Sex cord-stromal tumors of the ovary: road map for progress

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Received 16 December 2020
Accepted 17 December 2020
Published Online First 12 January 2021

► http://dx.doi.org/10.1136/ijgc-2020-002018

To cite: Hillman RT, Gershenson D. *Int J Gynecol Cancer* 2021;**31**:169–170.

Sex cord-stromal tumors of the ovary comprise a rare and enigmatic group of neoplasms defined by a beguiling paradox—indolent-behaving diseases that can nevertheless present serious clinical challenges in the advanced or recurrent setting. Al-Harbi et al[1] set out to synthesize and distil an extensive literature covering the epidemiology, treatment outcomes, and molecular pathogenesis of this heterogeneous group of neoplasms for which the published literature is far-ranging. In this attempt, they should be commended, even though several seminal publications failed to receive mention in their review. For adult-type granulosa cell tumors, these omissions include the original description of the *FOXL2* c.C402G mutation,[2] the more recent report that *KMT2D/MLL2* truncating mutations may be associated with recurrence,[3] and the original description of an association between *TERT* promoter mutations and adverse outcomes.[4] The original identification of *DICER1* mutations in Sertoli–Leydig cell tumors also deserves mention.[5] Despite these important advances in our molecular understanding of sex cord-stromal tumors, the unfortunate reality is that we are still seemingly quite far from realizing a rational, biomarker-based framework for the treatment of these tumors.

The general lack of targetable mutations in sex cord-stromal tumors has lent critical importance to studies, both retrospective and prospective, designed to establish the effectiveness of hormonal therapies and conventional cytotoxic chemotherapy regimens. Data on the efficacy of paclitaxel in these tumors has spurred a movement away from bleomycin/cisplatin/etoposide toward paclitaxel/carboplatin as a similarly efficacious but more tolerable cytotoxic regimen for advanced or recurrent sex cord-stromal tumors.[6 7] Data also support the use of bevacizumab in these tumors, both as a single agent[8] and in conjunction with weekly paclitaxel.[9] The authors reference key retrospective studies regarding the utility of hormonal agents in treating these tumors, but it is worth noting that the comparative effectiveness of these different hormonal therapies has not been evaluated prospectively, and their optimal use in relation to chemotherapy remains poorly defined.

The road map to future improvements in our ability to treat advanced and recurrent sex cord-stromal tumors must involve operationalizing our knowledge of their molecular underpinnings: first, through the development of genetically defined animal and in vitro model systems, and also through the design of biomarker-based collaborative clinical trials. For example, despite the high frequency and clear pathogenic implications of *FOXL2* c.C402G mutation in adult-type granulosa cell tumors, to our knowledge, a genetically engineered mouse model of this mutation has not yet been reported. The study of sex cord-stromal tumors has also been limited by the fact that the published literature in this area is diffuse and comprised of many small, often underpowered, studies examining similar populations and questions. The successful completion of the ALIENOR/ENGOT-ov7 international collaborative trial demonstrates the feasibility of generating high-quality, prospective data to inform treatment decisions for women with sex cord-stromal tumors. In building on the success of this trial, we advocate for continued efforts to develop parallel collaborative efforts for the pooling and shared analysis of retrospective treatment outcomes data and biospecimens. Insights generated through such collaborative science will in turn expedite and inform the next generation of clinical trials.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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