomized controlled trials, there are fewer consensuses regarding the utility of HPV testing after treatment for premalignant cervical lesions. Typically, CIN 2/3 lesions are treated with excisional or ablative procedures, and post-treatment these women are then entered into more intensive surveillance protocols. Post-treatment surveillance targets an important population, as women treated for CIN 2/3 have nearly a 300% greater risk of developing invasive cancer over the subsequent 20 years [7]. Two articles in this issue provide significant data to support the role of HPV testing after treatment for high-grade dysplasia. In "A human papillomavirus (HPV)-16 or HPV-18 genotype is a reliable predictor of residual disease in a subsequent hysterectomy following a loop electrosurgical excision procedure for cervical intraepithelial neoplasia 3", Kang et al. [8] evaluate 189 women who underwent a hysterectomy within 6 months of a loop electrosurgical excision procedure (LEEP) for CIN 3. They found residual disease in almost half of the women as well as early stage cancer in six patients. As expected, positive margins in the LEEP specimen were predictive of residual disease, but HPV viral load and HPV-16 or HPV-18 positivity were also predictive ($p<0.01$ and $p<0.001$, respectively). Based on their receiver operating characteristic curve for HPV viral load and predicting residual disease, a viral load of 220 relative light unit (RLU) could predict residual disease with 'a sensitivity of 65.2%, a specificity of 70.1%, and an accuracy of 67.7%.' In a multivariate analysis, the independent predictors of residual disease after LEEP were cone margin positivity, HPV viral load ≥220 RLU, positive endocervical cytology, and HPV-16 or HPV-18 positivity. Their data, including the use of hysterectomy specimen pathology provides short-term outcomes regarding

JOURNAL OF GYNECOLOGIC ONCOLOGY

residual or more advanced disease after LEEP for CIN 3 and demonstrates the clinical utility of HPV testing in this setting.

"Posttreatment human papillomavirus testing for residual or recurrent high-grade cervical intraepithelial neoplasia: a pooled analysis" by Onuki et al. [9] utilizes different methodology to lend the same support to posttreatment screening. A systematic review of 33 articles published between 1996 and 2013 found 5,319 cases; each case had been treated for CIN 2/3+, was tested for HPV within 12 months, and documented the presence or absence of CIN 2/3+ in follow-up. The rate of CIN 2/3+, either recurrent or residual, was 8.4%. The sensitivity of HPV testing was significantly better than ASCUS+ cytology threshold (0.92 vs. 0.76). More importantly, the negative predictive value of HPV testing alone was 0.99 with a 95% CI of 0.99 to 1.00. In addition, the presence of disease at the excisional margin did not significantly affect the sensitivity or specificity of carcinogenic HPV testing. The authors evaluated both cytology and HPV testing alone and in combination, for risk stratification of residual/recurrent CIN 2/3+ after treatment for CIN 2/3+. They found the highest risk in HPV+/cytology+ women, followed by HPV+/cytology–, and finally HPV–/cytology+.

Current guidelines in Japan and the UK recommend cytology alone during posttreatment follow-up for high-grade dysplasia [10,11]. United States guidelines recommend HPV testing for surveillance since 2012, albeit without level 1 evidence. However, the known pathogenesis and carcinogenic properties of HPV strongly support the use of HPV testing in this setting. The data presented in this issue by Kang et al. [8] and Onuki et al. [9] provide strong clinical evidence to support the use of HPV testing to evaluate risk for recurrent or residual high-grade dysplasia in patients previously treated for high-grade dysplasia. Their work continues to build on the library of data that demonstrate the utility and value of HPV testing in detecting cervical dysplasia and preventing cervical cancer.

REFERENCES

1. Bulkmans NW, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJ, Bulk S, et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. Lancet 2007;370:1764-72.
PUBMED | CROSSREF
2. Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol 2009;10:672-82.
PUBMED | CROSSREF
3. Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med 2007;357:1589-97.
PUBMED | CROSSREF
4. Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NW, Heideman DA, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol 2012;13:78-88.
PUBMED | CROSSREF
5. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol 2010;11:249-57.
PUBMED | CROSSREF
6. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014;383:524-32.
PUBMED | CROSSREF

http://dx.doi.org/10.3802/jgo.2016.27.e9

7. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. Int J Cancer 2006;118:2048-55.
PUBMED | CROSSREF

8. Kang WD, Ju UC, Kim SM. A human papillomavirus (HPV)-16 or HPV-18 genotype is a reliable predictor of residual disease in a subsequent hysterectomy following a loop electrosurgical excision procedure for cervical intraepithelial neoplasia 3. J Gynecol Oncol 2016;27:e2.
CROSSREF

9. Onuki M, Matsumoto K, Sakurai M, Ochi H, Minaguchi T, Satoh T, et al. Posttreatment human papillomavirus testing for residual or recurrent high-grade cervical intraepithelial neoplasia: a pooled analysis. J Gynecol Oncol 2016;27:e3.
CROSSREF

10. Takeda T, Wong TF, Adachi T, Ito K, Uehara S, Kanaoka Y, et al. Guidelines for office gynecology in Japan: Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists 2011 edition. J Obstet Gynaecol Res 2012;38:615-31.
PUBMED | CROSSREF

11. Luesley D, Leeson S. Colposcopy and Programme Management: Guidelines for the NHS Cervical Screening Programme [Internet]. 2nd ed. Sheffield: NHS Cancer Screening Programmes; c2010 [cited 2015 Dec 2]. Available from: http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.html

http://dx.doi.org/10.3802/jgo.2016.27.e9