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Review Article

Conundrums in the management of malignant ovarian germ cell tumors: Toward lessening acute morbidity and late effects of treatment

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HIGHLIGHTS

- Most patients with malignant ovarian germ cell tumors are cured
- An overarching theme in the management of malignant ovarian germ cell tumors should be reduction in morbidity
- We should seek resolution of differences in clinical management strategies between pediatric and gynecologic oncologists

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ABSTRACT

One of the most extraordinary stories in the chronicles of gynecologic cancers has been that of malignant ovarian germ cell tumors. Prior to the mid-1960s, most patients died of disease. Fifty years later, most survive. Precisely because high cure rates are achievable, the concentration over the past decade has been on minimizing toxicity and late effects. The present review focuses on five areas of interest related to the management of malignant ovarian germ cell tumors that highlight the different therapeutic strategies practiced by pediatric and gynecologic oncologists: 1) primary surgery, 2) surgery alone (surveillance) for patients with FIGO stage IA disease, 3) postoperative management of FIGO stage IC-III disease, 4) postoperative management of pure immature teratoma, and 5) postoperative management of metastatic pure dysgerminoma. All of these topics share a common overarching theme: Lessening acute morbidity and late effects of treatment.

Contents

One of the most extraordinary stories in the chronicles of gynecologic cancers has been that of malignant ovarian germ cell tumors. Prior to the mid-1960s, most girls and young women died of the disease. During this era, the only therapies available included surgery alone or

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combined with postoperative treatment consisting of external radiotherapy, radioisotope therapies, or single alkylating agent therapy [1–9]. Fifty years later, most patients survive. Cure is possible due to the evolution of both the surgical and chemotherapeutic approaches. However, precisely because high cure rates are achievable, a second wave of practice transformation over the past decade has been focused on minimizing toxicity and late effects. A remarkable aspect of this transformation is that it has been informed by intense debate between gynecologic, pediatric, and testicular cancer specialists as part of the Malignant Germ Cell International Consortium (MaGIC). This cross-discipline learning has led to recommended new approaches and a host of new questions for the next era of ovarian germ cell tumors investigations.

1. Surgical strategies

Consolidation of our strategies regarding surgical management of malignant ovarian germ cell tumors really took hold beginning in the mid-1970s. The fact that malignant ovarian germ cell tumors principally occur in girls and young women and are usually confined to one ovary makes fertility-sparing surgery generally feasible. Support for such an approach originally arose not from prospective randomized trials but rather from a retrospective review of the Armed Forces Institute of Pathology experience indicating that there was no worsening of prognosis associated with fertility-sparing surgery compared with hysterectomy and bilateral salpingo-oophorectomy [10]. Subsequent practice patterns confirmed the wisdom of this approach [11].

Other surgical strategies—comprehensive surgical staging for apparent early-stage disease [12], maximum primary cytoreductive surgery for advanced stage disease [13,14], second-look surgery [15], and secondary cytoreductive surgery [16,17]—were based on principles extrapolated from the much more common epithelial ovarian cancers. Fortunately, second-look surgery was largely abandoned several years ago [18,19]; however, comprehensive surgical staging and cytoreductive surgery continue to be practiced to varying degrees throughout the world-wide gynecologic oncology community. Largely missing from the comparison of epithelial ovarian cancer and malignant germ cell tumors has been the understanding that the latter is much more chemosensitive and may not require the same surgical approach for microscopic or occult metastatic deposits.

2. Chemotherapeutic strategies

The evolution of combination chemotherapy for patients with malignant ovarian germ cell tumors began in the 1960s with the introduction of the combination of actinomycin-D, 5-fluorouracil, and cyclophosphamide (AcFuCy). Although several reports documented modest success with this regimen, its popularity was short-lived, giving way to other combinations [7,15,20,21]. Another early regimen used was the combination of methotrexate, actinomycin-D, and cyclophosphamide (MAC) [22].

Throughout most of the 1970s, the combination of vincristine, actinomycin-D, and cyclophosphamide (VAC) was popularized and became the standard treatment. This regimen resulted in a significant improvement in outcome, especially for patients with stage I germ cell tumors, but resulted in sustained remissions in <50% of patients with stage II-IV disease [13,15,23–26].

The major breakthrough in improving outcomes for patients with malignant ovarian germ cell tumors occurred once the drug cisplatin was introduced and Einhorn and Donohue reported their promising results in 1977 with the combination of vinblastine, bleomycin, and cisplatin (PVB) for testicular cancer [27]. Subsequently, several reports documented excellent results with this regimen in patients with malignant ovarian germ cell tumors [14,28–31]. However, once Williams et al. reported equivalent efficacy combined with a superior therapeutic index for the combination of bleomycin, etoposide, and cisplatin (BEP) compared with the PVB regimen for men with testicular cancer [32], BEP was rapidly integrated into the treatment of patients with malignant ovarian germ cell tumors—both nondysgerminomatous germ cell tumors and metastatic dysgerminoma [33–36]. The BEP regimen has produced sustained remissions in over 95% of patients with stage I malignant ovarian germ cell tumors and at least 75–80% sustained remissions in stage III or IV disease. And for over two decades, the BEP regimen has been the standard chemotherapy regimen.

With this history as a backdrop for making further advances in this area, outcomes to date have generally been excellent. However, because most patients with malignant ovarian germ cell tumors are young and survive for several years following their diagnosis, there has been increasing concern about the late effects of treatment. For example, comprehensive surgical staging that includes bilateral pelvic and paraaortic lymphadenectomy is associated with potential chronic lower extremity lymphedema. Chemotherapy may be associated with acute toxicities and a myriad of late effects, including premature ovarian failure, premature menopause, impaired psychological and social functioning, physical effects, and secondary malignancies [37–43]. Given the enhanced appreciation for these late effects and the goal of minimizing them, the standard management of malignant ovarian germ cell tumors has incrementally been undergoing a transformation in approach over the past decade or so. Leading this effort in minimizing late effects while maintaining efficacy has been the pediatric oncology community as well as the European gynecologic cancer community.

3. Toward lessening acute morbidity and late effects of treatment

This review will focus on five areas of interest related to the management of malignant ovarian germ cell tumors, several of which highlight different therapeutic strategies practiced by pediatric and gynecologic oncologists: 1) primary surgery, 2) surgery alone (surveillance) for patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA disease, 3) postoperative management of FIGO stage IC-III disease, 4) postoperative management of pure immature teratoma, and 5) postoperative management of metastatic pure dysgerminoma. Some of these management issues have been evolving for some time, and others are under consideration for further study. However, all share the common feature of striving to lessen acute and/or late morbidity.

3.1. Primary surgery

As noted above, the principle of comprehensive surgical staging for apparent stage I malignant ovarian germ cell tumors was extrapolated from the standard for the much more common epithelial ovarian cancer as well as from the standard practice of retroperitoneal lymph node dissection in the treatment of nonseminomatous testicular tumors. In addition to resection of the primary site, comprehensive surgical staging—including peritoneal cytology, omentectomy, peritoneal biopsies, and bilateral pelvic and paraaortic lymphadenectomy—generally continues to be the standard for surgical management within the gynecologic oncology community. The most controversial component of comprehensive surgical staging is routine lymphadenectomy, which is related to the potential late morbidity of lymphedema [44,45]. The standard within the pediatric surgical community is quite different.

In a report from the pediatric intergroup, Billmire et al. detailed surgical staging in 131 children with malignant ovarian germ cell tumors [46]. Despite the fact that 21% of patients had no peritoneal cytology, 36% had no omentectomy, and 97% had no lymphadenectomy, 6-year survival rates for all stages were >90%. The authors concluded that survival was not compromised by deviations in surgical staging guidelines. As a standard surgical approach, they recommended the following: 1) collection of ascites or peritoneal cytology for cytologic evaluation, 2) examination of peritoneal surfaces and biopsy or excision of any nodules, 3) examination and palpation of retroperitoneal lymph nodes with sampling of firm or enlarged nodes, 4) inspection and palpation

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