and expected by those investigators who are engaged in the ongoing randomised screening studies in Europe and in the United States, screening will be shown to have an effect on prostate cancer mortality, this will not be the complete answer. Obviously, the most important question is: Does early diagnosis and aggressive management decrease prostate cancer mortality? The answer to this question alone however will not qualify screening as a health care policy in the critical judgement of most care providers around the world. The degree of over diagnosis, the impact on quality of life after treatment in relation to the risk of the untreated disease, the side-effects of treatment, the role of ageing and related chronic disease and life expectancy in decision taking, a better definition of the watchful waiting in prostate cancer management are all issues that are tightly connected to the question of whether prostate cancer screening can become a health care policy. Obviously, only the availability of such data will at the end allow a complete risk benefit and cost analysis. It is hoped that all these questions can be answered positively so that finally a preventive measure can be introduced into one of the most important disease entities of the male population.

In the meantime the powerful available early diagnostic capabilities cannot be withheld from well informed men. The accent here however has to be **well informed.** Standardised procedures for proper information prior to carrying out a PSA test are under development in various countries. To carry out testing without providing this information must be considered unethical.

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Immediate endocrine treatment is preferable and prolongs survival

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Trial data suggests that in men with advanced prostate cancer, immediate endocrine therapy improves disease specific survival, whether used as sole treatment (MRC PR03) or as an adjuvant treatment with radiotherapy (EORTC 22863). No trial data suggests an adverse effect of immediate treatment. The outcome is less clear when overall survival (death from all causes) is considered. In older men, with conflicting morbidity, prolongation of cancer survival will increase the opportunity of death occurring from other causes first. The possibility of a treatment induced mortality resulting from hormonal treatment has also been invoked, although the suggestion that hormone treatment may cause cardiovascular deaths has not been observed in PR03. Translation from the comparatively small number of patients studied in even the largest trials to the population as a whole is likely to translate the observed improvement of disease specific survival into an overall benefit. In addition, in PR03, clear benefits in reduction in complications such as spinal cord compression and control of the local tumour were seen, differences which have persisted as the trial data have matured. While quality of life data is not available from the quoted trials, it is as likely that patients will gain in benefit from control of their cancer as much as they lose from the side effects of treatment.

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Endocrine treatment should be delayed (until clinical evidence of progression)

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The widespread use of prostate-specific antigen (PSA) has induced a dramatic shift in the prostate cancer population: patients are now diagnosed with prostate cancer much earlier and failure of radical therapy is also detected at a very early stage. An ever increasing cohort of asymptomatic patients present threfore with minimal disease and prolonged expected survival. In addition significant advances in medical care have allowed correction of previously redhibitory comorbidities, thereby increasing the likelihood of longer survival. Should all these patients receive immediate endocrine treatment? In my view, there are compelling arguments in favor of delaying treatment: (1) Since endocrine therapy is only palliative and asymptomatic patients have no symptoms to palliate, delaying treatment avoids androgen ablation and its poorly tolerated side effects. When symptomatic progression occurs – and it will inevitably if the patient lives long enough – effective treatment is still available. (2) Observation means watchful waiting and not neglect: rapid progression and complications can be detected early by PSA based follow-up and modern imaging technology; treatment can therefore be started early enough to prevent catastrophic complications that inevitably occur when treatment is started too late. (3) Well-differentiated prostate cancer progresses slowly and many such patients will die of other causes, with cancer rather than from cancer. (4) Cost is reduced.

Admittedly, the timing of endocrine therapy in low-risk prostate cancer remains controversial because of the unpredictability of the two main variables: the evolution of a particular tumor cannot be reliably anticipated and the precise survival of a particular prostate cancer patient is unknown. Solid data however exist that can help the Urologist to individualize treatment, and his patient to make an informed choice. Patients with well differentiated tumors, low initial PSA, prolonged PSA doubling-time clearly do not need immediate therapy, local or general. Patients with severe comorbidities limiting foreseeable survival also can be observed expectantly. By contrast, patients with high-grade cancers, high initial PSA, symptomatic and/or rapidly progressing disease should be treated immediately. For the intermediate cohort of patients, strict watchful waiting is an option with initiation of therapy at early signs of progression. Unfortunately no strict clinical or biological criteria exist to trigger a change in therapeutic attitude.

Early treatment offers advantages in time to progression and disease specific survival, but there is no convincing evidence that it provides a clinically significant survival advantage counterbalancing its well-known side effects, especially in low-risk low-volume disease. Until now, in my view, no study has convincingly demonstrated a definitive benefit when androgen suppression was given early in low-risk low-volume prostate cancer, and watchful waiting therefore is a preferred – albeit temporary – option.

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Neo-adjuvant therapy for localized NSLC

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Neo-adjuvant or induction therapy for localized NSCLC (stage I-III) denotes the use of cytoreductive therapy before local-regional therapy. Its rationale is provided by the findings that survival after localized therapy leaves room for improvement, recurrences after surgery and/or radiotherapy are mainly at distant sites (+ 75%) and occult metastatic disease can be found in many 'early stage'patients (pts). Postoperative chemotherapy has been shown not to improve on survival in randomized controlled trials (RCT) mainly due to the inability to deliver the intended chemotherapy dose. Small RCT's of neoadjuvant chemotherapy in operable NSCLC pts demonstrated a survival benefit for those receiving chemotherapy, especially when complete resections could be performed. The survival benefit is retained at long term follow up. Most investigators agree that induction chemotherapy has acceptable toxicity and overall mortality/morbidity is low, although especially right pneumonectomy after induction therapy carries a considerable risk for postoperative mortality. Induction chemotherapy before radiotherapy in stage III pts improves survival. RCT of induction vs concomitant chemoradiotherapy have yielded conflicting results. A Japanese study did show a survival benefit for concomitant as opposed to sequential chemoradiotherapy but others failed to confirm these results. Toxicity of concomitant chemoradiation strategies is considerable (esophagitis) and should be reduced before it can be applied in routine clinical practice. Pivotal questions include the 'best' induction strategy (regimen?, chemotherapy alone vs chemoradiation for operable patients), restaging and 'best' local treatment (surgery vs radiotherapy) after induction therapy and management of patients with persistent nodal disease. These and other questions are the subject of large clinical trials which are underway. In conclusion: the use of neoadjuvant therapy is backed by data, is feasible and is promising for stage I-III NSCLC pts.

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Concomitant radiotherapy-chemotherapy for the treatment of lung cancer

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Synchronous use of chemotherapy and irradiation has become the standard of care for limited disease Small Cell Lung Cancer (SCLC) and increasingly the treatment of choice for locally advanced Non Small- Cell Lung Cancer (NSCLC). This approach has been adopted on the basis of limited clinical evidence and often without clarity for the basis on which an improvement in therapeutic index could be based. The fundamental aim of using common exposure time to chemotherapy and irradiation is the enhancement of the rate of local control from what can be achieved by radiotherapy alone. The effects on metastatic disease are secondary and determined by the effectiveness of the tolerable dose of the chosen chemotherapy regimen. Many of the old and new drugs with proven activity in lung cancer have radiosensitising properties in vitro and in vivo and need dose reductions when given with synchronous irradiation. The exception is the classical Platinum/Etoposide schedule in SCLC which in full doses with radiotherapy

produces the benchmark 40% 2 year survival(1). Current intergroup trials (SWOG, ECOG, CALGB) continue to use this combination for the concurrent chemoradiotherapy parts of their combined modality schedules.

In NSCLC this concept has been tested in a number of trials with a third of comparisons demonstrating significant advantage of the concurrent approach 2-5 giving a 5% survival benefit at 5 years. The challenge for the clinical community is to test whether this would be additional to increasingly possible radiation dose escalation and what would be the optimal way of scheduling an effective combined modality treatment regimen.

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The value of staging with PET

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New diagnostic and treatment strategies are needed to improve the survival rates of patients with lung cancer. Accurate tumor staging is essential for choosing the appropriate treatment strategy of lung cancer. The combination of whole-body positron emission tomography (PET) with 18F-Fluorodeoxyglucose (FDG) and computed tomography (CT) has made a major impact in the diagnosis and staging of lung cancer. FDG-PET is an established imaging technique which detects local differences in tissue metabolism.

It has been shown that whole-body FDG-PET is a very effective imaging modality for non-small cell lung cancer (NSCLC). PET is used to characterize solitary nodules, to screen for mediastinal and extrathoracic metastases (except the brain), and to detect persistent or recurrent disease. Sensitivity and specificity of FDG-PET for determining the dignity of solitary pulmonary nodules are 96% and 80%, 88% and 92% for mediastinal staging, 94% and 97% for detection of extrathoracic metastases, 99% and 89% for detection of recurrence. FDG-PET is useful too in evaluating and staging small cell cancer, lymphomas and mesotheliomas.

The combined strategy of CT and PET is cost-effective in staging of non small cell lung cancer because it prevents patients with unresectable disease from undergoing not curative surgery.

Currently, new combined in-line PET-CT-scanners are available. To our own experience, the availability of anatomic details afforded by integrated PET-CT scanning will contribute to the accurate staging of lung cancer. Fusion images can be intergrated in the radiotherapy treatment planning to adjust the radiation field.

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The surgeon's view

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The optimal algorithm incorporating positron emission tomography (PET) for the evaluation of pulmonary abnormalities and the detection of distant metastases has not yet been identified.

Clinical staging of bronchogenic carcinoma is performed using the TNM system, which requires accurate characterization of the primary tumor, regional lymph nodes and exclusion of distant metastases. The role of PET scanning is quite different for these three components of staging. Evaluation of solitary nodules of unknown origin by PET can identify nonmetabolically active lesions whereas the sensitivity for detection of malignant lesions is reported to be 100%, thus demonstrating that PET is superior to transthoracic needle aspiration. PET has limited usefulness in determining the T-status of the pulmonary lesion. Unfortunately, PET has poor accuracy in defining T3 and T4 disease (invasion of adjacent structures or pleural disease, resp.) Several studies in the last years examined the role of PET for detection of regional nodal disease. PET has been demonstrated to be superior to CT. The average sensitivity of PET for nodal disease was near that reported for mediastinoscopy, however is closely related to the spacial resolution. PET seems to be highly useful in defining the M-status identifying metastases in asymptomatic patients with negative CT-scans on the one hand and characterizing CT-findings as benign on the other. Taking into consideration the chance of cost saving due to the prevention of unnecessary invasive procedures PET will become an increasingly important part of staging lung cancer patients.