Early-stage intermediate-risk—the group with the most heterogenous management among patients with cervical cancer

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Of the entire clinical management algorithm in cervical cancer, the treatment of patients with early-stage intermediate-risk tumors is the least harmonized and raised many controversies. During the development of the first ESGO-ESTRO-ESP clinical practice guidelines in 2017, reaching the consensus of the working group in this area was the most difficult.1 There are several reasons for that, mainly the fact that it is an interface between two major treatment modalities. While no one disputes the dominance of surgical treatment in early stages and small tumors, radiation oncology in tumors with pelvic progression outside the cervix, or systemic treatment in metastatic disease, the management of intermediate-risk tumors today includes at least five different types of treatment: radical hysterectomy alone, radical hysterectomy followed by adjuvant treatment, neoadjuvant chemotherapy followed by radical hysterectomy with or without adjuvant treatment, neoadjuvant brachytherapy followed by radical hysterectomy with or without adjuvant treatment, and primary chemoradiation. On top of that, there is no international standard of adjuvant treatment, which nowadays consists of external radiotherapy alone, combined radiotherapy and chemoradiation. Each of the mentioned managements has its advocates, who are convinced that, based on their institutional results and indirect arguments from the literature, their strategy is the best.

However, the controversy concerning the intermediate-risk group does not end with the choice or combination of the main treatment modalities. The diagnostic criteria for the intermediate-risk group are also unclear. Some use the original GOG criteria, such as a combination of tumor size, presence of lymphovascular invasion (LVI) and depth of stromal invasion. Others calculate the GOG score or classify all patients with tumors over 2 cm in combination with LVI into the intermediate-risk group, considering LVI to be the most important prognostic factor. Even tumors of stage IB3, that is, over 4 cm in size, should be classified in the intermediate-risk category, however in clinical trials they are often part of locally advanced cancers, together with stages IIb–IVA. Differences in the diagnostic criteria of the intermediate-risk group ultimately affect both the size of this group and its prognosis and complicate the comparison of studies with each other.

This journal issue includes two articles dealing with a key controversy in the management of the intermediate-risk group and the role of adjuvant treatment after radical surgery. In the lead article, Juliana Rodriguez, Rene Pareja and David Viveros-Carreno did a very good job of analyzing current knowledge.2 They discuss the limitations of historical evidence on the importance of adjuvant treatment and provide an overview of recent retrospective studies that show a much better outcome of intermediate-risk group patients after radical surgery without adjuvant treatment compared with historical data. The main explanation for such a better outcome of the intermediate-risk group nowadays is much better accuracy of lymph node staging, especially when sentinel lymph node (SLN) pathological ultrastaging is performed, which allows categorizing a larger proportion of patients with positive lymph nodes into a high-risk group. These lymph node metastases remained undiagnosed in the past and these patients were part of the intermediate-risk group at the time of the GOG study.

The second paper is a trial in progress article that presents the CERVANTES study, launched a few months ago.3 The study design is similar to the original GOG 92, but with a few significant differences. Patients are registered in the study before surgery, a quality assurance program for radiotherapy and surgical treatment is in place, the imaging in clinical staging is mandatory, the pathological processing of the tumor and lymph node is standardized by the protocol, SLN biopsy is mandatory and adverse events and quality of life after treatment are followed prospectively using standardized tools. The study is now open for international collaboration.

It should be emphasized that the role of adjuvant treatment in the management of the intermediate-risk group is not only defining a single step in the management but represents a key issue for the position of radical surgery in the treatment of cervical cancer in the future. In the majority of patients, we already know about their affiliation to the intermediate-risk group before surgery thanks to accurate imaging. And the benefit of radical hysterectomy before chemoradiation in patients with early stage disease and negative lymph nodes is very unlikely. Therefore, if the benefit of adjuvant treatment is confirmed in
patients with intermediate-risk factors, there is little doubt that primary chemoradiation will become the treatment of choice. In addition, if the positive results of the SHAPE study are tentatively anticipated in 2024, and thus the confirmation of the safety of simple hysterectomy in tumors up to 2 cm, the group of candidates for radical surgery will remain so narrow that it will become almost impossible for the next generation to maintain sufficient surgical proficiency. The consequence would be a significant change in the management of the early stages, when patients would be referred to either simple hysterectomy or primary chemoradiation. Before this scenario happens, it should be the responsibility of our generation to challenge and define the optimal management of the intermediate-risk group in terms of survival, treatment morbidity and long-term quality of life prospectively.

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