

## Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer

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In November 2011, the Third European Consensus Conference on Diagnosis and Treatment of Germ-Cell Cancer (GCC) was held in Berlin, Germany. This third conference followed similar meetings in 2003 (Essen, Germany) and 2006 (Amsterdam, The Netherlands) [Schmoll H-J, Souchon R, Krege S et al. European consensus on diagnosis and treatment of germ-cell cancer: a report of the European Germ-Cell Cancer Consensus Group (EGCCCG). *Ann Oncol* 2004; 15: 1377–1399; Krege S, Beyer J, Souchon R et al. European consensus conference on diagnosis and treatment of germ-cell cancer: a report of the second meeting of the European Germ-Cell Cancer Consensus group (EGCCCG): part I. *Eur Urol* 2008; 53: 478–496; Krege S, Beyer J, Souchon R et al. European consensus conference on diagnosis and treatment of germ-cell cancer: a report of the second meeting of the European Germ-Cell Cancer Consensus group (EGCCCG): part II. *Eur Urol* 2008; 53: 497–513]. A panel of 56 of 60 invited GCC experts from all across Europe discussed all aspects on diagnosis and treatment of GCC, with a particular focus on acute and late toxic effects as well as on survivorship issues.

The panel consisted of oncologists, urologic surgeons, radiooncologists, pathologists and basic scientists, who are all actively involved in care of GCC patients. Panelists were chosen based on the publication activity in recent years. Before the meeting, panelists were asked to review the literature published since 2006 in 20 major areas concerning all aspects of diagnosis, treatment and follow-up of GCC patients, and to prepare an updated version of the previous recommendations to be discussed at the conference. In addition, ~50 E-vote questions were drafted and presented at the conference to address the most controversial areas for a poll of expert opinions. Here, we present the main recommendations and controversies of this meeting. The votes of the panelists are added as online supplements.

**Key words:** consensus conference, diagnosis, germ-cell cancer, late toxic effects, long-term follow-up, treatment

## diagnosis, management of the primary tumor and staging

Germ-cell cancer (GCC), cytogenetically characterized by abnormalities of 12p, is the most frequent malignancy in male Caucasians aged 15–40 years. The majority of patients present with a primary tumor in the testis. However, as GCC may also occur in midline structures of the body, an extragonadal germ-cell cancer (EGCC) should always be considered in young men with a retroperitoneal, supraclavicular or mediastinal mass.

Important insights have recently been obtained regarding the etiology of GCC. These relate to the recognition of established risk factors, supposed to be interlinked to each other according to the so-called testicular dysgenesis syndrome and disorders of sex development [1]. In addition, high-risk alleles have been identified [2, 3]. The most significant conclusion is that all these parameters are in accordance with an embryonic initiation of the pathogenesis of GCC, i.e. related to the initial formation and secondary development of the testes.

A histopathological examination of the orchiectomy specimen will establish the diagnosis in patients with gonadal GCC. The histopathological report must address the following issues: localization and size of the tumor, multiplicity, tumor extension (rete testis, tunica albuginea, tunica vaginalis, spermatic cord, scrotum), pT category according to the most recent International Union Against Cancer (UICC) classification, histological type (WHO-ICD-O-M), the presence or absence of carcinoma-*in situ*/testicular intraepithelial neoplasia (CIS/TIN) (synonym: intratubular germ-cell neoplasia) and the presence or absence of vascular invasion of blood or lymphatic vessels. In tumors with mixed structures, each individual component and its estimated relative proportion must be documented. Similarly, evidence of syncytiotrophoblasts should be indicated in seminoma as well

as any sarcomatous elements in spermatocytic seminoma as recommended by the World Health Organization [4–6]. Immunohistochemistry must include detection of alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) for identification of yolk sac tumor and choriocarcinoma, respectively [7]. Vascular invasion can be detected morphologically, supported by immunohistochemical detection of CD31/FVIII. Recent studies demonstrate that applications of pluripotency-related markers (OCT4, NANOG, AP-2 $\gamma$  or LIN28) are highly informative for the detection of CIS/TIN, seminoma and EC, to be combined with different fixation protocols [8]. Because of the clinical importance, it is highly recommended that all histological specimens be assessed by a pathologist experienced in GCC pathology [9, 10].

The issue of a contralateral biopsy in patients with a unilateral gonadal GCC divided opinions [11]. While the need for informing all patients about the pros and cons of a contralateral biopsy remained undisputed, only about a third of panelists recommended a contralateral biopsy at least to high-risk patients (supplementary material S1, available at *Annals of Oncology* online) followed by radiotherapy with 16–20 Gy to eliminate CIS/TIN (supplementary material S2, available at *Annals of Oncology* online). As the benefit of CIS/TIN detection and the possibility of assessing spermatogenesis, fertility is counterbalanced by infertility in 100% and in hypogonadism in ~30% of patients after radiotherapy with the subsequent need for testosterone supplementation, the majority of panelists opted against routine biopsies to detect CIS/TIN. Yet, as the majority of patients with untreated CIS/TIN in the contralateral testis will eventually develop overt GCC within the next 10 years, surveillance programs, e.g. by regular clinical examination and testicular ultrasound, are mandatory and the patients need to be informed that a contralateral GCC might develop with subsequent

hypogonadism and need for testosterone replacement after treatment.

In EGCC, the necessity of testicular biopsies in patients with proven EGCC was likewise questioned. The majority of panelists voted against performing biopsies in EGCC patients when both of the testes were normal upon clinical examination and ultrasound (supplementary material S3, available at *Annals of Oncology* online). Spiral computerized tomography (CT) scans of the thorax, abdomen and pelvis remain the staging investigation of choice (Table 1) [12]. Diagnostic imaging of the brain is recommended in patients with visceral metastases and mandatory in the presence neurological symptoms (supplementary material S4, available at *Annals of Oncology* online). Magnetic resonance tomography imaging (MRI) as an alternative staging procedure to CT scanning should be reserved to selected patient populations (e.g. intolerance to intravenous contrast agents) and to institutions with special expertise using MRI (supplementary material S5, available at *Annals of Oncology* online). Positron electron tomography–computerized tomography scanning (PET–CT) has no role as a staging procedure due to its low additional diagnostic yield over CT or MRI scans and its additional radiation exposure [13, 14].

Serum tumor markers AFP, HCG and lactate dehydrogenase (LDH) should be determined in all patients before and after orchiectomy and in patients with metastatic disease also immediately before chemotherapy. In metastatic patients, these pre-chemotherapy markers—and not the pre-orchiectomy markers—should be used for the correct allocation to the IGCCG prognostic category (supplementary material S6, available at *Annals of Oncology* online) [4–6, 15, 16]. Particular attention should be paid to patients with radiological stage I disease and elevated tumor markers: patients should be monitored with frequent post-orchiectomy serum marker determinations until complete marker normalization before these patients are classified as having true stage I disease. All other patients with an increase of serum tumor markers after

**Table 1.** Initial management of patients with suspected GCC

History and clinical examination
Testicular ultrasound
Serum tumor markers AFP, HCG and LDH <sup>a</sup>
CT of the thorax, abdomen and pelvis <sup>b</sup>
Orchiectomy in patients with gonadal disease <sup>c</sup>
Detailed histopathological report
Option of semen cryopreservation in patients scheduled for chemotherapy

<sup>a</sup>Also after orchiectomy in all patients with elevated markers as well as immediately before chemotherapy in patients with metastatic disease.

<sup>b</sup>CT or MRI scan also of the brain in patients with visceral metastases and/or neurological symptoms or signs.

<sup>c</sup>Orchiectomy should be delayed until completion of chemotherapy in patients with advanced disease at initial presentation and/or imminent organ failure. Patients with normal testes and suspected extragonadal germ-cell cancer (EGCC) may or may not have a testicular biopsy.

GCC, germ-cell cancer; AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; CT, computerized tomography; MRI, magnetic resonance imaging.

orchiectomy must be considered as having metastatic disease. Patients with normal serum tumor markers and equivocal retroperitoneal metastases in CT or MRI scans should be followed closely by repeat scanning or in case of a non-seminoma may receive upfront staging retroperitoneal lymph-node dissection (RPLND) or before a definitive treatment decision is made.

### clinical stage I disease in seminoma and non-seminoma

Clinical stage I in seminoma and non-seminoma is defined as disease limited to the testes with no radiological evidence of metastatic disease and normal serum tumor markers after orchiectomy.

In respect to the optimal management of seminoma stage I, the discussion revealed a spectrum of opinions among panelists (Table 2). The first discussion circled around the issue of prognostic factors. In contrast to the initial analyses from the Canadian group, rete testis infiltration and tumor size >4 cm could not be validated in two prospective series for the identification of seminoma patients with a high risk of occult metastases [17, 18]. However, contrary to these most recent publications, about one half of the panelists still believed that these factors are useful in decision making in seminoma stage I (supplementary material S7, available at *Annals of Oncology* online), since at least the negative predictive value of these factors has been prospectively shown in the most recent Spanish trial [19]. The second discussion focused on the optimal management strategy. Here, no consensus could be achieved. Whereas one-third of panelists considered

**Table 2.** Strategies in clinical stage I seminoma and non-seminoma

Seminoma	
Risk factors for occult metastases: <sup>a</sup>	Tumor size ≥4 cm Invasion of rete testis
Treatment options:	Surveillance (preferred in low risk patients) One cycle carboplatin AUC 7 Adjuvant paraaortic radiation 20 Gy <sup>b</sup>
Non-seminoma	
Risk factors for occult metastases:	Vascular or lymphatic invasion
Treatment options:	Surveillance (preferred in low risk patients) One adjuvant cycle BEP Two adjuvant cycles BEP Primary RPLND (rarely indicated) <sup>c</sup>

<sup>a</sup>Validity of risk factors have been challenged in recent analyses.

<sup>b</sup>Radiotherapy was a less favored adjuvant treatment option due to the long-term risk of induction of secondary malignancies.

<sup>c</sup>Indicated, e.g. in stage I patients with retroperitoneal lymph-nodes of equivocal size who are unwilling to accept surveillance (see the text for further details).

AUC, area under the curve; Gy, Gray; BEP, bleomycin, etoposide, cisplatin; RPLND, retroperitoneal lymph-node dissection.

surveillance the preferred treatment strategy in all stage I seminoma regardless of the risk factors for relapse, others opted for surveillance in 'low-risk' patients with a relapse rate of 5%–12%, and adjuvant treatment in 'high-risk' patients as had been pursued in the Spanish cooperative trial [19]. The use of radiotherapy as adjuvant treatment was less favored among panelists compared with single-agent carboplatin, because of concerns about the induction of secondary tumors even by reduced radiation doses and fields. On the other hand, a minority of panelists still considered surveillance, adjuvant carboplatin and adjuvant radiation as equal options irrespective of the risk factors (supplementary material S8, available at *Annals of Oncology* online) [18–24].

In non-seminoma, vascular invasion remains the most important prospectively validated and most widely accepted risk factor that can be used for treatment stratification [9]. Patients without vascular invasion have a low risk of occult metastatic disease/relapse of around 14%. In contrast, the patients with vascular invasion in the primary tumor have a high risk of occult metastatic disease and relapse of ~50%. Yet, the clinical decisions based upon these data remained controversial (Table 2). About one-third of panelists each favored surveillance in all non-seminoma stage I irrespective of the risk factors, surveillance in low risk and one or two adjuvant cycles of cisplatin, etoposide, bleomycin (BEP) in high-risk patients, respectively. Therefore, adjuvant chemotherapy remained the favored strategy in high-risk clinical stage I non-seminoma. Upfront staging RPLND in all patients was favored only by a small minority of panelists (supplementary material S9, available at *Annals of Oncology* online) [9, 25–29].

Thus, the optimal management of clinical stage I seminoma and non-seminoma remains an area of debate. The risks and benefits of each strategy must be discussed with patients in respect to its immediate and long-term impact, and the patient actively involved in the final decision. Non-compliance with surveillance strategies remained some areas of concern, which will have to be studied prospectively [30, 31].

## first-line treatment in metastatic seminoma and non-seminoma

In early-stage IIA seminoma with small retroperitoneal lymph-node metastases <2 cm, radiotherapy was still considered as an adequate treatment option, but chemotherapy was seen as an alternative or even preferred option among panelists avoiding an ~10% relapse rate (supplementary material S10, available at *Annals of Oncology* online) [18, 32]. In early-stage IIB seminoma, the majority of panelists favored chemotherapy with three cycles of BEP or four cycles of cisplatin and etoposide (EP) over radiation treatment (supplementary material S11, available at *Annals of Oncology* online) (Table 3) [32].

Patients with metastatic seminoma and non-seminoma should be classified according to the IGCCCG prognostic classification [16]. According to the panelists, classic 'Indiana BEP' remains the standard of care in metastatic seminoma and non-seminoma [33, 34]. Pre- and post-

**Table 3.** First-line chemotherapy regimens in metastatic seminoma and non-seminoma

BEP	(repeat cycles every 3 weeks) <sup>a</sup>	reference [97]
Cisplatin	20 mg/m <sup>2</sup> Day 1–5	
Etoposide	100 mg/m <sup>2</sup> Day 1–5	
Bleomycin	30 mg Day 1, 8, 15	
EP	(repeat cycles every 3 weeks) <sup>b</sup>	reference [33]
Cisplatin	20 mg/m <sup>2</sup> Day 1–5	
Etoposide	100 mg/m <sup>2</sup> Day 1–5	
VIP	(repeat cycles every 3 weeks) <sup>c</sup>	reference [98]
Cisplatin	20 mg/m <sup>2</sup> Day 1–5	
Etoposide	75 mg/m <sup>2</sup> Day 1–5	
Ifosfamide	1,2 g Day 1–5	

<sup>a</sup>Three cycles BEP in IGCCCG 'good prognosis' patients; four cycles BEP in IGCCCG 'intermediate prognosis' and 'poor prognosis' patients.

<sup>b</sup>Four cycles EP only in IGCCCG 'good prognosis' patients with contraindications to bleomycin.

<sup>c</sup>Four cycles VIP only in IGCCCG 'intermediate risk' and 'poor risk' patients with contraindications to bleomycin.

VIP, cisplatin, etoposide and ifosfamide.

hydration helps us to prevent renal toxicity. Routine furosemide or mannitol is not required. Neutropenic fever after BEP is infrequent and growth factor support is rarely needed except in individual patients with very advanced metastatic disease and in patients undergoing salvage treatment, who have a higher risk of febrile neutropenia. Growth factor support, empiric antibiotic treatment and antiemetic prophylaxis should be given according to the published guidelines. In 'good prognosis' patients according to IGCCCG (Table 4), three cycles of BEP were preferred to four cycles of EP [33, 34]. The latter were recommended to be used in 'good prognosis' patients with contraindications to bleomycin. Despite the recent European intergroup trial that prospectively compared four cycles of BEP with or without additional paclitaxel four cycles of BEP remain the standard treatment in patients with 'intermediate prognosis' (supplementary material S12, available at *Annals of Oncology* online) [35]. Four cycles of BEP also remain the standard treatment in patients with 'poor prognosis' (supplementary material S13, available at *Annals of Oncology* online) [36]. In intermediate and poor prognosis patients with contraindications to bleomycin, the equally effective combination of cisplatin, etoposide and ifosfamide (VIP) should be used instead of BEP (Table 3). Until the publication of an ongoing French prospective, randomized trial, the majority of panelists did not recommend intensification of first-line treatment by high-dose chemotherapy (HDCT) or recommended to limit the use of HDCT to patients with the highest risk of treatment failure (e.g. extensive liver, bone or brain metastases) (supplementary material S13, available at *Annals of Oncology* online). Patients with an inadequate tumor marker decline should continue to complete first-line treatment (supplementary material S14, available at *Annals of Oncology* online). Only a minority of panelists recommended switching to intensifying chemotherapy in patients with an inadequate marker decline [37, 38]. To avoid overtreatment,

**Table 4.** Prognostic classification of metastatic seminoma and non-seminoma according to IGCCCG [16]

‘Good prognosis’ Seminoma	(seminoma: 90% patients, 86% survival; non-seminoma: 56% patients; 92% survival)		
	any primary tumor location and no extrapulmonary visceral metastases		Normal AFP, any HCG or LDH
Non-seminoma	gonadal or retroperitoneal primary tumor location	AFP	<1000 ng/ml
	and ‘low’ markers	HCG	<5000 U/l
	and no extrapulmonary visceral metastases	LDH	<1.5 × ULN
‘Intermediate prognosis’ Seminoma	(seminoma: 10% patients, 72% survival; non-seminoma: 28% patients; 80% survival)		
	any primary tumor location and extrapulmonary visceral metastases		Normal AFP, any HCG or LDH
Non-seminoma	gonadal or retroperitoneal primary tumor location	AFP	1000–10 000 ng/ml
	and ‘intermediate’ markers’	HCG	5000–50 000 U/l
	and no extrapulmonary visceral metastases	LDH	1.5–10 × ULN
‘Poor prognosis’ Non-seminoma	(16% patients; >48% survival)		
	mediastinal primary tumor or ‘high’ markers or extrapulmonary visceral metastases	AFP HCG LDH	>10 000 ng/ml >50 000 U/l >10 × ULN

AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

caution should be exercised in initiating chemotherapy in stage IIA non-seminoma with normal markers and equivocal or minimally enlarged retroperitoneal nodes. As some of these patients may indeed have pathological stage I disease, close surveillance or staging RPLND is recommended.

### residual tumor resection after first-line chemotherapy

Seminoma with residual tumors after chemotherapy should not be scheduled for post-chemotherapy residual tumor resections (PC-RTR) due to the high morbidity and small therapeutic gain of the procedure in this group of patients. Seminoma with lesions ≥3 cm can be evaluated by PET-CT not earlier than 8 weeks after completion of chemotherapy—the only subgroup of GCC patients in whom PET-CT is recommended (supplementary material S15, available at *Annals of Oncology* online) [39]. The negative predictive value of PET-CT scans is high, and seminoma with negative PET-CT scans should be followed irrespective of the size of the residual lesion. The positive predictive value of a PET-CT scan is less reliable. In PET-CT positive patients after chemotherapy either biopsy, close observation with serial CT scans or, possibly, repeat PET-CT scans were recommended by the majority of panelists (supplementary material S16, available at *Annals of Oncology* online).

According to the panelists, PC-RTR is recommended in all non-seminoma patients with residual tumors ≥ 1 cm within 4–8 weeks after chemotherapy (supplementary material S17, available at *Annals of Oncology* online) comprising the left or right template plus all areas of initial tumor sites. Only a minority of panelists opted for a full bilateral resection in all patients (supplementary material S18, available at *Annals of Oncology* online) [40–43]. In patients with retroperitoneal as well as pulmonary residual lesions, no consensus as to the optimal management could be achieved although a great majority of panelists felt that some form of pulmonary resections was required even in patients with necrosis in the

retroperitoneal PC-RTR specimen (supplementary material S19, available at *Annals of Oncology* online) [44]. The majority of panelist would not consider PC-RTR even in non-seminoma, if the residual tumor is <1 cm in diameter (supplementary material S20, available at *Annals of Oncology* online) [40–48].

Patients with vital cancer at the time of PC-RTR may or may not be scheduled for two cycles of adjuvant chemotherapy (supplementary material S21, available at *Annals of Oncology* online). Patients with IGCCCG intermediate or poor prognosis, those with >10% viable tumor residuals as well as those with positive surgical margins have a better progression-free, but not overall survival with adjuvant chemotherapy. Adjuvant chemotherapy should, therefore, be discussed with these patients, but a surveillance strategy is also justified [49].

As the success of PC-RTR highly depends on the experience and skill of the urologic surgeon, the panelists attempted a definition of an expert center for residual tumor surgery: 20 interventions per surgeon per year as well as immediate and *ad hoc* access to an interdisciplinary team of vascular surgeons, liver surgeons and, possibly, also orthopedic surgeons as well as availability of high-level postoperative support (supplementary material S22, available at *Annals of Oncology* online) [50, 51].

### salvage treatment in seminoma and non-seminoma

Patients with seminoma or non-seminoma who relapse after surveillance should be treated as patients with *de novo* metastatic disease with three to four cycles of BEP depending on their IGCCCG score [16]. This extends to the patients who relapse after adjuvant carboplatin or adjuvant radiotherapy, although the optimal management and outcome in stage I seminoma who relapse after adjuvant treatment are currently unknown. Also unknown is the optimal management and outcome in stage I non-seminoma who relapse after one or two cycles of adjuvant BEP, who should be considered for four cycles of conventional-dose salvage chemotherapy (Table 5).

Seminoma and non-seminoma patients who relapse after full cisplatin-based first-line chemotherapy can be treated using either conventional-dose chemotherapy (CDCT) or HDCT [52–57]. Their prognosis should be assessed using the most recent international prognostic score [54]. No consensus could be reached in respect to their optimal first-salvage management

**Table 5.** Salvage chemotherapy in relapsed seminoma and non-seminoma

Conventional-dose regimens [99, 100]			
VIP	Repeat cycles every 3 weeks		4 cycles
Cisplatin	20 mg/m <sup>2</sup>	Day 1–5	
Ifosfamide	1,2 g/m <sup>2</sup>	Day 1–5	
Etoposide	75 mg/m <sup>2</sup>	Day 1–5	
TIP	(repeat cycles every 3 weeks)		4 cycles
Cisplatin	20 mg/m <sup>2</sup>	Day 1–5	
Ifosfamide	1,2 g/m <sup>2</sup>	Day 1–5	
Paclitaxel <sup>a</sup>	250 mg	Day 1	
VeIP	(repeat cycles every 3 weeks)		4 cycles
Cisplatin	20 mg/m <sup>2</sup>	Day 1–5	
Ifosfamide	1,2 g/m <sup>2</sup>	Day 1–5	
Vinblastine	0,11 mg/kg	Day 1 + 2	
High-dose regimens [52, 53, 56] (require stem cell support)			
Carboplatin <sup>b</sup>	500 mg/m <sup>2</sup>	Day 1–3	3 cycles
Etoposide	500 mg/m <sup>2</sup>	Day 1–3	
Carboplatin	700 mg/m <sup>2</sup>	Day 1–3	2 cycles
Etoposide	750 mg/m <sup>2</sup>	Day 1–3	

<sup>a</sup>Paclitaxel given as a 24 h continuous intravenous infusion.

<sup>b</sup>Carboplatin may be dosed to an area under the curve (AUC) of eight instead of mg/m<sup>2</sup>.

**Table 6.** Risk factors in seminoma and non-seminoma after failure of cisplatin-based first-line treatment

Histology	Favorable seminoma	Unfavorable non-seminoma
Localization of primary tumor	All except primary mediastinal non-seminoma	Primary mediastinal non-seminoma
Response to first-line chemotherapy	CR/NED or PRm–	PRm+ or SD or PD
Progression-free interval	Three months or more after last chemotherapy <sup>a</sup>	Less than 3 months after last chemotherapy
Metastases at relapse	Lymph-node or pulmonary as only metastatic sites	Extrapulmonary visceral metastases <sup>b</sup>
Serum tumor markers at relapse	AFP normal HCG ≤1000 U/l	AFP elevated HCG >1000 U/l
Salvage attempt	First salvage	Second or subsequent salvage

<sup>a</sup>Patients with late relapse relapses >2 years have an inferior prognosis.

<sup>b</sup>Liver, bone or brain metastases.

CR, complete remission; NED, no evidence of disease after surgery; PRm–, partial remission and negative tumor markers; PRm+, partial remission and positive tumor markers; SD, stable disease; PD, progressive disease; AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin.

(supplementary material S23, available at *Annals of Oncology* online). The opinions were divided among panelists and ranged from using HDCT in all relapsed patients irrespective of prognostic factors, to a risk-adapted approach using CDCT in low-risk and HDCT in patients with a high risk of failure, as well as to not using HDCT at all outside clinical trials, neither in first nor in subsequent salvage treatments (Table 6). In the discussion, a minority argued against using any HDCT in GCC despite retrospective data in favor of HDCT in the first-salvage setting and the fact that no conventional-dose regimen has proven to induce long-term remissions in a relevant number of patients when given as second or subsequent salvage treatment [58]. HDCT should be delivered as two or three sequential cycles using high-dose carboplatin and etoposide without additional agents such as ifosfamide, cyclophosphamide or thiotepa (Table 5) [52, 53, 56].

Oxaliplatin, gemcitabine and paclitaxel or combinations thereof have shown activity in the second or third-salvage setting and may be applied as single agents or combinations, if these drugs had not been used previously [59, 60]. Transient responses can also be achieved using oral etoposide.

Patients with complete remissions should be followed, patients with residual masses after salvage chemotherapy should be scheduled for PC-RTR within 4–6 weeks after the normalization of tumor markers or when a low-level marker plateau has been reached. Extensive surgery of all residual lesions after completion of chemotherapy is an essential part of any salvage treatment [52, 56, 59].

## desperation surgery

Desperation surgery refers to the situation of a high-level marker plateau or overtly rising markers after administration of salvage chemotherapy in patients with potentially resectable disease. With this approach, long-term survival may be achieved in some patients. No conclusive data allow a definitive prognostic assessment. HCG elevation and high AFP levels before surgery, residual retroperitoneal disease >5 cm and a previous RPLND have been reported to portend a poor prognosis [61]. However, according to the panelists, desperation surgery should be attempted in all patients in whom no reasonable chemotherapeutic options are available, and who have cancer that can potentially be completely resected (supplementary material S24, available at *Annals of Oncology* online).

## late relapse of seminoma and non-seminoma

Some discussions circled around the optimal definition of late relapse. There was a clear vote that the term late relapse should be limited to relapses occurring 2 years or later after full cisplatin-based chemotherapy. This definition excludes patients who relapse after adjuvant treatment or during surveillance who are usually cured by chemotherapy alone. Patients with late relapse represent a rare subgroup with an adverse prognosis as well as a high frequency of teratoma and/or non-GCC elements, who will have to be managed differently

than other cohorts with GCC relapses (supplementary material S25, available at *Annals of Oncology* online). Patients with resectable late relapse should undergo immediate surgical removal of all tumor manifestations at an experienced reference center irrespective of serum tumor marker levels [62, 63]. No consensus could be achieved, however, on the management of unresectable late relapse, although the majority recommended CDCT (supplementary material S26, available at *Annals of Oncology* online) [64].

## special scenarios in seminoma and non-seminoma

Human immunodeficiency virus (HIV)-positive GCC patients should be managed in an identical fashion to patients without an HIV infection. However, highly active antiretroviral therapy should be given concurrently during chemotherapy and antimicrobial prophylaxis instituted, if CD4 counts fall below 200 cells/ $\mu$ l (supplementary material S27, available at *Annals of Oncology* online) [65, 66].

In patients with advanced metastatic GCC and/or those with impending organ failure orchiectomy should be postponed until the completion of chemotherapy (supplementary material S28, available at *Annals of Oncology* online). The high risk of life-threatening treatment-related complications or even death in these patients can be reduced by avoiding full-dose chemotherapy as initial treatment [67]. However, data on how to optimally administer such a pre-phase induction chemotherapy are scarce. The majority of panelists considered 2 days of cisplatin plus etoposide an acceptable way to start chemotherapy in patients with a very high-tumor burden and normal renal function and continue with four cycles of full-dose BEP or VIP from day 11 onwards, when the patients have stabilized (supplementary material S29, available at *Annals of Oncology* online). In patients presenting with additional acute renal failure, bleomycin should not be used. The majority of panelists opted to start pre-phase induction chemotherapy either with carboplatin alone or with the combination of carboplatin and etoposide and continue with four cycles of full-dose BEP or VIP from on day 11 onwards when the patients have stabilized and recovered with their renal function (supplementary material S30, available at *Annals of Oncology* online). In patients with chronically impaired renal function, there was no consensus on the issue of replacing cisplatin by carboplatin (supplementary material S31, available at *Annals of Oncology* online).

Patients with brain metastases present a particular challenge. There was consensus that these patients have an inferior prognosis compared with other GCC patients. At initial diagnosis, panelists recommended immediate upfront chemotherapy. Opinions were divided, however, in respect to additional surgery or irradiation (supplementary material S32, available at *Annals of Oncology* online). In the even more unfavorable patients relapsing with brain metastases, the majority of panelists voted for full salvage chemotherapy, but again no consensus could be achieved in respect to additional treatments (supplementary material S33, available at *Annals of Oncology* online).

There was a strong and unequivocal vote to immediately transfer patients with advanced disease and particularly those with imminent organ failure to units experienced in treating these high-risk patients: with an agreement of about two-thirds of the panelists these were defined as centers treating >10 patients for metastatic GCC per year including 5 for salvage or intermediate or poor prognosis [68].

## reproductive health, late toxic effects and HRQoL

Testicular cancer patients are at risk to experience fertility distress and difficulty in fathering children. Fertility problems often precede GCC diagnosis and infertility is an accepted risk factor for GCC development [69]. The fatherhood rate among testicular cancer survivors wishing to father a child is ~70% within 15 years having a strong correlation with treatment intensity. Compared with the general population, the 10-year post-treatment paternity rate remains significantly reduced [70–72]. No increased risk of malformations is found in children of GCC survivors [73]. Patients should be counseled about these figures and pre-chemotherapy semen cryopreservation offered [74].

Male hypogonadism after treatment as defined by total testosterone serum levels <8 nmol/l is frequent and varies between 11% and 35% among GCC survivors [75]. Therefore, the determination of testosterone is recommended during follow-up and replacement offered to all patients with low testosterone levels and/or symptoms of hypogonadism to prevent long-term sequelae [76, 77].

There is about a two- to threefold increased risk of late cardiovascular toxicity (coronary heart disease, myocardial infarction, congestive heart failure and stroke) among GCC survivors treated with chemotherapy or radiotherapy compared with the general population, which is more prominent in GCC patients treated at a younger age or treated with a combination of chemotherapy and radiation [77–79]. Overall, the cumulative risk of such events over 20 years may be as high as 18%. Death mainly from coronary heart disease accounts for a higher overall non-cancer mortality among long-term GCC survivors. The exact reasons for late cardiovascular toxicity are unknown, but may be related to a direct endovascular damage and accelerated atherosclerosis or vascular ageing induced by cisplatin. The onset of a Raynaud phenomenon might possibly represent a clinical biomarker to identify survivors with augmented atherosclerosis, who could benefit from prophylactic interventions [80–82].

The frequency of metabolic syndrome is also increased and occurs in ~20%–30% of long-term GCC survivors [77–80]. Particularly relevant is the fact that the onset of metabolic syndrome is much earlier than expected from the general population starting ~3–5 years after GCC treatment [80].

Other clinical or subclinical organ toxicities such as pulmonary toxicity, renal toxicity, ototoxicity and neurological sequelae are frequent and dose-related [81, 82].

According to the available data, the relative risk of a second solid non-germ-cell tumor is approximately doubled after

radiotherapy or chemotherapy. The combination of both treatment modalities is associated with a threefold increased risk. The figures are particularly high for malignancies in the gastrointestinal and urinary tract. Solid second tumors usually occur  $\geq 10$  years after treatment as opposed to chemotherapy-induced leukemias which commonly emerge within one decade after treatment. The estimated cumulative risk of leukemia is 0.5% and 2%, after cumulative etoposide doses of  $< 2 \text{ g/m}^2$  and  $> 2 \text{ g/m}^2$ , respectively [83].

Health-related quality of life (HRQoL) in long-term GCC survivors seems to be similar to the normal male population, but persisting long-term treatment-related side-effects show a strong association with both impaired physical and mental HRQoL [84, 85]. The level of anxiety is higher in GCC survivors than in the general male population, possibly 'triggered' by the fear of recurrence. Anxiety and fear of recurrence might be higher in single or unemployed men and those with a lower education. GCC survivors with a more 'neurotic personality' (e.g. higher level of nervousness and vulnerability to stress) also seemed to have a higher level of anxiety and fear of recurrence and to report more side-effects [86–88].

The prevalence of self-reported chronic fatigue and cognitive complaints are common among patients with GCC, but not significantly related to cognitive test performance. No studies have so far demonstrated an elevated rate of objectively assessed cognitive difficulties in long-term GCC survivors [88, 89].

As there will be an increasing number of GCC survivors in all European countries, the aspects of late toxic effects and HRQoL should be addressed in the management of all GCC survivors [83]. GCC survivors need counseling on a healthy lifestyle in order to minimize the risk factors such as smoking and physical inactivity. Patients should be screened and treated for known risk factors such as high blood pressure, hyperlipidemia and testosterone deficiency. And, perhaps most importantly, GCC patients should be provided with a written cancer survivorship plan at the end of their treatment that addresses late toxic effects and HRQoL in addition to the risks of recurrence and cancer-specific follow-up.

## follow-up schedules

The dramatic increase in the exposure to medical radiation since the 1980s from 0.5 mSv to  $\sim 3.0$  mSv is threatening for young GCC patients because of the related risk of radiation-induced secondary tumors [90–92]. Many follow-up recommendations that have been published most likely expose GCC survivors to unnecessary radiation. Statistically, in long-term GCC survivors, the risks from radiation exposure might even be higher than the risk, e.g. from a late relapse GCC [93]. The issue of replacing CT by MRI scan was one area of controversy, but considered as not feasible in the majority of European countries by the majority of panelists. Rather every effort should be made to reduce the frequency of CT scans and limit their total number. Similarly, it was stressed that PET–CT scanning has no role in the follow-up of GCC patients.

There were controversial discussions and several E-votes on the issues of follow-up (supplementary material S34–39,

available at *Annals of Oncology* online). No consensus as to an authoritative follow-up schedule or recommendation for an optimal follow-up duration could be reached. However, those suggested during the meeting closely resembled most recently published follow-up schedules [94–96]. Several discussants stressed the fact that recommendations for follow-up will have to be adapted according to the national and institutional requirements. These need to be, however, oriented towards published recommendations and large differences avoided [94–96]. Several aspects should be considered in designing follow-up schedules: the schedules should be straightforward and easy to follow, the risk of recurrence has to be taken into account (e.g. high versus low risk), the localization of relapse should be considered (e.g. retroperitoneal versus pulmonary relapses) and the time to relapse should be incorporated into follow-up plans (e.g. early versus late relapses). Except in rare clinical circumstances or suspected late relapse, it was recommended that no routine CT scans be carried out beyond 5 years of follow-up [23, 94–96].

## summary

Whereas many of the discussions during the Third European Consensus Conference on Diagnosis and Treatment of GCC represented optimizing and fine tuning of the treatment particularly of GCC patients with rare presentations and those, who are 'difficult-to-treat', the goals for the majority of GCC patients are straightforward: (i) close multidisciplinary collaboration in diagnosis and management; (ii) active involvement of patients in management decisions; (iii) reducing treatment burden by offering surveillance strategies to clinical stage I patients whenever possible; (iv) maintaining cure and optimizing treatment as well as supportive care for patients with metastatic disease; (v) optimizing the care for GCC survivors by addressing issues such as fertility, late toxic effects and HRQoL through development of straightforward and rational follow-up and survivorship plans.

There was a strong and uniform consensus that these goals can best be achieved by centralization of care at experienced centers particularly for patients with intermediate and poor prognosis at initial presentation as well as for all relapsed GCC patients. Too many patients with GCC still suffer from unnecessary toxic effects or even die without ever having had the chance of optimal expert treatment.

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