Lucena et al have studied the intraobserver and interobserver reproducibility of cervical cytopathology according to previous knowledge of whether patients received radiotherapy (RT) treatment or not. They analyzed a sample of 95 cervix cytological slides; 24 with cytological abnormalities (CA) and presence of RT; 21 without CA and presence of RT; 25 without CA and without previous RT; 25 with CA and without previous RT. The original CP evaluation of the cytological exam prior to the study was used as gold standard. Post radiotherapy effects were identified in 44.4% of cases that undergone previous pelvic RT. The agreement for RT status was 66.3% (unweighted K=0.31, 95%CI: 0.13; 0.49, moderate agreement). The intraobserver agreement, regarding the cytological diagnoses, regardless of radiotherapy status, was 80.3% (weighted K=0.52, 95%CI: 0.34; 0.68). In no RT group, the intraobserver agreement was 70% (weighted K= 0.47, 95%CI: 0.27;0.65) and in patients that received RT, the intraobserver agreement was 84.1% (unweighted K=0.37, 95%CI: 0.01;0.74). The interobserver agreement between cytopathology result (abnormal or normal) in the group with RT, considering normal and abnormal CP diagnosis was 14.0% and 12.5%, respectively. In conclusion, the study showed that RT has an important impact in CP diagnosis because the agreement, also in interobserver and intraobserver analysis, had high discrepancy in patients that received RT. Also, demonstrated that it is difficult to recognize the presence of RT in cytological slides when this information is not provided.

Comments

Page 3, line 65-66, "The Pap test is a useful tool for the follow-up and evaluation of patients treated with RT"

This is not documented in the reference 3 and 4. Actually, cytology has limited sensitivity for detection of residual cervical cancer after radiotherapy (de Azevedo 2012, Wright 2003). The significance of dysplasia in postradiation smears is not entirely clear, and in certain instances it is difficult to distinguish severely dysplastic cells from either repair cells or malignant cells (McLennan 1975). Colposcopy alone and in combination with HPV positivity showed the highest sensitivity for the detection of recurrent diseases, whereas other methods had limited reliability (Slama 2017, Okuma 2016, Intharaburan 2012). HPV DNA clearance was associated with a better patient outcome because the majority of the HPV cleared women showed a complete response (Badaracco 2010). Persistent HPV DNA within 24 months after treatment indicates a high risk of local recurrence (Song 2011). Follow-up of patients treated for cervical cancer based on routine Pap smears does not permit earlier
detection of recurrence and does not increase survival (Morice 2004).

Page 4, line 75-76, "The literature is scarce regarding information on intraobserver performance and reproducibility in cytological exams after radiotherapy"

It should be commented that cytology has limited accuracy also in women not treated by radiotherapy (Sorbye 2017, Wright 2014).

Page 5, line 108-110, "In the first CP re-evaluation, 95 slides were evaluated with no information regarding the result of the original CP evaluation of the cytological exam (gold standard report prior to the study)"

It is unusual to use cytology as a gold standard. In most studies histologic confirmed cervical intraepithelial neoplasia (CIN2+) served as gold standards for diagnostic values analysis. In women with cervical cancer treated by radiotherapy, the gold standard of follow-up should be recurrence of cancer.

Page 6, line 146-147, "Patients with abnormal cytology (49 individuals) were divided according to their age (below and above 50 years old)"

How many of women with abnormal cytology had histologically confirmed CIN2+ or cervical cancer?

Page 8, line 183-184, "The results suggest that radiotherapy has a strong influence in CP diagnosis also in normal or abnormal CP results"

In Norway, it is not recommended to use cytology in follow-up of women treated with radiotherapy. Even though some studies recommend HPV-testing in follow-up after radiotherapy, this is not included in Norwegian guidelines because 50% of the women will have a positive HPV-test 3-6 months after treatment.

Page 9, line 214-218, "In evaluations by Tsilalis et al (10), regarding telecytological diagnosis of cervical smears not related to RT, the intraobserver variability was near perfect among the five cytopathologists and presented a gradual increase during the diagnostic evaluations with values for kappa ranging from 0.76 to 1.00"

Add "In a Norwegian study, the number of Pap smears evaluated as abnormal (ASC-US+) by the four pathologists varied from 61 to 85. The number of high-grade cytology (ASC-H+) varied from 26 to 50. There was moderate agreement (weighted kappa 0.45-0.58) between the observers (Sorbye 2017). In the ATHENA study, there were considerable differences among the laboratories both in overall cytological abnormal rates, ranging from 3.8 to 9.9%, and in sensitivity of cytology to detect CIN grade 2 or worse (CIN2+), from 42.0 to 73.0% (Wright 2014)."

Page 11, line 254-256, "Adequate knowledge about these abnormalities is imperative in order to avoid false positive diagnoses, since most of them are not associated with new intraepithelial/invasive lesions or tumor recurrence"
Add "Cytology and HPV cotesting increases the sensitivity and may reduce false positive diagnoses (Wright 2016)".

References


https://www.ncbi.nlm.nih.gov/pubmed/22585730


Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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