Editorial

Future Perspectives for Uterine Cervical Cancer Treatment based on Integrative Genomic and Molecular Characterizations

Perspectivas futuras para o tratamento de câncer de colo de útero baseado em caracterizações genômica e molecular integrativa

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Cervical cancer is the most frequent gynecologic malignancy in developing countries nowadays.[1] Surgery is an effective treatment for the early stages of the disease. However, most patients are still diagnosed with inoperable locally advanced cervical cancer (LACC).[2] In Brazil, the scenario is not different, and, according to Fundação Oncocentro de São Paulo (FOSP), from 2000 to 2016, 34,784 cervical cancers were recorded in their database.[3] A total of 15,270 were in situ carcinomas and, among all invasive tumors, 10,386 patients were diagnosed with stage II, III or IV (53%), and the rate of incidence of LACC has not changed over the past 15 years (►**Fig. 1**). The standard approach for advanced tumors is a combination of chemo and radiation therapy. Chemoradiation is a curative treatment for locally advanced cervical cancer. Nevertheless, as many as 30–65% of patients experience residual disease after treatment, and there is not a current effective therapy for resistant diseases.[4–6]

The use of high-throughput technologies has enabled the identification of the molecular classification for multiple malignant tumors.[7] A recent study conducted by the Cancer Genome Atlas Research Network, entitled "Integrated genomic

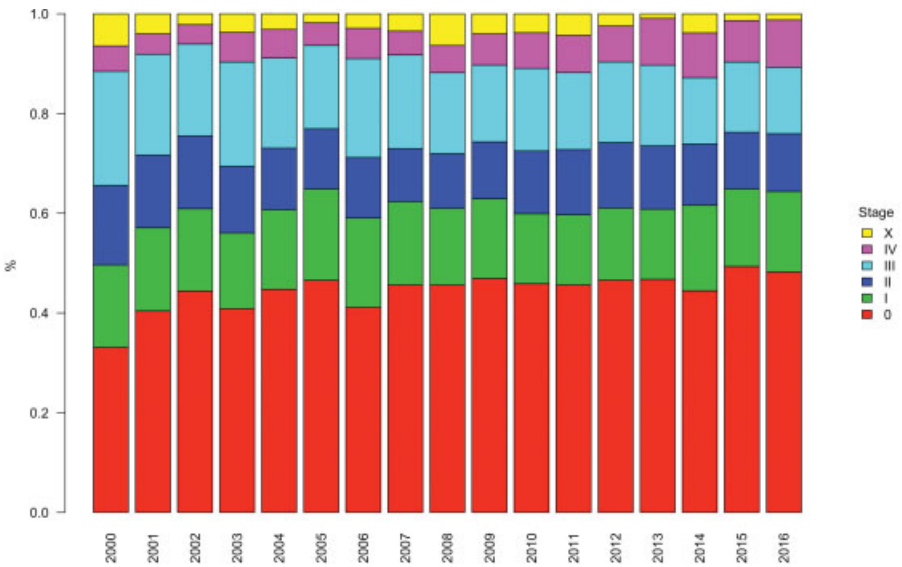

Fig. 1 Cervical cancer report from FOSP. The graph shows the stage distribution over the past 15 years in the state of São Paulo, Brazil (Fundação Oncocentro de São Paulo, 2016).[3]

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and molecular characterization of cervical cancer", reported a comprehensive mutational and molecular profile for cervical cancer.[8] We demonstrated that some genomic and molecular analyses are able to identify subgroups of patients who may benefit from alternative therapies.

The integrative clustering segregates tumors into adenocarcinomas and most squamous cell carcinomas. It is interesting to note some squamous tumors display the molecular and genomic features of adenocarcinomas. The tumors in an adenocarcinoma cluster are mostly HPV negative, and some of them are considered endometrial-like tumors. According to the protein expression profile, adenocarcinomas have high hormone scores, and the pathway representation and analysis by direct reference on graphical models (PARADIGM) demonstrated enrichment in the ER/FOXA1/FOXA2 pathway. This observation suggests that ovarian preservation in cases of cervical adenocarcinoma should be taken with caution, and anti-estradiol endocrine therapy may be effective in advanced and recurrent diseases. Additionally, those tumors frequently exhibit *BCAR4* amplification and fusion. *BCAR4* is a metastasis-promoting long non-coding ribonucleic acid (lncRNA), and its expression is associated with cell proliferation in estrogen-resistant breast cancer by activating the human epidermal growth factor receptor 2/3 (HER2/3) pathway. Lapatinib, a tyrosine kinase inhibitor, is able to revert the *BCRA4*-driven tumor growth in vitro,[9] and it is an alternative for prospective clinical trials in cases of advanced and recurrent *BCAR4* positive cervical cancer.

There is a group of tumors (21%), most of them with squamous histology, with focal amplification at 9p24.1 involving *PDL1* and *PDCD1LG2* (PDL2) genes. Those genes encode important proteins involved on immune checkpoints. Monoclonal antibodies blocking the programmed death 1 (PD-1) receptor or its ligand, the programmed death-ligand 1 (PD-L1), relieve the suppression of antitumor immune responses in a variety of cancers. Programmed death-ligand 1 check point blockage is an effective therapy for *PDL1* positive metastatic melanomas. Recent studies have demonstrated up to 50% positive *PDL1* tumor expression in squamous cell carcinomas of the uterine cervix.[10] The use of immune checkpoint blockage should be investigated in recurrent or resistant *PDL1* positive cervical cancer.

Treating cervical cancer patients is challenging mainly due to the frequent diagnoses when the diseases are locally advanced. Most patients benefit from chemoradiation therapy. However, a considerable percentage of patients do not respond to the conventional therapy, or experience early recurrence. In such situations, the disease is virtually untreatable. This recent report has elucidated some molecular pathways and potential new targets to guide drug development for resistant diseases. Prospective randomized trials must be proposed to confirm the effectiveness of those alternative therapies.

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