older cancer patients is influenced not only by the tumor itself but also by the various comorbidities and geriatric problems associated with old age. The health status of each older individual should be evaluated in order to optimize cancer decision making in this age group.
Oncologists are aware of a procedure for detecting older patients whose health problems may interfere with cancer treatment. Multidimensional geriatric assessment (MGA) addresses the major concerns of geriatric assessment (GA), i.e. patients' physical and mental status, their social, environmental and economic situation, their functional status, and geriatric syndromes. The MGA process involves a trained interdisciplinary team usually including a nurse and a geriatric-trained oncologist or a geriatrician, and sometimes a physical therapist, a dietician, a social worker, a pharmacist and a psychologist. Patients' health problems are detected through different validated screening tools: Katz's Activities of Daily Living and Lawton's Instrumental Activities of Daily Living scales; Cumulative Illness Rating Scale for Geriatrics; Timed Up & Go test or Performance-Oriented Assessment of Mobility instrument; Folstein's Mini Mental Status Examination; Geriatric Depression Scale; Mini Nutritional Assessment; medication review and appraisal of potential drug interactions. The findings from these tests provide a better picture of older patients' health status before cancer treatment decision making.
Nevertheless, the MGA approach requires geriatric skills that are hardly available in conventional oncology units. Thus, specific screening tools are currently being developed to help oncologists differentiate healthy senior adults from patients whose problems might interfere with cancer treatment and who require more in-depth GA. These instruments must be easy to administer and quick to complete, and not require geriatric resources.
The French National Cancer Institute has sponsored a prospective study, ONCODAGE, to validate an innovative geriatric screening tool designed to identify older cancer patients requiring GA before cancer treatment decision-making. The screening tool called G8 is composed of one question about the patient's age and 7 items from the Mini Nutritional Assessment instrument. Results of a pilot study have shown that a total score lower than 14 out of 17 indicates that the patient needs a full GA procedure. G8 will also be compared with the VES-13 instrument and a set of validated geriatric screening tools described earlier.
A total population of 1650 newly diagnosed cancer patients will be included in around 15 centres over a 1-year period. Preliminary results are expected by the beginning of 2010.
In conclusion, older cancer patients require both cancer and geriatric assessments. The more efficient model could be a two-step procedure including a preliminary screening test followed by a true GA for older patients identified as frail or vulnerable. This approach allows to characterize the patient's health status and to offer appropriate cancer treatment options. Consistent guidelines on cancer treatment in the elderly should be issued after the GA process is standardized.

163 INVITED

Radiotherapy in older patients for early breast cancer

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With the age related rise in incidence of breast cancer and the raising of the upper age limit of the UK breast screening programme to 69 years, the number of patients potentially eligible for adjuvant irradiation has risen dramatically over the last decade. However exclusion historically of patients over the age of 70 from clinical trials has led to a dearth of level 1 evidence on the role of postoperative radiotherapy (RT). The Oxford overview provides information on over 24,000 women treated with adjuvant radiotherapy (1) for operable breast cancer. However only 550 (9%) of the 6097 patients with axillary node negative breast cancer treated by breast conserving surgery were over the age of 70.
Despite the evidence that older patients can tolerate RT (2), there is evidence that the receipt of radiotherapy falls with age (3), irrespective of comorbidity status and stage of disease. The use of RT fell from 77% to 24% in women with no comorbid conditions between the ages of 65−69 and 80 years or older. A study from the SEER database of 29,760 women aged 65 or older diagnosed between 1991–2002 and treated by breast conserving surgery (BCS) showed that 22,207 (75%) received radiotherapy. Patients were more likely to receive radiotherapy if they lived in urban areas, were white, married and had fewer comorbidities.
There are few level 1 data on the impact of adjuvant RT after BCS in older patients. In women over the age of 70 the absolute risk reduction for 5 year ipsilateral breast tumour recurrence rate was smaller (11% vs 22%) compared to women under the age of 50 (1). The CALGB trial showed that in women 70 years or older with TI, NO hormone receptor positive tumours that adjuvant RT reduced the 5 year risk of IBTR from 4% to 1% (4). The difference was modest but statistically significant ($p < 0.001$). The international PRIME 2 trial (target accrual 1300 patients) is currently assessing the omission of postoperative RT in low risk (T1−2 [<3 cm], MO) hormone receptor positive breast cancer after BCS and adjuvant endocrine therapy (5). The EORTC 22881–10882 boost trial has provided level 1 evidence of the value of a boost dose after BCS and whole breast RT. The absolute of benefit of the boost in reducing the 10 year IBTR rate is smaller in women over the age of 60 (3.5%) (7.3% vs 3.8%, $p = 0.008$). A boost should offered to all fit older patients.
Shorter hypofractionated dose fractionation regimes are more convenient for older patients. Recent evidence from the START trial (6) demonstrates equivalent 5 year local control with 40 Gy in 15 daily fractions to 50 Gy in 25 fractions. A total of 11.5% of the patients in the trial were over the age of 70.
There is a paucity of data on the impact of postoperative whole breast RT on quality of life. The PRIME trial showed no overall difference in global quality of life using the EORTC QLQ C30 and QLQ B23 modules when RT was omitted in a low risk group of T1−2, NO, MO axillary node negative patients at follow up of 15 months (7).
The role of partial breast irradiation (PBI) in older patients remains investigational. Level I evidence is needed to validate this approach in this age group.
No trial of postmastectomy radiotherapy has been conducted exclusively in older patients. The survival advantage in the DBCG 82c trial in patients treated with adjuvant PMRT and tamoxifen only emerged after 5 years. Patients with 4 or more involved axillary nodes should be considered for PMRT if they have a life expectancy in excess of 5 years. The role of postmastectomy RT in women with 1−3 involved nodes or node negative with other risk factors is uncertain and under investigation in the BIG 2−04 MRC/EORTC SUPREMO trial (8).

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164 INVITED

Clinical management of the elderly: surgery

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The risk of developing cancer increases with age. The elderly population is growing world wide as a result of medical advances. Consequently, the incidence of cancer within the geriatric population is set to rise. It is predicted that cancer will soon become the leading cause of death, with over half of new solid cancer cases occurring in patients $\geqslant 70$. This epidemiological shift explains the progressive change in the clinical setting, where surgical wards are frequented by elderly patients more than previously. Surgeons are more often having to decide upon whom they should operate. Surgery, the treatment of choice for most solid tumours, carries associated risks of mortality and morbidity which increase with age due to several factors including a reduced physiological reserve and co-morbidities. However, these should not preclude surgical treatment as it has been shown that neither the number nor the gravity of associated medical conditions correlate with operative death and complications.
Life expectancy is very important in tailoring treatment plans but it is not a reliable prognosticator of the outcomes of cancer surgery. The decision whether to treat should not be based on age alone; a careful multi-dimensional pre-operative assessment is needed. Pre-operative assessment by means of Comprehensive Geriatric Assessment (CGA) defines individualised operative risk. CGA assesses a variety of areas where elderly patients often present problems (impaired functional

status, co-morbidity, polypharmacy, poor nutritional status, diminished cognitive function and altered emotional status). It has been shown that patients classified as "frail" from the CGA may present more post-operative complications when compared to the "not frail" ones. The Pre-operative Assessment of Cancer in the Elderly study (PACE) has identified factors which have a negative impact on short-term outcomes after cancer surgery in the elderly. 400 patients over the age of 70 with various types of cancer had a geriatric assessment performed using tools to assess co-morbidity, activities of daily living, cognitive function, fatigue, depression and Eastern Cooperative Oncology Group Performance Status (ECOG PS). The American Society of Anesthesiologists (ASA) classification, Physiological and Operative Severity Score for enumeration of Mortality and Morbidity (POSSUM), and the Portsmouth variation of POSSUM were incorporated into the questionnaire. Disability, measured as dependency in instrumental activities of daily living (IADL), correlated with a 50% increase in the relative risk of experiencing post-operative complications. PACE concluded that IADL, fatigue (as measure by the Brief Fatigue Inventory) and ASA score were the strongest predictors of poor post-operative outcomes. Because of our poor understanding of frailty in onco-geriatric series, elderly cancer patients are often excluded from clinical trials. This aggravates the lack of evidence-based knowledge and perpetrates mis-management. Even when they are included, there is often insufficient baseline information about PS, co-morbidity, cognitive state and nutritional status making accurate interpretation of results difficult. The implementation of these tools into surgical practise will allow better framing of the cohort undergoing surgery, resulting into more comparable outcomes within clinical trials. The CGA is also a useful adjunct to the consent process. Routine assessment of frailty in elderly patients is warmly recommended before cancer treatment, either through CGA or via a quick screening tool, e.g. Groningen Frailty Indicator. This will allow tailoring the appropriate treatment after evidence-based consenting; it will also enable one to correct for differences in pre-operative variables, allowing more accurate comparison of results within trials. The result of this knowledge will permit drafting guidelines and treatment protocols and, eventually, an improved standard of care for the elderly.

165 INVITED

Systemic therapy

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This presentation will review the three main modalities of systemic treatment in the elderly: hormonal therapy, chemotherapy, and targeted therapies. Hormonal therapy is usually considered a well tolerated approach but we will review some aspects of the side effect profile of particular importance in the elderly, such as musculoskeletal, vascular, and cognitive side effects. The proper prescription and delivery of chemotherapy in older patients is a major dilemma for oncologists. Recent research can however help us target more precisely our treatment to the individual patient, both in terms of tumor and host. This fits in the lines of a personalized cancer care approach. When targeted therapies first appeared, large hopes were held that they would provide low toxicity treatments to older patients. This hope has only been partially fulfilled. Nevertheless, such therapies have increased our options for designing the care of older cancer patients. It is important to recognize that host senescence can significantly affect the mechanism of action of targeted therapeutic approaches. As our longevity increases, the oldest old (patients aged 85 and older) are increasingly being seen in oncology clinics. There is a dearth of prospective data to guide treatment in this population, but cohort data can provide us with some insights and will be reviewed in this presentation.

Scientific Symposium (Tue, 22 Sep, 14:45−16:45)
Biomarkers in early clinical drug development

166 INVITED

Biomarkers and personalized models in oncology drug development

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Biomarker discovery in oncology has been robust but development has been plagued by the need to validate these markers at various key phases. Target discovery in tumors and or in cell lines with differential sensitivity usually starts the process. Then, simple cutoffs must first be identified and established in samples of convenience. Robust technology assessment and implementation must take place to ensure reliable and accurate results. Retrospective clinical analysis must be done, testing the biomarker in key studies where clinical drug sensitivity is established. Eventually, a prospective clinical analysis must be performed to validate use of the marker, though this can be done in prospectively collected samples. Finally, either a laboratory or a commercial entity must offer the predictive biomarker to ensure its integration in the clinic. We will discuss various biomarkers including key genetic and epigenetic markers in development and those already in the clinic. We will also discuss the development of new predictive personalized models which are at the nexus of integrating biomarkers and drug testing.

Preclinical oncology drug development typically originates from high passage number immortalized cell lines. While information from these models is useful in discovery and initial proof-of-concept studies, their clinical relevance is often limited due to alterations and adaptations from successive passages in tissue culture and animals. Preclinical personalized models established from donor patient tumor fragments passaged only a few times in vivo may better represent clinical disease. Following establishment, models can be characterized at the molecular level and then correlated with in vivo sensitivities of various agents and clinical information from patient donors as well as current standards of care. Molecular characterization studies identified known mutations in several signaling molecules important in cancer progression as well as novel markers of sensitivity and resistance to standard agents. These low passage models offer an alternative to standard xenografts and may be more representative of clinical disease. Data collected from molecular characterization and in vivo evaluation of these models will aid greatly in development of novel agents and predictive biomarkers.

167 INVITED

The need for robust statistical designs to bring biomarkers to the clinic

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New technology and understanding of tumor biology make it increasingly feasible to develop prognostic and predictive biomarkers that provide information about which patients require systemic therapy and which are most or least likely to benefit from a specific treatment. Using such biomarkers to target treatment can greatly benefit patients, reduce societal medical costs and improve the chance of success in new drug development. Although it is often said that use of genomic biomarkers can make drug development simpler, quicker, and cheaper, co-development of new drugs with companion diagnostics often increases the complexity of drug development.

There is considerable confusion in the literature on the role of biomarkers in drug development and how such biomarkers should be "validated". In this presentation we will distinguish the different types of applications of biomarkers, will clarify that "validation" means "fit for purpose" and will identify different steps of validation for different biomarker indications. We will provide a roadmap for the development of candidate predictive biomarkers and for the use and evaluation of such biomarkers in phase III trials of new drugs. We will address some of the difficulties in development of predictive biomarkers prior to their use in phase III trials. Several strategies for development will be described and critically discussed. Sample size requirements for development of predictive biomarker candidates and the implication of biomarker development on the structure of early clinical trials will be addressed. Reprints of some relevant publications are available at http://brb.nci.nih.gov.

168 INVITED

Circulating tumour cells as biomarkers in clinical trials

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Circulating tumor cells (CTC) are thought to represent the "leukemic phase" of solid tumors. Their isolation, separation and enumeration can now be reproducibly performed by validated assays utilizing multi-parameter cytometry. Several isolation and quantitation assays have been described. CTC have been shown to be most commonly detected in breast and prostate cancer and not detected in healthy volunteers. The presence of CTC associates with more advanced stage, but may also reflect disease biology. Three trials in patients with advanced breast, prostate and colorectal cancers have shown that patients with a CTC count above a predefined threshold ($\geqslant$5 in breast and prostate cancer, $\geqslant$3 in colorectal cancer) have a poorer overall survival. Overall, these studies showing that patients with higher CTC counts both pre- and post-treatment have poorer overall survival have clinically qualified this assay as a prognostic biomarker and have led to its FDA clearance. These studies also suggest that changes in CTC counts following treatment could potentially be utilized to guide changes in treatment. These data support the further evaluation of CTC as potential intermediate endpoints of treatment outcome.