



## Commentary

# Cervical cancer genomics: an initial step towards personalized approach to therapy



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Cervical cancer, well known to be associated human papilloma virus (HPV) infection and considered as a preventable cancer by HPV vaccination and organized screening for pre-cancerous lesions, continues to be an important cause of cancer related mortality especially in the developing world [1]. Majority of patients present with locally advanced disease when surgery is not feasible and concurrent chemoradiation therapy which consists of 45–50 Gy external-beam radiotherapy of the primary tumour with concomitant platinum-containing chemotherapy, followed by intracavitary brachytherapy is the standard of care [2]. The predominant radiation based treatment of cervical cancer makes extrapolation of *in vitro* laboratory studies using cell lines and animal models to the bedside very challenging unlike cancers which are predominantly treated by chemotherapy. Therefore, studies using patient tissue samples are particularly relevant.

Cervical cancer has been impacted by the 'omics' revolution with many studies on gene expression profile and proteomic analysis reviewed by Lin et al. [3] These 'big data' technologies have been used to address the differences between cervical cancer vs normal cervix, Human Papilloma virus genomic integration and carcinogenesis and biomarkers of prognosis and prediction of response to radiation therapy [2]. The Cancer Genome Atlas (TCGA) and one previous publication addressed the genomic characterization of cervical cancer [4,5]. Notably, the specimen used in these studies were sourced from cervical cancers subjected to surgery, indicating that these represented early stage cervical cancers. In this issue of E-BioMedicine, Scholl et al. in their work titled "Clinical and genetic landscape of treatment naive cervical cancer: alterations in PIK3CA and in epigenetic modulators associated with sub-optimal outcome' have evaluated the genetic landscape of cervical cancer by whole exome sequencing and next generation sequencing using patient tissue samples sourced from RAIDs (Rational Molecular Assessment and Innovative Drug Selection) network representing seven EU countries and 18 centers [6]. The merit of this study is in the fact that the samples of cervical cancer reflect the usual spread of cases across the FIGO (International Federation of Gynecology and Obstetrics) stages. Majority of patients included in the cohort underwent chemoradiation and their progression-free survival data using both the old and current versions of the FIGO classification was demonstrated [6].

Surgery in early stage cervical cancer is generally curative whereas the overall response rate in patients treated with chemoradiation is 60–70% with an overall mortality of 50–55% as per Globocan estimates [1]. It is in this set of women that alternative therapeutic strategies may be considered to salvage them. However, genomics is but an initial step in this direction as understanding the complex mechanisms of chemoradiation resistance and sensitivity is important in order to hit where it matters.

The most common gene mutations were in the PIK3CA gene with reported mutation frequency in the 3 major studies being 14% [5], 26% [4] and 40% [6], providing an opportunity for intervention. Arjumand et al. working on cervical cancer derived cell lines have provided crucial evidence that PIK3CA-E545K mutation confers resistance to cisplatin and radiation [7]. The mechanisms of PIK3CA-Akt pathway activation and its role in radiation resistance in Non-small cell lung cancer is reviewed by Schuurbiers et al. and parallels may be drawn with cervical cancer [8]. Clearly more studies on direct or indirect targeted inhibition of this pathway to overcome radiation resistance may improve the overall mortality rates in advanced cervical cancer.

Another interesting aspect of the study by Scholl et al. is the application of Reverse Phase Protein array analysis which analyses signalling pathway activation [6]. Tumours could be broadly classified into 3 clusters based on their signalling pathway activation. Cluster1 tumours showed EMT biomarkers were associated with upregulated PD-L1 and B7-H4, both candidates for immune checkpoint inhibitor treatments. On the other hand, significant number of tumours showed epigenetic alterations due to loss of function mutations in the KMT2A-D genes and may be targeted by histone deacetylase inhibitors. Thus, this study is an initial step towards a molecular classification of cervical cancer, but requires further validation by immunohistochemistry on tissue microarrays of cervical cancer samples. Indeed, it would be interesting if the most relevant proteins predicting for chemoradiation resistance could be identified and suitable antibody cocktails are developed for use in routine pathology laboratories heralding the era of predictive diagnostics with complementary new therapeutic approaches involving epigenetic modulators and immunotherapeutics.

Tumours evolve acquiring mutations that are beneficial for their survival and future studies should be designed to address intratumoural genetic heterogeneity. For instance, cancer stem cells in cervical cancer are implicated in radiation resistance [9,10], but how they differ from the rest of the tumour cells at the genetic level needs exploration.

DOI of original article: <https://doi.org/10.1016/j.ebiom.2019.03.069>.

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<https://doi.org/10.1016/j.ebiom.2019.04.025>

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It is clearly emerging that cervical cancer is not a single entity from the molecular and genetic viewpoint and that tumours with different genetic alterations behave and respond differently to standard of care. Novel alterations in DNA repair and epigenetics open new venues in treatment strategies. Future clinical trials will have to necessarily take this into account and besides conventional histopathology, molecular typing of tumours would be more relevant. Lastly, identification of key signalling pathway alterations and their targeted inhibition by biological or immunological or even cellular therapies are the future of cervical cancer.

### Disclosures

None.

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