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Biomechanics Based Microfluidic Biochip for the Label-free Isolation and Retrieval of Circulating Tumour Cells

C.T. Lim[1], S.J. Tan[2], W.T. Lim[3], M.H. Tan[3]. [1]*National University of Singapore, Division of Bioengineering & Department of Mechanical Engineering, Singapore,* [2]*National University of Singapore, NUS Graduate School for Integrative Sciences & Engineering, Singapore,* [3]*National Cancer Centre, Department of Medical Oncology, Singapore, Singapore*

Immunomagnetic separation methodologies are currently the gold standard for circulating tumour cells (CTCs) isolation but face various drawbacks such as complex sample preparation and biomarker specificity. We developed a label-free biomechanics based microfluidic biochip that is capable of physically isolating and retrieving rare viable CTCs from cancer patient's blood. The principle is simple and makes use of the fact that cancer cells have biomechanical properties that are significantly different from that of blood cells. The key innovation lies in the unique crescent-shape microstructures which form the cell traps within the biochip. Instead of using biomarkers, these cell traps gently 'filters' CTCs from other blood components based on the biomechanical property differences between red blood cells, white blood cells and CTCs. Following this, the CTCs caught in these traps can then be retrieved in their wholly intact and viable state. Here, no sample pre-preparation of whole blood and antibodies is required. Blood collected in an EDTA tube can be processed straightaway in this biochip. Clinical blood samples from metastatic patients further verifies the applicability of the technique. Also, results from clinical tests showed that not all CTCs isolated were tested positive for EpCAM or CK. In fact, the CTCs were observed to be heterogeneous not only in terms of morphology such as cell size but also expression of EpCAM or CK. Significant number of CTCs where found to be EpCAM(−) or CK(−), CD45(−) but DAPI(+). This indicates that there are subpopulations of CTCs that warrants further investigation.

Society Session (Sun, 25 Sep, 16:45−18:15)
European Society for Therapeutic Radiology and Oncology (ESTRO)

206 INVITED

The Challenge of Tumour Heterogeneity

B.G. Wouters[1]. [1]*Ontario Cancer Institute, Princess Margaret Hospital, Toronto Ontario, Canada*

Important advances in clinical care have been made through the development and implementation of standardized, evidenced based, treatment protocols in a variety of human diseases including cancer. Implicit in such standardization is an assumption that the nature of the disease amongst different individuals is similar, and that patients have equal probabilities of benefiting from the treatment in question. For cancer therapy in general, and radiation therapy in particular, this assumption holds only to a first approximation, as several known biological variables that influence treatment response vary significantly amongst patients. For radiotherapy, these include differences in proliferation, hypoxic fraction, and the intrinsic radiosensitivity of the tumour cells in question. Importantly, these biological phenotypes differ significantly both amongst patients and within tumours themselves. These two levels of heterogeneity represent both a significant challenge to treat patients effectively and also an opportunity for delivery of more personalized medicine. Understanding the genetic basis for this heterogeneity is assisting in the development of such personalize approaches to treatment. I will discuss our efforts to both understand the mechanisms that contribute to hypoxia tolerance in tumours and the genetic basis for these differences amongst tumours.

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Emmanuel van der Schueren Lecture − Intraoperative Radiotherapy in Multidisciplinary Oncology: Results and Innovations

F. Calvo[1]. [1]*Hospital General Gregorio Maranon, Radioterapia, Madrid, Spain*

Intraoperative radiotherapy (IORT) is a multidisciplinar cancer treatment technique developd to improve the therapeutic-index of the combination of surgery and radiotherapy through the optimization of irradiation precision and the promotion of normal tissue tolerance (physical protection of non-cancer involved adjacent mobile organs and structures structures. IORT is a real-time vision guided and surgically supported (intra-pathology, normal tissue displacement, post-IORT reconstructive procedures). IORT as a dose-component (boost) for dose-escalation strategies has reported local control rates over 95% In adjuvant or high-risk post-resection cancer models (locally advanced primary rectal cancer, soft tissue sarcomas, breast cancer, etc.), over 70% in resection involved margin status (pelvic recurrences, oligotopic metastasis, etc.) and over 50% in unresected cancer patients categories (pancreatic cancer model). IORT is investigated as the sole component of irradiation (in the range of 20−22 Gy) in prospective non-inferiority randomized trials for early breast cancer with preliminary favourable results. Recent clinical innovations in IORT included the development of trials with IORT component and hypofractionated external radiotherapy, the incorporation of IORT to laparoscopic cancer surgery and the systematic evaluation of in-vivo dosimetry. Technical innovations are the development of miniaturized radiation devices specifically designed for intra-surgical use including high energy electrons or low X-rays source, together with treatment planning systems including virtual simulation, surgical navigation and dosimetric distribution estimations features. Surgeons, Radiation Oncologists and Medical Physicists will be guided by treatment planning systems in the decision-making process with an integrated multidisciplinary team-approach vision. IORT scientists and experts institutions have actively reported technical developments, clinical results and innovative projects. In the decade 1997–2007, 694 Pubmed indexed publications were available with accumulative impact factor over 1.300,000. An update up to May 2010, identifies 104 (277,856 I.F.) new additions. IORT belongs to the present multidisciplinary healthcare science imperative challenges to promote efficient human cancer control and improve patient quality of life.

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Radiation Oncology as a Clinical Specialty in a Multidisciplinary Environment: QUO VADIS?

C. Perez[1]. [1]*Washington University St Louis, Department of Radiation Oncology, St Loius, USA*

The incidence of cancer continues to increase throughout the world. Over the past century Radiation Oncology has solidified the basic foundations developed by the outstanding pioneers in our Specialty, it has established itself as a critical element, along with Surgery, Medical Oncology and other Specialties, in the multidisciplinary care of patients with cancer and it has evolved into a complex, clinically and technologically challenged medical discipline. Exciting developments in genetics and molecular biology/chemistry enhance the capability of Oncologists to more accurately classify the pathological features, behavior and prognostic implications of the cancer cells and the immunological mechanisms in the patients that may destroy them. Better understanding of radiobiological and physics principles have greatly contributed to te refinements in Radiation Oncology. There have been substantial advances in the ability of the Radiation Oncologist to evaluate our patients and the extent of their tumours, largely thanks to the advances in medical imaging, including MRI, PET and other modalities. Computational developments, imaging and sophisticated treatment planning algorithms have substantially contributed to the precision in treatment planning of radiation therapy, both with external beam and brachytherapy, leading to dose optimization, even in irregularly shaped target volumes, which has allowed dose escalation while preserving surrounding organs at risk in numerous anatomical sites. I envision cloud computing amplifying capacity and efficiency in radiation treatment planning and delivery, facilitating real time image-guided and adaptive radiation therapy. In the future new devices will have more refined imaging modalities with better anatomical and metabolic detail and they will incorporate more functional capabilities for dose delivered verification. The increasing use of combined modality therapy with cytotoxic or biologically targeted agents hormones, etc has enhanced the radiation effects in normal tissues and the probability of sequelea that may compromise quality of life of the patients. In the future it will be mandatory for Radiation Oncologists, Biologists and Physicists to continue basic science investigations to better understand the interaction of radiation with DNA and other molecular components of cancer and normal cells, to optimize the application of radiations to the treatment of patients with cancer. Nanotechnology is a most promising field, with potential applications in equipment design, specifically targeted anticancer drugs and agents to protect normal tissues from the effects of radiation. Radiation Oncologists must continue to foster and actively participate in pre-clinical research and in prospective clinical trials, such as those designed by ESTRO and RTOG and other Cooperative Groups, to maintain the scientific leadership that will ensure the active participation in the multidisciplinary care of the patients with cancer. Due to the complexity and increased possibility of errors in treatment planning or delivery of radiation, it is mandatory now and in the future to reinforce Quality Assurance and Continuing Quality Improvement Programs, to ensure the accurate treatment and safeguard the safety of our patients. Economic considerations play a most important role in everyday activities and the practice of Radiation Oncology is not an exception. We are motivated to use new technologies not only because of their marvels and

patient or peer pressure, but also, because reimbursement for services is more generous for Intensity Modulated Radiation and Particle Therapy, the same as for complex Surgical (robotic) techniques, new Biological Targeted and other complex drugs. In the future it will be critical to foster research studies of innovative diagnostic, staging or treatment modalities with well designed prospective trials on cost benefit, and Comparative Effectiveness, including evaluation of cost of care of patients with cancer throughout the lifetime of the patient and taking into account quality of life and productivity after treatment. Because of the concerns at political and administrative levels of governments with the cost of health care, Radiation Oncologists must remain vigilant and active in these circles, to defend our interest and those of our patients. As our distinguished colleague Anthony Zietman noted a few years ago, the seduction of technology should not detract from our primary objective, which is to be COMPLETE ONCOLOGISTS. In the future, that should continue to be a major emphasis in Radiation Oncology Training Programs and in the everyday practice of the Specialty.

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Personalized Medicine and Prostate Cancer Radiotherapy

R.G. Bristow[1]. [1]*Princess Margaret Hospital and University of Toronto, Department of Radiation Oncology, Toronto, Canada*

In intermediate risk prostate cancers (CaP) localized to the prostate, treatments such as active surveillance, radical prostatectomy (RadP), image-guided external beam radiotherapy (IGRT), or brachytherapy are used. Current prognostic factors such as T-category, serum PSA, and pathologic Gleason score explain only a proportion of the variation in clinical outcome. Better predictors of treatment outcome and patient prognosis are required to individualize CaP treatment and to provide optimal therapy with minimal side effects; this includes novel assays based on DNA Copy Number Variation and whole genome sequencing.
The Canadian Prostate Cancer Genome Network (CPC-GENE) is an outcomes-based initiative that will sequence specimens from 300 localized-prostate cancer patients who underwent surgery or radiotherapy. These samples are derived from pre-treatment biopsies, radical prostatectomies, and paired bloods and are directly linked to clinical outcome databases in which patients have more than 6.5 years median follow-up after treatment. Patients either responded (~70%) or did not respond to therapy (~30%). Using this approach, these DNA-based studies are directly linked to clinical outcomes and glean important new information regarding the genetic signature of localized versus occult metastatic diseaseto optimize treatment with radiotherapy in combination with molecular targeted therapies.
We are currently conducting pilot studies in which 40−50 specimens from fresh frozen pre-IGRT biopsies and radical prostatectomies, all with Gleason score 7, are being analyzed by array CGH/SNP array and whole-genome sequencing. The carefully selected samples will allow us to focus on characterizing the inter- and intra-tumoural heterogeneity of intermediate risk prostate cancer for a given Gleason score. As a first approach, our initial data using pre-IGRT biopsies in 120 modern-era radiotherapy patients with high-resolution, array CGH, demonstrates that copy number gains in *c-MYC* and losses in *NKX3.1* and *PTEN* are associated with increased genome instability (e.g. increased percent genome alteration). In a multivariate analysis, adjusting for the clinical prognostic factors PSA, Gleason score and T-category, we found that *NKX3.1* loss was prognostic for biochemical relapse (HR = 2.94, 95% CI: 1.19–7.26, p = 0.019) alone or when combined with *c-MYC* gain (HR = 4.32, 95% CI 1.36–13.71, p = 0.013). A similar negative prognosis (e.g. significant HRs greater than 2) was associated with allelic loss of PTEN or loss/mutation of p53. Interestingly, our data with TMPRSS2:ERG suggests that it may be a positive predictive factor in radiotherapy patients for response.
CNV and whole-genome sequencing of prostate cancers could help to generate predictors of treatment outcome and patient prognosis, enabling personalized medicine to become a reality.

Society Session (Sun, 25 Sep, 16:45−18:15)
European Association of Urology (EAU)

210 INVITED

The Role of Screening in Prostate Cancer

F. Schroeder[1], The European Randomized Screening for Prostate Cancer Study Group. [1]*Erasmus MC, Department of Urology, Rotterdam, The Netherlands*

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a randomized cotrolled trial of men aged 50−74 years (core age grouup 55−69) recruited in 8 European countries. To the core age group, to which all centers contributed, 162,243 men were randomized. 20,437 tested positive, 20,437 tested positive with PSA values ges;3.0 ng/ml and 85.8% of these were biopsied resulting in a PPV of 24.1%. In the screen arm 5,990 cancers were found (8.2%) and 214 died of prostate cancer, in the control arm these figures amounted to 4,307 (4.8%) and 326 cancer deaths.
At the time the described information was obtained with a median 9 year follow-up. Relative risk reductions of 21%, 27% and 31% were found in intention to screen analyses (ITS) and analyses adjusting for non compliance alone or in conjunction with adjustment for contamination in the control group. The data of the ITS analysis translated into numbers needed to screen (NNS) and to treat (NNT) to save one cancer death of 1,410 and 48 (Schröder et al NEJM 2009).
The Swedish partner of the ERSPC study, the Göteborg Randomized Screening Trial was initiated in 1994 as an independent study but joined the ERSPC in 1996. It applied a population based randomization which allowed the inclusion of the whole population of participants at the same time. As a result, non participation occurred only in men randomized to screening, and a 14 year follow-op period was reached with a complete data set to the end of 2008. The analysis was carried out in line with predesigned power calculation, the resulting data were published in 2010 (Hugosson et al Lancet Oncology). With the longer follow-up achieved in this part of the ERSPC study the relative risk reductions in the ITS analysis and after adjustment for non compliance amounted to 44% and 56% with NNS and NNT of 293 and 12.
The main down side which at this time and with the applied screening remains is seen is an amount of over diagnosis which is estimated to be in the range of 42−66% (Draaisma et al 2003 and 2009). Mechanisms are available to reduce over diagnosis and will be described. The best solution to the problem, the development of amor selective marker whic identifies potentially indolent disease is a future perspective.
Regular evaluations of the ERSPC data will be carried out, the data set will be updated every six months. At this time only about 25% of the participants have died. The end point of the study is to be determined based on future development of the data.

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Radical Prostatectomy − the Gold Standard in the Treatment of Localised and Locally Advanced Prostate Cancer

M. Wirth[1]. [1]*Universitätsklinikum Carl Gustav Carus, Department of Urology, Dresden, Germany*

In Europe, prostate cancer is the most common non-skin malignancy in males. The application of PSA as a tool for early detection has led to a stage shift with localized and thus potentially curable stages representing the majority of newly detected cases. Among patients referred for radical prostatectomy, recently, an inverse stage shift has been observed because of an increased use of active surveillance in low-risk cases. Up to now, however, only radical prostatectomy has been demonstrated to improve survival in clinically diagnosed prostate cancer in the setting of a randomized trial, compared with watchful waiting. Radical prostatectomy is the standard treatment of localized prostate cancer in men with an adequate life expectancy. It enables overall disease-specific 10-year survival rates of more than 90%, when considering histopathologically organ-confined cases, disease-specific 10-year survival rates reach narrowly 100%.
The treatment of clinically locally advanced prostate cancer (cT3−4) is subject to some controversies. Patients with lymph node metastases as well as patients with overstaged localized and thus curable disease may fall into this category. Radical prostatectomy, external beam radiotherapy and early or deferred hormonal therapy are possible treatment options for clinically locally advanced prostate cancer. Multimodal treatment (a combination of these options) is frequently used, but there is only few evidence available defining patients who could benefit from such aggressive treatment. After radical prostatectomy, the Gleason score-adjusted disease-specific survival does not differ meaningfully between the tumour stages pT2 (localized) and pT3−4 (locally advanced). Radical prostatectomy for locally advanced disease has the advantages of the remaining option of adjuvant radiotherapy. Furthermore, in patients with localized tumours in the prostatectomy specimen (about 25% of clinically locally advanced cases), adjuvant hormonal therapy (that would be given after external beam radiotherapy) is spared. Adjuvant radiotherapy may improve biochemical and local control in locally advanced prostate cancer. A survival benefit has, however, only been shown in one study yet, whereas others found no difference. External beam radiotherapy alone provides unfavourable survival rates in locally advanced prostate cancer. Adjuvant hormonal treatment for three years improves outcome in this setting. When no curative treatment is chosen, early hormonal treatment seems to provide modest benefit compared with deferred therapy. In the future, patients with locally advanced prostate cancer should be enrolled in controlled clinical trials to find out which treatment is best.