Methods: An *in-silico* analysis of the EMT markers on TGCTs was performed using the cBioPortal software. Cisplatin-resistant cells (NTERA-2R) were derived by incubation with stepwise increasing cisplatin concentrations during the 8 months and EMT markers and stemness were analyzed by real-time PCR and Western blot. The colony formation and migration cell capacity were also evaluated.
Results: The *in-silico* analysis showed that among the transcription factors, Slug was the only one that had an impact on disease/progression-free survival. Slug showed a positive correlation with markers related to EMT, Cancer Stem cells, invasion and migration and with some signaling pathways including Notch, Wnt and TGF-β. The protein and gene expression analysis of NTERA-2R showed an increase of EMT markers (Fibronectin, Vimentin, α-SMA, Col1A1), EMT inducers (Slug and TGF-β) and CSC marker (CD44). NTERA-2R had an increase in the colony formation and migration. Understanding the molecular mechanisms that induce EMTs in TGCTs will allow a better knowledge of cancer development, metastasis and cisplatin resistance.

GCT-76 Cisplatin resistance in the ovarian yolk sac tumour cell line is associated with upregulation of adult cancer stem cell (CSC) markers

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Background: Ovarian yolk sac tumour (YST) represents a highly malignant rare neoplasm. Cisplatin resistance emerging during the treatment of ovarian YST represents a significant clinical challenge. Molecular profiling of a stable *in vitro* generated chemoresistant human ovarian YST subclone NOY-1 CisR was performed in order to unravel mechanisms of cisplatin resistance and exploring potential targeting strategies to overcome this chemoresistance.
Methods: A chemoresistant subclone of YST cell line NOY-1 was derived by continuous sublethal dose exposure to cisplatin *in vitro*. The obtained stable chemoresistant subclone NOY-1 CisR was characterized using flow cytometry, RNAseq and methylation (EPIC) profiling, targeted gene expression, protein arrays, and functional assays. Tumorigenicity *in vivo* was determined using an immunodeficient mouse model. The chemoresistant subclone was treated with inhibitors interfering with CSC properties to examine possible chemosensitization to cisplatin treatment.
Results: NOY-1 CisR subclone exhibited seven-fold higher resistance to cisplatin, cross-resistance to oxaliplatin and carboplatin, increased migratory capacity and tumorigenicity. Increased expression of genes associated with stemness such as prominin-1 (CD133), ATP binding cassette subfamily G member 2 (ABCG2), aldehyde dehydrogenase 1 isoform A3 (ALDH1A3), ALDH3A1 isoform correlating with reduced gene and promoter methylation, and higher overall ALDH activity were detected in the NOY-1 CisR subclone. The CSC targeting agents salinomycin and tunicamycin were significantly more toxic for the NOY-1 CisR subclone. Pretreatment with napabucasin resensitized the cells to cisplatin. In summary, we identified CSC markers associated with cisplatin resistance and showed that their targeting may represent a novel treatment option for chemorefractory YST.

Global Challenges in GCT Care

GCT-77 Burden of late effects and challenges faced in the long-term follow-up of paediatric germ cell tumour survivors: A report from India

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Background: Survivors of paediatric extracranial germ-cell-tumours (PEGCTs) have varying burden of late-effects, depending on host factors and treatment exposures. Long-term follow-up is especially challenging in survivors from resource-limited settings.
Material and methods: Data regarding demographics, treatment details and late toxicities (graded as per National-Cancer-Institute Common-Terminology-Criteria for Adverse Events (NCI-CTCAE) were retrieved from the prospectively maintained database of the 'After-Completion-of-Treatment' (ACT) Clinic, Tata Memorial Hospital, Mumbai, India.
Preliminary results: There were 171 5-year survivors of PEGCTs (female:male = 1.2:1), treated 1982–2013. Median-age at diagnosis was 4 years (range 6 mo–18 years), median follow-up duration 9 years (5–29 years) and median-age at last follow-up 17 years (5–42 years). Most (75%) had received chemotherapy and surgery; the rest had received combinations of surgery, chemotherapy and radiation. Around 40% had at least one documented late toxicity, with grade 2 toxicities in 7% and grade 3 toxicities in 10%. Three survivors had second malignancies: 2 gonadal adenocarcinoma and 1 Ewing sarcoma; all subsequently died. Common late-effects included (in % tested) abnormal pulmonary function, asymptomatic (25%) and symptomatic (1%), abnormal audiometry without intervention (28%), requiring hearing aid (6%), and hypogonadism (13 females, all post bilateral oophorectomy and on hormone replacement; 1 married). Of 9 documented married female survivors, 8 had normal reproductive outcomes. Only a single male survivor had documented azoospermia, post testicular radiation. Notably, 34.5% of survivors were lost to long-term follow-up. This is of concern since 20% of survivors had late effects requiring intervention. Risk-adapted treatment approaches with frequent interval-monitoring for toxicities will assist reduction of late-sequelae.

Radiotherapy

GCT-78 Role of radiotherapy for extracranial germ cell tumours: A re-visit

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Background: During the pre-cisplatin era, radiotherapy had a significant role in the management of extracranial (gonadal and extragonadal) germ cell tumours (GCTs). The evolution of highly effective primary and salvage chemotherapy regimens in the Western world made radiotherapy obsolete in the management of extracranial GCTs. Recognition of significant long-term side effects of older radiotherapy techniques has also contributed to the diminished use

of radiotherapy. However, in the modern era of high precision radiotherapy techniques including particle beam therapy, it is important to re-visit the therapeutic efficacy of radiotherapy in the primary and salvage treatment of patients with extracranial GCTs.
Methods: Systematic review of radiotherapy in the primary and salvage treatment of extracranial GCT patients.
Results: Curative radiotherapy is currently reserved only for focal residual, refractory or recurrent disease which cannot be salvaged with surgery or chemotherapy. Radiotherapy is also effective in obtaining an effective palliation in metastatic relapses. Utility of radiotherapy should be carefully evaluated in the management of patients with extracranial GCTs in the low- and middle-income countries where availability of chemotherapy resources are limited.

GCT-79 Status and recommendations for radiotherapy within interdisciplinary treatment concepts of paediatric extracranial germ cell tumours

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Background: Radiotherapy (RT) has no standardized role in treatment concepts for paediatric extracranial/extragonadal germ cell tumours. We would like to further elaborate the role of external beam RT.
Methods: Literature and current protocols were reviewed. RT data and outcome of the MAKEI 96 study together with institutional experiences were retrospectively evaluated.
Results: According to recent protocols like MAKEI 96, RT is only considered for recurrent or residual disease after intensive multimodal therapy and particularly for mediastinal and sacrococcygeal localizations. However, data supports that RT (≥45 Gy) seems to be beneficial for local control (LC) [1]. The majority of patients are irradiated on an individual basis according to heterogeneous dose concepts. Within the analysis of the MAKEI study, 36 patients (median age 12 y, 0.1–18 y, RT in 1987–2017) with different histological findings (predominantly dysgerminoma and yolk-sac tumour) in several localizations (particularly sacrococcygeal and ovarian tumours) could be reviewed for RT strategies. So far, RT concepts varied widely (total dose 20–60 Gy, single dose 1.5–4 Gy). More recently, highly conformal techniques were increasingly used (n = 7). RT is effective to achieve and support LC. Due to possible sequelae, RT needs to be used with caution and every case should be discussed in interdisciplinary boards. However, recommendations for a standardized RT-concept are needed and should be implemented in a prospective treatment protocol for further prospective evaluation and quality assurance of RT. Furthermore, highly conformal techniques e.g. proton therapy should be considered to limit the dose burden to normal tissue in paediatric patients.

Reference

[1] Schneider *et al.*, 2001 Treatment of recurrent malignant sacrococcygeal germ cell tumors: analysis of 22 patients registered in the German protocols MAKEI 83/86, 89, and 96. *JCO*.

Late Effects and Quality of Survival

GCT-80 Late effects and quality of survival

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Background: The 5-year survival for children, adolescents and young adults (CAYA) treated for cancer has increased from 30% in the 1970s to more than 80% at present. There are up to 300,000 childhood cancer survivors in Europe and this number is increasing. Years after treatment, CAYA cancer survivors are at high risk for developing health and psychosocial late effects, resulting in excess morbidity and mortality compared the general population. The impact on the quality of life (QoL) of survivors and their families are significant. CAYA cancer survivors, especially germ cell tumour survivors, are at increased risk for fertility impairment if cancer treatment adversely impacts reproductive organ function. Survivors and their families highly desire having biological children. Treatment that involves reproductive organs can cause impaired spermatogenesis, testosterone deficiency, and physical sexual dysfunction in male CAYA cancer survivors. Female CAYA cancer survivors are at increased risk of primary ovarian insufficiency associated with infertility but also with other sequelae secondary to estrogen deficiency, such as osteoporosis, cardiovascular disorders, impaired psycho-social well-being, and compromised sexual health.
Methods: Literature and guideline review.
Results: Clinical practice guidelines (GPG) can facilitate these survivors' access to optimal surveillance and management of potential adverse effects that could improve cancer survivors' health and quality of life. PanCare (www.pancare.eu) and the International Late Effects of Childhood Cancer Guideline Harmonization Group (www.ighg.org), developed evidence-based harmonized surveillance recommendations for gonadotoxicity in male and female CAYA cancer survivors, and CPG for fertility preservation in both male and female CAYA cancer patients.

GCT-81 Survivorship and the True North (TrueNTH) Testicular Cancer Tool

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Background: Testicular cancer survivors (TCS) suffer from various short-term and long-term physical, psychological, and social consequences of diagnosis and treatment. Some TCS experience high levels of clinical anxiety and distress. Psychological distress immediately after diagnosis can be a significant problem; over 50% of men reported a 'crisis reaction' soon after diagnosis. Since existing supports focus on long-term survivors, the provision of information and peer-support immediately post diagnosis may significantly reduce distress and fulfil this unmet need.
Methods: TrueNTH Testicular Cancer (TC) is a web-based resource, optimised for mobile devices that is funded and operated by the Movember Foundation. TrueNTH TC provides personalised information and peer support to newly diagnosed TC patients, and comprises of Testicular cancer and treatment related information, 'Ask an Expert' functionality providing direct access to the knowledge base of TC experts and men with a lived experience and 'Connect with a man' functionality that provides peer-support from a matched TCS. Our