

Special Session (Mon, 21 Sep, 14:00–15:00) Management of peritoneal disease

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INVITED

Present and future of HIPEC (hyperthermic intraperitoneal chemotherapy) in colorectal carcinomatosis

D. Elias¹. ¹Institut Gustave Roussy, Villejuif, France

In 2009, the treatment of colorectal peritoneal carcinomatosis (PC) with curative intent must be proposed in selected patients. More and more guidelines have included this therapy. The principle is to perform a complete cytoreductive surgery (CRS) to treat the visible tumour disease (>1 mm), and to use HIPEC to treat the non visible remaining tumour disease. HIPEC is contraindicated if the first step (complete cytoreductive surgery) is not reached. Postoperative mortality rate is acceptable, ranging from 4 to 8%. Two large multicenter registries including more than 500 patients treated with this combined approach reported median survival of more than 30 months and 5-year survival of more than 30% [1,2]. When considering the results of experimented centres, 5-year survival rate range between 40 and 50% [3–5]. This is similar to the results obtained with hepatectomy for liver metastases, leading us to consider that peritoneum is an organ like liver and that using the good therapy for each organ results in the same survival [6].

Indications of CRS plus HIPEC concerns the patients with a good general status, with no extraperitoneal localization and with a peritoneal score extent (Sugarbaker's index) lower than 20–24. Techniques of HIPEC are multiple and not yet standardized.

A randomized Dutch trial compared classical systemic chemotherapy to CRS + HIPEC with mitomycin C: 2-year survival rate was 16% in the control group versus 43% in the HIPEC group ($p = 0.01$) [7]. A non randomized study compared, for similar patients (PC was potentially resectable in both groups) recent systemic chemotherapy to CRS + HIPEC with oxaliplatin: median survival was 24 months in the first group versus 63 months in the second [5]. So, the package CRS + HIPEC seems efficient, with a predominant impact of complete CRS. The next step is to appreciate the real impact of HIPEC by itself: a multicentric randomized trial is on going in France comparing, after complete CRS, HIPEC versus no HIPEC.

A new concept is to make effort to treat PC earlier. Treating PC at an early stage is less morbid and gives better survival. But the only way to early detect PC is to perform a second look. This was successfully proposed to patients presenting a high-risk to develop PC: asymptomatic PC was discovered and treated in 55% of the patients [8]. This study also showed that HIPEC should be performed even if no macroscopic PC was found. In these high-risk patients, a randomized trial comparing the classical attitude (adjuvant systemic chemotherapy alone) to the same plus second-look and HIPEC will begin soon.

References

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INVITED

Comprehensive management of gastrointestinal cancer: Focus on appendiceal mucinous neoplasms, primary gastric cancer and gastric cancer with peritoneal seeding

P. Sugarbaker¹. ¹Washington Cancer Institute, Surgical Oncology, Washington DC, USA

Appendiceal mucinous neoplasms with peritoneal metastases are currently treated as a standard of care using cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. In order to make this assessment of data regarding management of this disease long term (20 year) follow-up was necessary.

Advanced gastric cancer at stage III or resected stage IV has a poor prognosis. A recent meta-analysis included randomized studies testing all forms of intraperitoneal chemotherapy. Ten were appropriate for data extraction. A significant improvement in survival was seen when chemotherapy was added to gastrectomy (HR = 0.60; 95% CI = 0.43–0.83; $p = 0.002$). The use of chemotherapy was associated with an increased risk of intraabdominal abscess and neutropenia.

In treating gastric cancer with peritoneal seeding, perioperative intraperitoneal chemotherapy when added to gastrectomy will prolong survival

if the treatments can be safely completed. Patient selection for these modest improvements in survival is important because the treatments are of necessity very aggressive. There are a few long term survivors (10%).

Special Session (Mon, 21 Sep, 14:00–15:00) Advances in fertility preservation for children and adolescents with cancer

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INVITED

Improving success rates of sperm banking in adolescents

L. Schover¹. ¹UT M.D. Anderson Cancer Center, Department of Behavioural Science, Houston, USA

Adolescent boys are excellent candidates for banking sperm before their cancer treatment. They often have malignancies, such as testicular cancer or Hodgkin lymphoma that have high rates of long-term survival. Once they have reached the stage of puberty in which spermatogenesis occurs, a number of recent surveys show that most have semen quality quite adequate for cryopreservation, particularly with modern infertility treatments such as in vitro fertilization with intracytoplasmic sperm injection.

However, the percentage of eligible teens who bank sperm is far from optimal. In many cancer centers in the United States and Europe. Some of the lack is due to failure to provide education and referrals on the part of the oncology treatment team. Recent efforts have focused on improving oncologists' knowledge about the benefits of sperm banking, producing appropriate patient education materials, and encouraging the involvement of oncology nurses and social workers in the process of counseling the family. It is also important to have a sperm bank either within the oncology treatment center or in a convenient location nearby. In the United States, some sperm banks offer express mail kits so that semen can be collected at home, mixed with a cryopreservative, and sent to a more distant laboratory. Some loss of semen quality is likely, but it is a better option than foregoing fertility preservation.

Patient and family factors also can be barriers to banking sperm. In the United States, out-of-pocket costs may not be affordable for poor or working class families, although some subsidies and payment plans are available. In Europe and Japan, sperm banking is typically covered under national health plans. More, often psychosocial barriers include fear that banking sperm will delay cancer treatment (despite the fact that even one stored sample is worthwhile), difficulty for young men in producing a sample by masturbation when they feel ill and have little privacy, the emotional pressure of feeling that they could be losing their chance to have a biological child if they cannot produce a sample, cultural and/or religious beliefs about masturbation and assisted reproduction, difficulty envisioning wanting to be a father later on in life, and emotional pressure from parents that can exacerbate the young man's anxiety. In one British study, teens were less likely to produce a semen sample when a parent accompanied them to the sperm bank.

A number of solutions can overcome these psychosocial barriers. A professional or slightly older peer counselor can discuss the semen collection process and suggest ways to feel more comfortable. Having a sound-proofed, homelike collection room with erotic magazines or DVD's is highly desirable. Teens can be encouraged to bring a personal music player to shut out noise and help with the mood. Any erotic materials furnished in the collection room should be soft core and conventional, although for teens who are gay, same-sex materials could be provided. Teens who are more sexually experienced could also bring their own DVDs and even a small DVD player. Depending on the age of consent in a country, the patient's committed partner could help in semen collection by providing manual stimulation. Having a vibrator available may also help.

For teens who are too ill or anxious to provide a semen sample, options include a medical grade vibrator, electroejaculation under anesthesia, or sperm extraction from the epididymis by a urologist or andrologist.

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INVITED

Advances in ovarian cryopreservation

J. Donne¹, M.M. Dolmans¹. ¹Université Catholique de Louvain, Department of Gynecology, Brussels, Belgium

Advances in the diagnosis and treatment of childhood, adolescent and adult cancer have greatly increased the life expectancy of young women with cancer, but have resulted in a growing population of adolescent and adult long-term survivors of childhood malignancies, who may experience premature ovarian failure (POF) and infertility as a result of aggressive chemotherapy and radiotherapy treatments (indicated for both cancer and bone marrow transplantation (BMT)).

Ovaries are very sensitive to cytotoxic treatment, especially to radiation and alkylating agents, which are classified as high risk for gonadal dysfunction. The type and dose of chemotherapeutic agent are known to influence the progression to ovarian failure, with alkylating agents increasing the risk of POF by a factor of 9. Cyclophosphamide is the agent most commonly implicated in causing damage to oocytes and granulosa cells in a dose-dependent manner. This follicular destruction generally results in the loss of both endocrine and reproductive functions, depending on the dose and the age of the patient. Indeed, Larsen *et al.* reported a four-fold increased risk of POF in teenagers treated for cancer, rising to 27-fold in women between 21 and 25 years of age.

Several options are currently available to preserve fertility in cancer patients and allow them to conceive when they have overcome their disease: embryo cryopreservation, oocyte cryopreservation and ovarian tissue cryopreservation. The choice of the most suitable strategy depends on different parameters: the type and timing of chemotherapy, the type of cancer, the patient's age and partner status. The only established method of fertility preservation is embryo cryopreservation, according to the Ethics Committee of the American Society for Reproductive Medicine, but this option requires the patient to be of pubertal age, have a partner or use donor sperm, and be able to undergo a cycle of ovarian stimulation, which is not possible when chemotherapy has to be initiated immediately or when stimulation is contraindicated according to the type of cancer. Cryopreservation of oocytes can be performed in single women who are able to undergo a stimulation cycle, although the effectiveness of this technique is still low, with pregnancy and delivery rates ranging from 1 to 5% per frozen oocyte.

Cryopreservation of ovarian tissue is the only option available for prepubertal girls, and for women who cannot delay the start of chemotherapy. Ovarian tissue can theoretically be frozen using three different approaches: as fragments of ovarian cortex, as entire ovary with its vascular pedicle or as isolated follicles. The indications for cryopreservation of ovarian tissue in case of malignant and non-malignant disease are summarized in a recent review. For patients who need immediate chemotherapy, ovarian tissue cryopreservation is the only possible alternative.

The main aim of this strategy is to reimplant ovarian cortical tissue into the pelvic cavity (orthotopic site) or a heterotopic site like the forearm or abdominal wall once treatment is completed and the patient is disease-free. To date, we have performed 11 reimplantations of cryopreserved ovarian cortex. All of them have recovered their ovarian function.

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INVITED

Advances in male fertility preservation

A. Pacey¹. ¹University of Sheffield, School of Medicine and Biomedical Sciences, Sheffield, United Kingdom

For post-pubertal males diagnosed with cancer (or any other medical condition where the curative treatment has a high risk of causing subsequent infertility) the technology of sperm banking is now well established. This means that if infertility is subsequently present after medical treatment has finished, the male has the option to use his frozen sperm samples, in association with an appropriate Assisted Reproductive Technology (see below), in order to try and father a child at a later date. It is estimated that many thousands of men each year across Europe will bank their sperm prior to cancer treatment and may keep it in storage for many years. However, audit data suggests that of these relatively few men (10–20%) actually return to use their samples in assisted conception. This may reflect the fact that in a high proportion of men natural fertility is restored following treatment, or that the initial motivations for banking sperm may not have been for reproductive reasons. Alternatively, it may be that access to assisted conception services (e.g. funding) is too difficult or that the treatments involved are too off-putting.

For those men who do use their frozen sperm, the options in assisted conception include relatively simple treatments such as Intra-uterine insemination (IUI). This is where a prepared sample of sperm is inseminated into his partner's uterus at the most fertile part of her cycle. However, this can only be achieved when the post-thaw quality of sperm is very good and where enough sperm were banked initially to allow several attempts at treatment. Where banked sperm is too poor, or the amount of sperm too limited, more complex assisted conception techniques such as in vitro fertilisation (IVF) or Intra-Cytoplasmic Sperm Injection (ICSI) need to be attempted. Successful births have been reported from sperm samples that have been frozen nearly 30 years and there is no evidence that babies born from the use of frozen sperm are any less healthy than their naturally conceived counterparts.

Sadly, for pre-pubertal boys (or any male who is temporarily azoospermic at the time sperm banking is first attempted) there are currently no proven strategies to protect fertility. Although experimental strategies have been attempted, none have been proven and entered mainstream clinical practice.

Scientific Symposium (Mon, 21 Sep, 16:15–18:15) Genetic aberrations in lung cancer

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INVITED

The role of biomarkers in selecting the right targeted agent to combine with chemotherapy

G. Giaccone¹. ¹Medical Oncology Branch CCR, National Cancer Institute NIH, Bethesda MD, USA

Several genetic biomarkers have been investigated retrospectively and some prospectively to select patients for single agent treatment. The most successful example is the use of EGFR mutations to select patients to treat with EGFR tyrosine kinase inhibitors, in first line treatment of advanced non-small cell lung cancer (NSCLC). However, when it comes to combination of chemotherapy and a targeted agents, the use of biomarkers is less intuitive, because of the potentially confounding markers that make tumors more sensitive to chemotherapy and their interaction with the potential targets of targeted agents. Genetic markers of chemotherapy efficacy has also been investigated, but they have so far not been used extensively for selection of treatment outside clinical trials. Furthermore, for targeted agents such as the angiogenesis inhibitors, there is really no good genetic marker that is well established for patient selection, and combination of chemotherapy and angiogenesis inhibitors has been performed empirically, with variable results.

Probably the use genetic markers of targeted agents activity when they are combined with chemotherapy, should take into consideration the effect of these markers when the targeted agents are given alone. For instance, it is likely that patients with advanced NSCLC who have an EGFR mutation or an Alk translocation will respond better to combinations of EGFR tyrosine kinase inhibitors or Alk inhibitors, also when combined with chemotherapy. However, the effects of combinations in unselected patients have been so far surprising, in that either no additive effect has been shown or even detrimental effects. So, clearly more efforts should be devoted to investigated markers that would identify patients who benefit, also for combined treatments and these markers may somewhat differ from those that are used for single agent selection.

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INVITED

Molecular mechanisms of lung cancer development – how to use our knowledge of molecular biology in more effective therapies

Y. Yarden¹, S. Lavi¹. ¹Weizmann Institute of Science, Department of Biological Regulation, Rehovot, Israel

Growth factors and their transmembrane receptors contribute to all phases of tumor progression, from the initial phase of clonal expansion, through angiogenesis to metastasis. A relevant example comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinase, namely ErbB-1/EGFR, which belongs to a prototype signaling module that drives carcinoma development. The extended module includes two autonomous receptor, EGFR and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor (ErbB-3). This signaling module is richly involved in human cancer and already serves as a target for several cancer drugs. Due to inherent complexity and a large amount of experimental data, we propose a systems approach to understanding ErbB signaling. EGF – to – ErbB signaling is envisioned as a bow-tie configured, evolvable network, sharing modularity, redundancy and control circuits with robust biological and engineered systems.

Along with autocrine loops involving one of the seven ligands of EGFR, and overexpression of EGFR due to amplification of the corresponding genomic locus, mutations within the catalytic tyrosine kinase domain are prevalent in lung cancer, whereas deletions in non-catalytic portions of EGFR are frequently diagnosed in brain tumors of glial origin. Concentrating on catalytic site mutants of EGFR, we found that mutant receptors gain oncogenic activity by evading a universal mechanism of receptor inactivation. This mechanism entails recruitment of an ubiquitin ligase, CBL, to the active receptor, thereby enabling ubiquitinylation and sorting for lysosomal degradation. How exactly EGFR mutants evade CBL and ubiquitinylation remains unknown, but potential mechanisms include enhanced heterodimerization with HER2/ErbB-2 or altered interactions with the HSP90 chaperone. The implications of the mode of oncogenesis of EGFR mutants will be discussed in the context of drug interceptors.