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Review

Management of malignant dysgerminoma of the ovary

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Abstract

The evolution of treatment for malignant ovarian germ cell tumors has been one of the most successful in the history of gynecologic oncology, with dysgerminoma as the most common type of malignant ovarian germ cell tumors. Since the introduction of platinum-based chemotherapy in the 1980s, 5-year survival rates for early-stage dysgerminomas have been close to 100%, and as high as 98% for advanced stages. Despite this remarkable achievement, many questions remain in routine treatment. By performing a literature review, we aim to highlight both the current treatment of malignant dysgerminoma and unanswered questions in the modern management of this disease. These issues relate firstly to surgical therapy, such as the role of routine omentectomy and lymphadenectomy, the value of complete surgical resection, and the possibility of fertility-sparing surgery. Second, chemotherapy and the question of the possibility of de-escalation in early stages and the potential of neoadjuvant chemotherapy in advanced stages will be addressed. Finally, a brief overview of the current developments of new drug treatment regimens will be given.

Keywords: non epithelial ovarian cancer; ovarian germ cell tumor; dysgerminoma; surgery; chemotherapy; targeted therapies

1. Introduction

Non-epithelial ovarian cancers (NEOCs) are heterogeneous and account for approximately 8% to 10% of all ovarian cancers. While carcinosarcomas belong to the epithelial ovarian carcinomas and account for 1% to 4% of all ovarian cancers (OC), they represent a pathologically challenging differential diagnosis due to the biphasic histological component with epithelial and mesenchymal content, which accounts >10%. The poor prognosis with a median overall survival of 8 to 26 months makes it urgent to clarify the biology of this disease as well as common genetic alterations and activated molecular signaling pathways to offer better therapeutic strategies [1]. Current in 2020, the first joint guideline by pediatric oncologists and gynecologic oncologists regarding non-epithelial ovarian cancers was published [2]. Malignant ovarian germ cell tumors (MOGCTs) and sex cord stromal tumors (SCSTs) are the largest subgroups of NEOC [3,4]. The most common type of MOGCTs with about 30% to 40% is the dysgerminoma (DYS) [3,5] followed by immature teratomas, yolk sac tumours and mixed germ cell tumours. The most common subtype of SCST is the granulosa cell tumour, which is divided into juvenile (5%) and adult types (95%) [6]. Also included in SCST are the Sertoli-Leydig cell tumours, theca cell tumours and rare SCST with annular tubules. The group of SCST is very heterogeneous and is composed of sex cord and stromal tumours of different components. Occasionally, the different appearance can lead to diagnostic problems, which is why immunohistochemistry is of particular importance. Entities as diverse as carcinomas, sarcomas, germ cell tumours and melanomas can be considered as differential diagnoses for this group [3,7]. DYS originates from primordial germ cells whereas SCSTs arise from pure ovarian stroma or tertiary follicle (Fig. 1) [8,9]. In contrast to other MOGCTs, DYSs occur in 10% to 15% bilaterally [6] and are usually detected at an early stage with

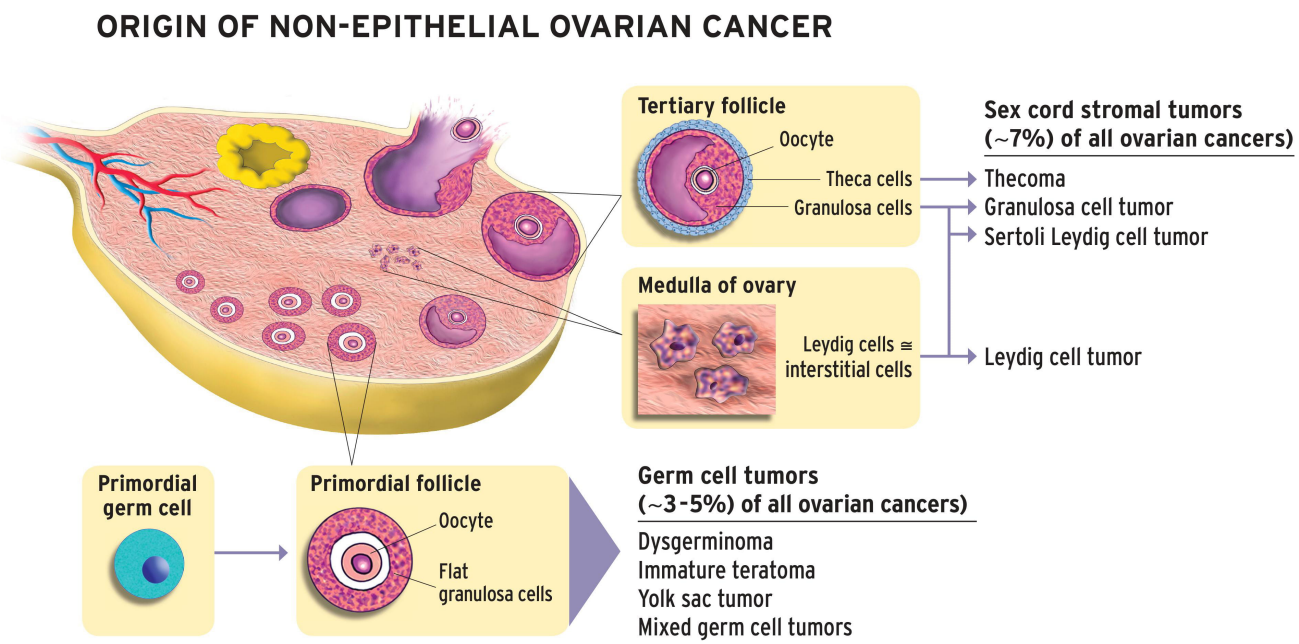

Fig. 1. Schematic illustration of the origin of non-epithelial ovarian cancers.

about 75% at stage IA, 10% at stage IB, 15% at stages II and III and 5% at stage IV, respectively [6]. Around 10% to 20% of patients with DYS experience relapse. Most patients recurring within the first two years after diagnosis [10–13]. The introduction of platinum-based chemotherapy since the 1980s onwards has resulted in 5-year survival rates approaching 100% in early stages of DYS and over 90% for advanced stages [6,14–19]. These excellent survival data and the age of the patients have led to increased efforts in the last ten years to minimize both, toxicity and long-term side effects of surgery and chemotherapy [20]. Within this framework, the professional exchange between specialists in gynecologic oncology, pediatric oncology and pediatric surgery has grown, accelerated by the Malignant Germ Cell International Consortium (MaGIC) founded in 2009 and in European efforts between European Society of Gynaecological Oncology (ESGO) and European Society for Paediatric Oncology (SIOPE) to define standards of diagnosis, treatment and follow-up of these patients cross group disciplines [2,21–23]. Despite these encouraging developments in the treatment of MOGCTs, there are remaining issues in the management of DYS. This review summarizes the modern clinical management and the current controversies in the treatment of DYS.

2. Incidence and Epidemiology

Of all ovarian malignancies, DYS is rare and accounts for 1% to 2% and mainly occur in adolescent and young adult women [12]. About 75% of DYSs arise between the age of 10 and 30 years, 5% even under 10 years [24]. The incidence rate of DYS decreased over the last 30 years, whereas it steadily increased in male testicular seminoma, the male counterpart of DYS [6,25]. Precise data on the age specific incidence of DYSs are hardly available due to the rarity of the disease (Table 1, Ref. [6,25]) [26]. The median age of the patients with DYS is between 14 and 21 years, according to the data found in literature.

Table 1. Table of age-specific incidence of Dysgerminoma.

Author	Incidence/100.000/year	Age (range)
Smith *et al*., 2006 [6]	approx. 0.02*	0–9
	approx. 0.13*	10–14
	approx. 0.45*	15–19
	approx. 0.29*	20–24
	approx. 0.25*	25–29
	approx. 0.16*	30–34
	approx. 0.06*	40–49
	approx. 0.02*	50–59
	approx. 0.01*	60–65
Bleyer *et al*., 2019 [25]	approx. 0.36*	15–19
	approx. 0.30*	20–24
	approx. 0.28*	25–29
	approx. 0.10*	30–34
	approx. 0.08*	35–39

*The data are estimated to be taken from a graphical representation of the corresponding work [6,25].

3. Pathology

DYS share several conventional-morphological and immunohistochemical features with testicular seminomas. They have monotonous populations of polygonal round or

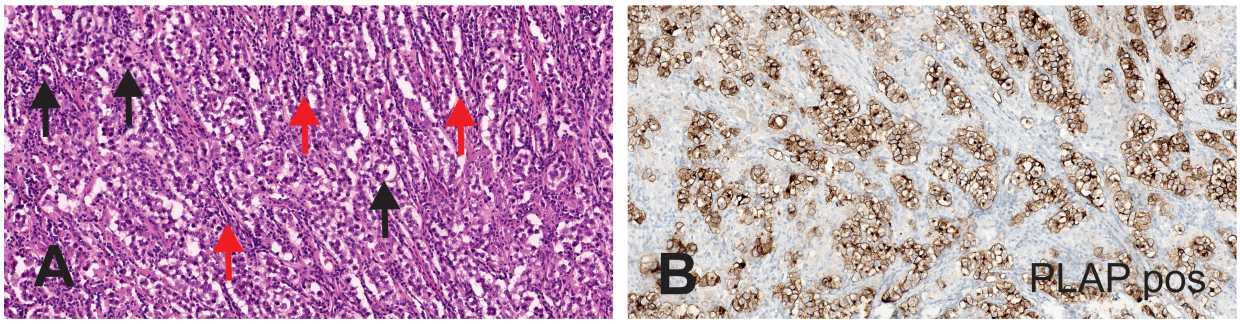

Fig. 2. Hematoxylin-eosin (HE) and immunohistochemical staining in pure ovarian dysgerminoma. (A) Black arrows show large germ cells. Red arrows show lymphocytes. Germ cells are separated by fibrous septa that show rich lymphocyte infiltrates (H & E stain, × 100). (B) PLAP staining was positive (PLAP, × 100).

oval tumor cells with well-defined cell membranes and clear or slightly eosinophilic cytoplasm containing large vesicular nuclei with one or two eosinophilic nucleoli and high mitotic activity [27]. The patterns of growth present as solid, trabecular, insular, pseudoglandular and individually arranged cells separated by fibrous septa with infiltration of cytotoxic lymphocytes and epitheloid histiocytes, often with tumor invasion (Fig. 2) [28,29]. About 5% of DYS show syncytiotrophoblastic cells, mostly with elevation of ß-human chorion gonadotropin (ß-HCG) serum levels. A partial chorio-carcinoma must be excluded by thorough sample analysis. Additional immunohistochemical tests can help to differentiate between the different germ cell tumors (GCTs): Sal-like protein 4 is typically positive in all malignant ovarian GCTs, OCT3/4, D2-40, NANOG, and CD117 are commonly positive in DYS (Fig. 2) [2].

4. Clinical Diagnosis

In terms of clinical appearance, there are no specific clinical symptoms for DYS. An indication of DYS could be a large tumor size, due to the tendency of rapid growth [30]. The initial symptoms are abdominal distension and subacute pelvic pain in 85% of all cases. Due to torsion, hemorrhage or rupture, 10% of patients present with acute abdominal pain. Less common signs are fever, ascites, vaginal bleeding and menstrual irregularities [31–34]. The dominant metastatic spread of DYS, when detected in advanced stages, is the nodal route. DYS has the highest rate of nodal metastasis (28%) of all MOGCTs [35–37]. Hematogenic spread and direct expansion through the capsule of the ovary are also possible [38]. The diagnostic workup for patients with an adnexal mass suggestive for malignancy should include imaging of the abdomen and pelvis preferred by transvaginal ultrasound and magnetic resonance imaging (MRI) as well as a chest X-ray [3,39]. On ultrasound, DYSs are depicted as highly vascularized, large, solid, lobulated adnexal mass with irregular internal echogenicity [40]. Biologic markers should be determined like a-fetoprotein (AFP), ß-HCG and lactat dehydrogenase (LDH) and may help to stratify between the different subtypes of MOGCTs [26,41]. Cancer antigen 125 (CA-125) should also be assessed. Pure DYS produces no hormones. More than 50% of DYSs have elevated LDH and up to 5% produce low levels of ß-HCG, which is associated with the presence of multinucleated giant syncytiotrophoblastic cells, whereas AFP is normal [13,42,43]. Full blood test, liver and renal function tests should be performed preoperatively [33,41]. DYS, at 5% to 10%, are the most common germ cell tumors observed in phenotypic females with abnormal gonads, particularly in Swyer syndrome [38,44]. So that in premenopausal women with DYS and suspected gonadal dysgenesis, consideration should be given to performing karyotyping and, if indicated, removing both ovaries [33,41,42].

5. Staging and Prognostic Factors of Non-epithelial Ovarian Cancer

NEOCs are staged like epithelial ovarian cancers (EOCs) originally defined by the International Federation of Gynecology and Obstretics (FIGO) [3]. Prognostic factors for MOGCTs in general have not been well defined, including DYS [45]. To date, only few factors have been identified that increase the risk of recurrence of MOGCTs in univariate and multivariate analysis: age >45 years, stage >I and treatment outside a referral center [18,46–48]. In addition, Meisel *et al.* [45] showed that histology was significantly associated with PFS, with dysgerminoma patients doing better than those with other histologies. Interestingly, a family history of cancer seems to be inversely correlated with the risk of developing DYS and, so far, no genetic susceptibility has been identified to the development of DYS [49].

6. Role of Surgery in Malignant Dysgerminoma: Current Controversial Issues

6.1 Comprehensive Surgical Staging

Until the 1980s, radical resections and comprehensive surgical staging (CSS), as performed in EOC, were car-

ried out in DYS because of their dismal prognosis [48,50]. With the introduction of platinum-based chemotherapy, outcomes for patients with DYS have been excellent [17, 31,51] and the necessity for extensive surgical staging procedures was questioned and is still unresolved [52]. Worldwide, numerous variations in the practice of CSS exist side by side [53]. Most controversies are related to omentectomy and systematic lymphadenectomy [54,55]. According to the European Society for Medical Oncology (ESMO) guideline for NEOC, fertility-sparing surgery (FSS) with preservation of the uterus and contralateral ovary is the gold standard for all patients with early- and advanced-stage DYS. Further, CSS should include an examination of the abdominal cavity, infracolic omentectomy, biopsy of the diaphragmatic and pelvic peritoneum and paracolic gutters as well as peritoneal washings, unilateral salpingo-oophorectomy, nodal inspection and dissection from bulky nodes [3]. Other guidelines regarding NEOC, such as those issued by the Royal College of Obstetricians and Gynaecologists and the recently published guideline from the European Society of Gynaecological Oncology (ESGO) and the European Society for Paediatric Oncology (SIOPE) recommend performing an omental biopsy instead of an infracolical omentectomy if it is macroscopic inconspicuous [2,56]. Regarding the literature, signs are mounting that omental biopsy is sufficient in the treatment of DYS [20]. Nasioudis *et al*. [57] reviewed Surveillance, Epidemiology and End Results (SEER) database between 1994 and 2014 identifying 2238 female patients under 40 years with MOGCT, 663 of those with DYS, who underwent cancer directed surgery. In this scientific evaluation of data, it was found a decreasing trend in omentectomy and, more important, no differences in 5-year cancer specific survival between patients who did and did not undergo omentectomy [57]. In accordance with this, a previous retrospective study by XU *et al*. [58] analyzed 223 patients with MOGCTs, of which 61 patients had early-stage DYS. 72% of these 61 patients had omentectomy. The 5-year overall survival rate was 100%. The 10-year overall survival rate for patients who did and did not undergo omentectomy was comparable with a non-statistically significant trend favoring the non-omentectomy group (94% and 100%, $p = 0.47$) [58]. These findings suggest that routine omentectomy should be avoided in the absence of grossly abnormal omentum and omental biopsies performed instead. Furthermore, omentectomy in early-stage DYS may not help to improve patient survival [57].

The recommendation of the ESMO and ESGO-SIOPE guideline for NEOC to avoid routine systematic lymphadenectomy is supported by several studies from the literature [56,57,59]. Mahdi *et al*. [60] evaluated SEER data between 1988 and 2006 from 1083 patients with MOGCTs, 354 of those with DYS stage I and surgical treated. The highest frequency of lymphadenectomy was seen in patients with DYS (62, 4%). Mahdi *et al*. [60] found out that the presence of lymph node metastases had no adverse effect on long-term outcome and lymphadenectomy was not an independent predictor for survival. One limitation of this study is the lack of information on the adjuvant chemotherapy after initial surgery [60]. For DYS stage IA, surgery and active surveillance is the standard treatment. In this case, knowledge of accurate disease stage and, therefore, performing lymphadenectomy may be of value in order to omit chemotherapy [17,38]. To date, there are no studies that directly compare the outcomes of comprehensively staged patients (including lymphadenectomy) to those who had a minimal staging followed by surveillance only [20,57].

Published data suggest active monitoring of stage IA DYS and reservation of chemotherapy in case of recurrence after surgery because of the relatively low recurrence rate of DYS in stage IA at 15% to 25% and the high probability of cure in the event of recurrence [16,47]. For DYS stage IB and IC 2/3, according to ESMO guideline for NEOC, active surveillance after lymph node inspection is possible but not officially recommended [2,3]. In summary, there is a shift towards less extensive surgical staging. Further, there is a consensus that CSS should include collection of ascites or washings, examination and biopsy of the peritoneal surfaces with excision of any nodules, inspection and palpation of the opposite ovary with biopsy of any abnormal areas and complete resection of the tumor-containing ovary [50,57].

6.2 Possibility of Fertility Sparing Surgery in Young Patients

Considering that current cure rates for DYS are excellent and as the affected patients group is mainly aged between 10 and 30 years, the possibility of FSS is increasingly important [61]. In regard to the ESMO and ESGO-SIOPE guideline for NEOC and the literature, the standard of care for premenopausal women with DYS, in early and also in advanced stages, who desire future childbearing, is FSS [33]. Until now, FSS has not been prospectively investigated, but there are numerous studies in the literature that show an excellent outcome for patients treated with FSS, also in advanced stages [62,63]. Ertas *et al*. [64] retrospectively analyzed the outcome of 42 patients with MOGCTs, 18 of whom had DYS, treated with FSS with or without subsequent chemotherapy. The reported survival was 100% with no detected recurrence. The study by Yang *et al*. [65] analyzed 104 patients with MOGCTs, of which 59 patients were treated with FSS and 45 patients received non-fertility sparing therapy. Yang *et al*. [65] found no statistically significant difference ($p > 0.05$) between FSS and non-FSS treated patients in terms of progression-free survival (67.6% *vs*. 63.3%), overall survival (70% *vs*. 64.1%) and mortality rate (15.3% *vs*. 31.3%). On the contrary, the reported data favor FSS. Although DYSs are bilateral in 10% to 15% of cases, contralateral ovarian biopsy should be avoided because it could lead to future infertility [66,67]. As FSS is the treatment standard for young pa-

tients with DYS, the focus of recent studies has shifted to long-term menstrual and reproductive outcomes after FSS and chemotherapy [11]. The corresponding studies show that the reproductive ability remains basically unaffected with a reported pregnancy rate after FSS, with or without subsequent cisplatin-based chemotherapy, between 75% to 90%. FSS should not be performed on dysgenetic gonads (streak gonads), then a bilateral adnexectomy is indicated to prevent further malignancies [33,68,69]. In the rare event that, postmenopausal women are diagnosed with Dysgerminoma and show advanced stage disease or bilateral ovarian involvement abdominal hysterectomy and bilateral adnexectomy should be considered [3].

6.3 How Important is Complete Resection?

The surgical goals, such as maximum primary cytoreductive surgery in advanced EOC, are based on the therapeutic concepts of the much more common EOC and may not apply to DYS which are much more chemosensitive. It has been shown that for patients with advanced DYS, the prompt initiation of chemotherapy, is the critical factor and enhances the therapeutic effect [17]. Expeditious start of chemotherapy seems much more important in DYS than in EOC, while the absence of tumor after salvage surgery due to good chemosensitivity is somewhat less important [3]. In the single institutional experience by Al Husaini *et al*. [12] of 65 patients with pure DYS, 16 patients with advanced DYS had residual tumor disease after cytoreductive surgery and received cisplatin-based chemotherapy. Thirteen patients (72.2%), of these 16 patients, had complete response and remain disease free at last follow-up with a median of 54 months [12]. Gershenson DM *et al*. and Dimopoulos MA *et al*. [70,71] also reported long-term outcome for patients with residual disease after cytoreductive surgery followed by cisplatin-based chemotherapy. In the rare cases where residual tumor tissue remains after chemotherapy (in peritoneum, remaining ovary or lymph nodes) a second surgical resection is required.

7. Adjuvant Chemotherapy: When to Stop and Which Regime?

The 5-day BEP (bleomycin, etoposide and cisplatin)-regime is most widely used [51,72] with a high likelihood of return of menstruation and following pregnancies [71,73,74]. For stage IA DYS, surgery alone and active surveillance is the preferred approach if the DYS has been completely resected and tumor markers that were severely elevated preoperatively, such as LDH, normalize postoperatively [42]. In stage IB and IC adjuvant chemotherapy is recommended but active surveillance is also an option and data from pediatric patients, supporting active surveillance, are encouraging [3,75]. The recent published ESGO-SIOPE guideline furthermore differ between DYS stage IC1 and IC2/IC3. For IC1, chemotherapy (maximum two cycles) or active surveillance is possible and should be discussed with the patient. DYS stage IC2/3 should receive chemotherapy (maximum three cycles) [2]. For all other stages of DYS, surgery with prompt initiation of chemotherapy is the favored therapy. The question of the optimal number of cycles could not be answered by randomized trials [3,76]. Recommended by guidelines and literature, are three cycles of the 5-day BEP-regime in fully resected disease and four cycles of the BEP-regime for patients with residual macroscopic disease, with bleomycin omitted after the third cycle to avoid lung toxicity and omitted altogether in >40-year-olds [3,31,77,78]. Further options are: cisplatin, etoposide and ifosfamide (PEI); cisplatin, etoposide and dose-reduced bleomycin; or carboplatin, etoposide and bleomycin (JEB) as used in pediatric protocols [2]. Even in advanced cases, the focus of current studies addresses the possibilities of de-escalating chemotherapy to avoid long-term toxicities of the BEP-regime [51,79]. In pediatric patients with DYS reduced-toxicity treatments are already established. JEB has replaced BEP in the treatment of DYS in children [80]. In the new Intergroup MAKEI V study, patients with FIGO IC to FIGO II stages are treated with a two-drug regimen cisplatin/etoposide or Carboplatin/cisplatin and etoposide (PE or CarboPE) [50]. Also, for adult patients with DYS it has already been shown that carboplatin-based chemotherapy is equivalent to the use of cisplatin which is taken up by the recent published SIOPE-ESGO guideline [2,81]. Furthermore, there are efforts to delete bleomycin. In a phase II trial of the gynecologic Oncology Group (GOG), 39 patients with completely resected metastatic dysgerminoma, stages IB-III, were treated in the adjuvant setting with four cycles of carboplatin-etoposide combination with a high activity and an acceptable toxicity profile. None of the patients relapsed with a median-follow up time of 7.8 years [82]. Alternative chemotherapeutic regimes, particularly in high-risk patients with advanced MOGCTs reporting high activity, are POMB/ACE (cisplatin/vincristine/methotrexate/bleomycin/actinomycinD/cyclophosphamide/etoposide) and CBOP/BEP (carboplatin/bleomycin/vincristine/cisplatin/BEP). Unfortunately, none of these regimes were evaluated in randomized studies compared to the BEP-regime. During adjuvant chemotherapy, tumor markers (α-fetoprotein, β-human chorionic gonadotropin (β-HCG) and lactate dehydrogenase) should be determined. Patients with MOGCTs who do not have negative markers after cycle four are considered non-responders to the treatment and may receive vincristine/actinomycinD/cyclophosphamide (VAC) or paclitaxel/gemcitabine or gemcitabine/oxaliplatin as salvage therapy. Patients in whom the tumor markers do not fall according to their expected half-life after the second treatment cycle, should be considered high-risk patients and an intensification of therapy should be discussed [3,56].

8. Neoadjuvant Chemotherapy: Who Needs It?

Primary surgery with or without subsequent chemotherapy is still the standard of care for DYS. The current ESMO and ESGO-SIOPE guideline for NEOC do not mention the option of neo-adjuvant chemotherapy (NACT) for DYS [2,3]. The Royal College of Obstetricians and Gynecologists recommends the urgent start of NACT of women in advanced stages IIIC and IV with MOGCTs instead of primary surgery [56]. In addition, the literature contains encouraging results from individual case reports of advanced DYS treated with NACT [83–85]. This approach could be particularly beneficial for patients in whom primary complete resection does not seem possible. NACT may enable complete resection, avoid major surgery and possibly even allow FSS [53,84]. The number of optimal cycles of NACT remains uncertain [83]. Treatment response could be evaluated with each cycle of chemotherapy by symptoms, tumor markers, physical examination and imaging to determine the earliest reasonable time for surgery.

9. Follow-up: What is Necessary?

Follow-up should include clinical examination, abdominal/pelvic ultrasound, tumor markers (ß-hCG, LDH, CA-125, AFP), imaging of chest, abdomen and pelvis. Active surveillance extends over a decade and should be tightly planned in the first two years after diagnosis, as 75% of all relapses occur in the first year. Pregnancy should therefore be discouraged in the first two years after the diagnosis of DYS. The temporal intervals vary somewhat between the individual guidelines, but an intensive early care about every four weeks for the first six months seems appropriate. From the second half of the year onwards the intervals can be extended to every two months and then gradually increase over the years. Whenever possible, patients should be included in studies or prospective registries [2,3,10–12,31]. Follow-up for patients who have undergone surgery followed by chemotherapy is provided for at least 5 years. Every 3 months for the first two years, every 6 months for the third year, and annually from the fourth year or when symptoms appear [2,3]. Particular regard should be given to the side effects of chemotherapy and the risk of secondary malignancies should always be kept in mind [2,3,56].

10. What to Do in Case of Relapse?

Approximately 15%–25% of patients with stage I DYS who are not treated with chemotherapy relapse. These chemo naive patients can be successfully treated with systematic chemotherapy (BEP-regime, PE, PEI) at the time of relapse with a high probability of cure [3,17,30]. Since a recurrence of DYS after chemotherapy is rare, there is a lack of data from randomized controlled trials regarding the therapeutic options. Patients who received primary chemotherapy and experience recurrence have a poor prognosis [26]. Platinum-based combinations should be considered in patients with platinum-sensitive (in dysgerminoma defined as progression >4–6 weeks after completion of chemotherapy) relapses. Patients resistant to platinum-based chemotherapy may receive paclitaxel/gemcitabine or gemcitabine/oxaliplatin as therapy. Another approach is to treat recurrence with high dose chemotherapy (HDCT) and stem cell infusion. A recent report suggests that HDCT for recurrent ovarian germ cell tumors may result in durable and prolonged remissions [86]. The role of secondary cytoreductive surgery for patients with recurrent or progressive DYS remains controversial [87]. Studies analyzing the optimal use of HDCT and new therapeutic agents in refractory germ cell tumors of the ovary are still ongoing [2,3,56,88]. In the event of relapse, radiotherapy could be considered as an option as a local strategy [11,56].

11. MOGCT and Pregnancy

Up to 2017, 193 cases of malignant non-epithelial ovarian tumours in pregnancy have been described in the English literature. These included 145 patients with MOGCT and as many as 45 patients with DYS [89]. Most patients with NEOC in pregnancy are detected at stage I, so that FSS with optimal staging is to be favoured in midgestation by laparatomy or laparascopy [90]. If indicated, chemotherapy should be administered in the second and third trimesters. Platinum-bleomycin based chemotherapy appears feasible and was administered in 68 of the 145 patients with NEOC. Among these, intrauterine growth restriction (14.5%) and spontaneous abortions (3.4%) occurred most frequently [91–94]. The abortion rate in women with a history of GCT are as common as in the general population (11.5%). The malformation rate, on the other hand, is higher at 7.27% versus 3% [89]. This difference is related to the tumour biology and the mutations in the karyotype, which occur more frequently in bilateral ones. Karyotyping should therefore be carried out especially in patients with a history of DYS and a desire to conceive, to exclude a genetic disorder. 5%–10% of patients with DYS have a female phenotype and an XY karyotype [41].

12. A Glimpse into the Future: Where Do We Stand?

Current clinical studies focus—among others—on the role of HDCT with stem cell transplantation as well as new agents in relapsed MOGCTs and improved diagnostic and monitoring techniques. An ongoing phase 3 trial (NCT02375204) is evaluating conventional-dose chemotherapy with HDCT followed by stem cell transplantation in the treatment of patients with relapsed GCTs. The study from Cheng *et al.* [95] demonstrated that *KIT* (type 3 tyrosine kinase receptor) mutations occur in approximately

one-third of cases of DYS and are associated with advanced stage at presentation. Therefore, tyrosine kinase inhibitors might be of particular interest for DYS and could be a potential therapeutic target for those with the mutation [95,96]. With regard to checkpoint inhibitors, a prospective study with pembrolizumab in male patients with recurrent germ cell tumors did not achieve any response [97]. An ongoing Phase II study including female patients with DYS, investigate dual checkpoint blockade with durvalumab, a PD-L1 inhibitor, and tremelimumab, an anti CTLA-4 immune checkpoint inhibitor, and may yield more promising results (NCT03158064) [98]. However, so far none of the new substances has made it into clinical practice and the results observed to date for testicular germ cell tumors regarding new drug targets are inconclusive [3]. In terms of miRNA profiles, one study compared nine benign and malignant GCT and three SCST and found that mir-199a5p is lower expressed in MOGCT than in benign GCT and in SCST. Mir-199a-5p is a down regulator of the autophagy gene Beclin 1 (BECN1). BECN1 has been reported to be highly expressed in MOGCT, suggesting the oncogenic role of autophagy in MOGCT [99]. Regarding surveillance management for MOGCTs, circulating biomarkers, the micro-RNA oncogenes, miR-302 and miR371-373, represent a promising approach. These biomarkers are overexpressed in all active MOGCTS, independent of histologic subtype or age, and disappear in most patients after removal of the primary tumor. A multi-institutional pilot study reported that recurrences in testicular cancer could be accurately identified by using the biomarker miR371 with a positive and predictive value of 100% during follow-up — even outperforming CT or conventional tumor markers in low-volume disease [9,100]. The clinical role of microRNA molecules for MOGCTs in surveillance is currently being validated in clinical studies such as AGCT1531, SWOG/NCTNS1823 and MAKEI V [17]. Klicken oder tippen Sie hier, um Text einzugeben.

13. Conclusions

The prognosis for adolescents and young adult women with DYS is excellent. Therefore, a primary focus is to de-escalate the surgical and chemotherapeutic therapy to reduce long-term side effects. In this sense, the data concerning a less intensive CSS with omission of routine omentectomy, and lymphadenectomy are encouraging. FSS should be the goal over all stages of DYS and is mostly feasible. Less toxic chemotherapeutic regimes without bleomycin or replacing cisplatin with carboplatin are on a promising path and are already being used in some pediatric patients with DYS such as the Intergroup MAKEI V trial. NACT may become more important in the future for advanced stages of DYS. The optimal treatment for recurrent DYS is still unanswered and needs further randomized trials. The final role of targeted therapy in DYS has not been clarified in randomized trials and is currently under investigation in various studies. MiR-371 could play an important role in surveillance of MOGCTs in the future. In order to further improve the therapeutic management of DYS and to answer open questions, interdisciplinary and international cooperation is essential, as is the initiation of multi-center clinical trials that include patients with this rare disease.

Author Contributions

KP had the idea and designed the structure of the review. TA performed the literature research and helped to design the structure of the review. GC offered great help and advice from the important pediatric oncologist's perspective and supplemented literature research. HED and KR provided help and advice on the essential topic of pediatric oncology. ETT provided help and advice on the essential topic of pathology. KP and JS provided help and advice on the major topic of gynecologic oncology. TA wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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