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Editorial

Innovations in Cervical Cancer Treatment—There is Still Room for Improvement

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Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related death in women. The 5-year survival rate ranges from 50 to 80%, and survival rates vary greatly due to variations in disease burden, access to optimal treatments, and diagnostic methods [1–3].

The stage of the disease at the time of diagnosis is one of the most important prognostic factors for survival, and cervical cancer treatment is tailored according to disease stage. Stages IB2 and IIA2 are typically treated with hysterectomy, while stages IIB and higher are treated with concurrent chemoradiotherapy (cCRT), which consists of pelvic radiotherapy and cisplatin-based chemotherapy [4–6]. A clinical advancement indicating a survival benefit for adding platinum-based chemotherapy to radiotherapy (RT) in FIGO (Federation International of Gynecology and Obstetrics) stages IB2–IVA was published in 1999 [7], and meta-analysis has confirmed the survival benefit of cCRT over RT alone [6,8].

Radiotherapy is the gold standard treatment for locally advanced diseases, but toxicity remains a major concern, especially when using the standard three-dimensional conformal RT technique. Intensity-modulated RT (IMRT) and image-guided RT (IGRT) may be able to decrease toxicity while increasing the dose and improving the outcome by targeting only the diseased tissue. However, when comparing IMRT to two- and three-dimensional techniques in a definitive setting, there is no evidence that IMRT improves disease-specific or overall survival.

Over the past two decades, external RT with high-dose-rate intracavitary brachytherapy has rapidly replaced external RT with low-dose-rate intracavitary brachytherapy. Due to the close proximity of the cervical tumor to surrounding organs, IMRT is favored over three-dimensional conformal RT for gynecological applications [9]. Newer data suggests that IMRT can reduce toxicity without compromising oncologic outcomes after surgery. In the randomized RTOG (Radiation Therapy Oncology Group) 1203 study, IMRT was found to significantly reduce gastrointestinal and genitourinary toxicity compared to conventional four-field irradiation [10]. The PARCER trial [11] that used bone marrow-sparing IMRT for locally advanced cervical cancer demonstrated decreased toxicity and comparable disease outcomes [12]. Finally, ASTRO (American Society for Radiation Oncology) strongly recommends definitive cCRT with IMRT and brachytherapy in this patient population [13]. In addition, image-guided brachytherapy for cervical cancer improves pelvic control and overall survival at all stages. Improvements in pelvic control are more significant in advanced stages, but survival rates are comparable across stages. The Retro-EMBRACE cohort study investigated this disparity by analyzing failure patterns [14,15]. Although stereotactic ablative body RT and MR-LINAC with adaptive RT are currently being studied, there is currently no conclusive evidence that either is clinically advantageous [16].

Despite the fact that RT continues to be the most effective treatment strategy for locally advanced disease with improved local disease control, the most common site of progression is distant; consequently, there needs to be more effective systemic treatment strategies, as patients with stage III/IV LACC (locally advanced cervical cancer) have a poor prognosis [15,17,18]. Because 30–40% of patients have distant recurrence, researchers are investigating the elimination of micrometastasis and improvement of survival through the development of various therapeutic strategies, such as the use of higher doses of cisplatin, adjuvant chemotherapy after cCRT, and neoadjuvant chemotherapy before cCRT.

The introduction of new agents for the treatment of recurrent, persistent, and metastatic cervical cancer is a major improvement for this group of patients. Clinical and statistically significant survival benefits of adding immune checkpoint inhibitors have been demonstrated in post-platinum progression and first-line settings in randomized phase III trials [19,20]. Despite the discouraging preliminary results of the CALLA trial, the role of immunotherapy in the high-risk locally advanced disease setting will soon be defined by several ongoing clinical trials. Therapeutic HPV (Human Papilloma Virus) vaccination and adoptive cell transfer are two examples of novel immunotherapy approaches being studied in early-stage clinical trials for cervical cancer.

In summary, LACC has a dismal prognosis, whereas local recurrence and distant metastases continue to be a common problem directly affecting survival. Although numerous improvements have been made in imaging modali-

ties [21,22] as well as in local and systemic treatments, these changes have not translated into better treatment outcomes. This issue of "Cervical Cancer Therapy and Prognosis" will share some insights from current data on cervical cancer treatment.

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