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Mini commentary on BJOG-19-0729.R1: Long-term predictors of residual or recurrent cervical intraepithelial neoplasia 2-3 after treatment with a large loop excision of the transformation zone: a retrospective study

Longterm predicition of failure after treatment of cervical precancer

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It is common knowledge that presence of neoplastic cells at the margin of the tissue specimen excised because of a cervical intra-epithelial neoplasia of grade 2 or worse (CIN2+) is associated with treatment failure (Ghaem-Maghani, Lancet Oncol 2007; 11:985-93; Arbyn, Lancet Oncol 2017, 18:1665-79). However, presence of high risk Human Papilloma Virus (HPV) post-treatment is a more accurate predictor (substantially higher sensitivity, similar specificity) of residual or recurrent CIN2+ (Arbyn, Gynecol Oncol 2005, 99: S7-S11). These findings were challenged by Fernandez-Montoli et al (published in this BJOG issue) who followed 242 CIN2+ patients treated with large loop excision of the transformation zone (LLETZ) at the Bellvitgein Hospital (Barcelona, Spain), over a period up to 20 years. Seventy five (31%) of treated women had involved margins, among whom 56% (42/75) at the endocervical margin, whereas for 13%

(31/242) margin involvement was uncertain. The rate of treatment failure was overall 5.4% (13/242). This rate varied from 1.5% (2/134) if clear margins, to 5.3% (4/75) if any involved margin, 9.4% (3/32) if positive endo-cervical margin and 19.4% (6/31) if margin status was uncertain. The relative risk of treatment failure associated with any or endo-cervical involved margins, was 3.6 (95% CI 0.67-19.1) and 6.2 (95% 1.1-36.0), respectively. Fernandez-Montoli et al reported also post-treatment cytology and HPV data. The most sensitive predictor of therapeutic failure was post-treatment HPV testing (89%) with HC2 (Qiagen), followed by cytology at cut-off ASC-US+ (54%) and margin status (33%). Cytology was the most specific predictor (84%) followed by HC2 (80%) and margin status (69%). When uncertain margins were considered as positive, the sensitivity increased to 83%, whereas the specificity decreased to 58%. The combination of margin and HPV post-treatment status (for those cases where data for both were available) increased the sensitivity of the prediction of treatment failure to 100% (9/9) but decreased the specificity to 42%.

The Barcelona study perfectly fits to the inclusion criteria of a recent meta-analysis that compared the accuracy of margin involvement and HPV assessment as tests of cure (Arbyn, Lancet Oncol 2017, 18:1665-79). Although the proportion of positive margins was higher in Fernandez-Montoli (56% vs 33% in the meta-analysis), the rates of residual/recurrent CIN2+ were similar (5.4% vs 6.6% [95% CI 4.9-8.4%] on average for LLETZ treatments). The accuracy of the margin status in the Barcelona study was lower than in the meta-analysis: sensitivity of 33% vs 56% (95% CI 46-67%) and a specificity of 69% vs 84% (CI 80-88%) However, HPV testing and the combination of HPV and margin status showed similar accuracy as in the meta-analysis.

Particular to the Barcelona study was the great proportion of uncertain margins and the similar predictive value of uncertain and positive endo-cervical margins.

To conclude, the Barcelona study corroborates prior observations: positive margins are significantly associated with treatment failure but the accuracy of margin status to predict therapeutic failure is poor. On the other hand, a HPV test three to nine months after the excision shows good sensitivity and reasonable specificity.

Disclosure of interests

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