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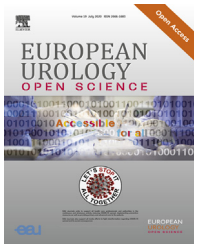

European Association of Urology

Opinion: Open Science

Management of Late Relapses in Metastatic Testicular Germ Cell Tumors: Still a Challenge

In a recent issue of *European Urology Open Science*, Jay et al [1] report on the outcomes for 101 patients with testicular germ cell tumors who experienced late relapse (LR) following initial local or systemic treatment. It has to be emphasized that the authors did not use the typical LR definition, which is reserved for patients with recurrence at least 2 yr after completion of systemic chemotherapy [2]; they also included relapses for patients with clinical stage I (CSI) disease under active surveillance.

Jay et al [1] are to be congratulated for this extensive and clinically important retrospective analysis of a large cohort of patients with LR that allows several clinically important conclusions. (1) Patients with CSI disease experience early relapse and need close follow-up strategies during the first 2 yr after initial treatment, including physical examination, imaging studies, and evaluation of serum tumor markers (STMs). (2) LR disease contains chemorefractory elements in the majority of cases, so properly performed surgical resection before chemotherapy in STM-negative patients or after chemotherapy in STM-positive patients represents an integral part of the multimodal treatment of those patients. (3) Postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) needs to be performed in highly experienced centers and is truly a scenario for centralization.

There are some findings that deserve specific attention since they might have an important impact on management of LR: (1) 30.6% patients had CSI disease and their median time to relapse was much shorter than for men with metastatic disease; (2) chemotherapy-naïve patients experienced relapse much earlier than those who received induction chemotherapy; (3) 20/41 patients (48.8%) experienced a retroperitoneal relapse following PC-RPLND; and (4) the overall survival rate was 77%.

The data for patients with CSI disease reflect the experience in a previous multi-institutional analysis of 51 patients with relapse following one cycle of PEB and who had 5-yr progression-free survival and overall survival rates of 67% and 81%, respectively [3]. Some 37% of the relapses were LRs and were associated with a significantly higher risk of death compared to cases of early relapse. Interestingly, relapses with teratoma only occurred much earlier than nonseminomatous relapses (9 vs 20 mo; $p < 0.001$) but the overall survival rate was 100%. The survival rates for patients with early and late nonseminomatous relapses were 13% and 28%, respectively, which is related to the different histological composition of metastases. On the basis of those data and taking into consideration the findings of Jay et al [1], individualized salvage treatment needs to be initiated, involving surgery for patients with STM-negative and completely resectable disease, and salvage chemotherapy followed by PC-RPLND or resection of extraperitoneal disease for the remainder of patients.

A total of 86 patients underwent surgical resection of LR masses and the majority of specimens harbored teratoma (52.3%), yolk sac tumor (17.4%), or other viable GCT elements 11 (12.7%). These data are in line with other series that demonstrated that the majority of relapses develop in the retroperitroneum, but they differ in that viable GCT with yolk-sac tumor elements represented the most common histology (80% of cases) in other series [4,5]. In addition, many lesions contain somatic malignant transformation, so that surgery remains the therapeutic approach of choice if the mass is completely resectable. Systemic chemotherapy is associated with inferior oncological outcomes because a complete remission can only be achieved in 26% of cases and relapse-free survival without surgery in only 3% [4–6]. In patients with extensive disease at the time of LR not amenable to upfront surgery, systemic chemotherapy followed by surgical resection will result in complete remission in 50% of cases and median overall survival of 23.9 mo [6]. However, when it comes to the issue of PC-RPLND or resection of metastatic lesions, surgery needs to performed in experienced centers only, as evidenced by a retroperitoneal relapse rate of 48% following PC-RPLND as part of the initial management of metastatic germ cell tumors [2]. As demonstrated in other series, repeat RPLND is

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associated with an inferior survival rate compared to properly performed PC-RPLND, and salvage chemotherapy cannot compensate for an inadequate initial surgery [7,8].

The relatively high overall survival rate of 77% is in line with other recent series [9]. It becomes evident that survival rates for patients with LR of CSI disease following adjuvant chemotherapy are better than those for men with relapse following systemic therapy for metastatic germ cell tumors, but inferior to those for patients with de novo metastatic disease. Those findings highlight the impression that LR represents a specific biological entity for which the molecular background needs to be explored more extensively in the future.

Conflicts of interest: The author has nothing to disclose.

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