(3) Isotope or blue dye are both: Many methods are described using different isotopes and different routes of administration. Which blue dye and which isotope and the timing and route of administration require further evaluation.

(4) Immunohistochemically positive nodes: The significance of immunohistochemically positive sentinel nodes is unknown. How we should manage these patients is unclear. The value of PCR positive sentinel nodes is even less clear.

(5) Internal mammary nodes: what to do with internal mammary nodes that light up on the lymphoscintigram remains uncertain. The prognostic significance and the value in excising these nodes may need to be re-evaluated in the sentinel node era.

(6) Credentialling for Surgeons: This remains a controversial issue for surgeons in practice.

Sentinel lymph node mapping has established itself as a valid technique in the management of breast cancer, however before it is acccepted as standard of care the aforementioned controversies need to be addressed.

1561

Sentinel node biopsy in melanoma. Is it worthwhile?

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Lymphatic mapping and sentinel node biopsy is one of the major developments in surgical oncology in this decade. This minimal invasive procedure allows for the identification of clinically occult lymph node metastases, avoiding needless extensive lymphadenectomy. In melanoma patients the technique of sentinel node biopsy is well cristallized, with an identification rate of the sentinel node in 99% of the cases. Reported false-negative basin recurrences, approaching 15% of expected node-positive basins in some series, however, is a matter of concern.

A clear advantage of sentinel node biopsy is that it allows for improved staging, now that the pathologist has the unique opportunity to focus his diagnostic tools on one node only, instead of on a whole dissection specimen. The clinical relevance of this pathological scrutinizing by serial sectioning, immunohistochemistry and the molecular staging technique of RT-PCR for tyrosinase mRNA, however, still has to be proven. The same applies to the intriguing supposition that earlier entry of lymph node positive melanoma patients into adjuvant regimens might be of benefit.

The most crucial question to be answered is, if a positive sentinel node biopsy with subsequent lymph node dissection improves regional tumour control and survival. This issue is at present addressed in a randomized study, initiated by the inventor of the method, D.L. Morton. The outcome of this trial will hopefully bring the long standing debate on the value of elective lymph node dissection to a conclusion. Until then sentinel node biopsy remains an experimental procedure.

1562

Early stage prostate cancer – Watchful waiting or radical treatment?

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The management of early prostate cancer has been described as the most controversial issue in contemporary oncology. Outcome data are simply too inadequate to allow the formulation of any scientifically wellfounded guideline for decisionmaking. As a corollary, conflicting recommendations have been issued and widely differing treatments used by various professional organizations. The best we can look for is an open debate about issues of a broad range: biological, clinical, ethical, economic, and others. We need to respect differences in opinion while walling for data from randomised, controlled trials.

The management of early stage prostate cancer need also be discussed and understood in the context of screening with prostate specific antigen. Such screening is not only likely to advance the time of diagnosis of cancers that would otherwise have surfaCed clinically at a more advanced stage, perhaps many years later; it may also entail overdiagnosis of histopathologically malignant lesions with limited or no potential to progress to mortal cancer. Since there are no methods available – clinical, histopathologic, molecular, or other – that reliably distinguish mortal cancers from more innocent lesions, the risk for overdiagnosis and overtreatment becomes substantial notably when PSA-screening is used widely.

Given the lack of solid scientific evidence, this lecture will rather address conceptual issues in an attempt to summarize the advantages and the disadvantages of watchful waiting as well as radical local treatment.

1563

Can surgery provide cure in clinical T3?

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Radical prostatectomy is considered as a standard treatment for locally confined prostate cancer while for locally advanced (cT3) prostate cancer, surgery is traditionally discouraged. These patients have an increased risk of lymph node metastases and local or distant relapse. A combination treatment (radiotherapy with hormonal treatment) is now becoming popular in this particular patient category.

While several reports exist on the outcome of pathologically T3 tumors only few studies have been published on the value of surgery for clinically T3 tumors. Most of the reports have treated patients with combinations of surgery and hormonal treatment. From the available reports (Rotterdam, Würzburg and the Mayo Clinic) it is obvious that there is a high incidence of lymph node involvement. On the other hand these reports have also Shown that surgery can be performed with acceptable morbidity. From our own data, it became obvious that there is a relevant subgroup of clinical T3a patients that are amenable for a curative treatment option by radical prostatectomy. Patients with clinically obvious massive extracapsular extension (cT3b) or seminal vesicle invasion (cT3c) are not good candidates but patients with limited extracapsular extension and a low PSA proved to have a good five year PSA relapse free survival.

These data will need further confirmation in a multi-institutional setting. There is a subgroup of patients with locally advanced disease that can be cured by radical prostatectomy alone. Patients with even more advanced local disease will rather be candidate for a combined radiotherapy-hormonal therapy combination.

1564

Conformal radiotherapy for prostate cancer

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Three-dimensional conformal radiation therapy (3D-CRT) is a technique of high precision radiotherapy that targets a prescribed dose to the tumor conforming to its spatial configuration, while decreasing the dose to surrounding normal tissues. The latter leads to decreased normal tissue complications, and permits tumor dose escalation to improve local tumor cure. This paradigm was confirmed in a study of 1050 patients with localized prostate cancer treated between October 1988 and March 1998. Prostate biopsies performed at $\geq$2.5 years after radiotherapy showed that patients receiving 81 Gy had 6% positive biopsies, compared with 29% after 75.6 Gy ($p = 0.04$) 43% after 70.2 Gy and 57% after 64.8 Gy. Radiation doses of $\geq$75.6 Gy also significantly improved the 5-year actuarial PSA relapse-free survival. The overall grade 3 rectal and bladder complications was 1.5%. However, the 5-year actuarial risk of grade 2 rectal bleeding for patients receiving 75.6–86.4 Gy was 17% compared to 6% for those treated with 64.8–70.2 Gy ($p < 0.001$). The application of intensity modulated radiotherapy (IMRT) significantly improved the tumor conformality, reduced the exposure of normal tissues, and decreased the rate of grade 2 rectal bleeding. These data indicate that conformal radiotherapy represents an advancement in the ability to deliver the high radiation doses required to improve the local cure of prostate cancer.

1565

Androgen regulated gene expression in prostate cancer

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Androgens are required for the development of prostate cancer and at least 80% of tumouts respond to androgen deprivation therapy. However, progression to an androgen-independent (AI) state usually occurs and the tumours become increasingly refractory to hormonal manipulation or other therapies.

The mechanisms underlying this transition are unclear but androgen receptor dysfunction, via mutation, amplification or structural changes in the AR protein accounts for some cases although the frequency is controversial. We have examined the CAG microsatellite repents in the transcription activation domain of the AR gene and find limited polymorphism in prostate cancers with a significant predominance of 19 repeats.

We compared the androgen-sensitive cell line LNCaP to a clonal variant, LNCaPr, which is androgen insensitive, to identify differences in the gene expression profile using suppression subtraction hybridisation. Three genes

were differentially expressed, Fibronectin, basic breast conserved gene (BBC 1) and ubiquitin enzyme variant -1 (UEV-1/CROC1) which all Inocalise to regions of chromosomal aberration in prostate cancer (2q 3.4, 16q 24.3 and 20q 13.2 respectively). Further data on the expression of these genes in prostate cancer will be present.

We have also examined the relationship between androgen-regulated gene expression and all cycle regulation and apoptosis using an AR-cell line, doubly transfected with the AR gene and bcl-2 gene, (the latter being closely associated with the AI state). Bcl-2 overexpression confers and antiapoptotic effect against both androgen deprivation and cytotoxic chemotherapy.

An understanding of the mechanisms of AI prostate cancer will provide new therapeutic options to treat this presently incurable disease.

1566

Meta analysis of the randomised trials in prostate cancer

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The Prostate Cancer Trialists Collaborative Group (PCTCG) is performing an overview of randomised trials of the treatment of prostate cancer. The aim of the cycle 1997–2000, is to bring together mortality results from randomised trials that began before 1991. Two hundred randomised studies were identified that included 40,000 patients. Data from each individual patient in each study was requested. Three main questions were addressed by many of these studies and for these an overview was considered relevant:

MAB vs castration alone;

Immediate vs deferred hormone treatment;

Chemotherapy vs no (or delayed) chemotherapy;

In 1995, a first cycle an overview by the of the results of these trials organised by the PCTCG found no significant overall survival advantage by MAB as compared to androgen suppression alone. However, the confidence limits were rather large and, therefore, the possibility of a small improvement in survival was not excluded. This second cycle of the overview includes in excess of 40% more information (8,000 patients with almost 6,000 deaths).

For the question of immediate vs deferred hormonal treatment 15 trials were identified including more than 7,000 patients. Analyses of mortality and cause specific mortality were performed.

Concerning the question of (first line) immediate chemotherapy vs no (or delayed) chemotherapy 9 studies were identified including circa 2000 patients. Results of this cycle will be presented.

1567

Biology of lung tumours: Targeting bcl-xL and EGP-2

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We have previously demonstrated the anti-apoptotic protein Bcl-2 to be a promising target for antisense-based therapy of small cell lung cancer. In contrast to small cell lung cancer, in non-small cell lung cancer the Bcl-2 homologue and related cell death antagonist Bcl-xL is more commonly overexpressed. Using the secondary structure of the bcl-xL mRNA to predict the most promising target sites for antisense binding a series of dodecamer phosphorothioate antisense oligonucleotides were designed. Oligonucleotide 3011 was found to most effectively downregulate Bcl-xL protein levels and to induce apoptosis in non-small lung cancer cell lines. However, sequence control oligonucleotides also revealed a certain degree of unspecific cytotoxicity, making it difficult to discern the true antisense effect. To overcome this limitation, novel 2'-O-methoxyethly modified gapmer oligonucleotides with improved binding affinity and stability were designed. Three compounds were tested, including oligonucleotide 4259 (identical sequence as 3011), 4625 (with specificity for bcl-2 and 3 mismatches to bcl-xL) and 4627 (with one mismatch to bcl-2 and 2 mismatches to bcl-xL). Although oligonucleotide 4259 reduced bcl-xL message and protein levels in a dose dependent manner in non-small cell as well as small cell lung cancer cell lines, its effect on cell viability was more pronounced in non-small cell compared to small cell lung cancer cell lines. In contrast to the deoxy compounds the 2'-MOE modified sequence control oligonucleotides did not significantly reduce cell viability. Induction of apoptosis in non-small cell lung cancer cell lines was demonstrated by induction of caspase-3-like activity. The potentially bispecific antisense oligonucleotides 4625 and 4627 inhibited both bcl-2 and bcl-xL expression and reduced cell viability of non-small cell and small cell lung cancer cell lines. Our results imply the importance of the Bcl-xL protein in the tumorigenesis of non-small cell lung cancer and suggest the use of gene therapy approaches to counteract the expression of this cell death antagonist. Moreover, we show for the first time that it is possible to target the expression of Bcl-2 and Bcl-xL with a single antisense compound.

The epithelial glycoprotein-2 (EGP-2) is a surface antigen highly expressed in small cell and lung adenocarcinoma. Based on the monoclonal antibody MOC-31, we developed a single-chain antibody fragment (scFv) against EGP-2. To stabilize the unstable scFc we chose rational loop grafting of the binding residues on a stable antibody framework with favorable biophysical properties. The resulting molecule 4D5MOCB retained the high binding affinity of 10-9 M, while exhibiting a better expression behavior and serum stability, and demonstrated good tumor to blood ratios in a xenograft model. 4D5MOCB new serves as a basis to develop better targeting molecules directed against small cell and non-small cell lung cancer, as well as other solid tumors.

1568

Early non small cell lung cancer: The need for combined treatments

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As result of several randomized studies and the large meta-analysis published in 1995 on the BJC, locally advanced non-small cell lung cancer (NSCLC) is nowadays mainly treated by combined modality treatments. Chemotherapy including a platinum compound is generally part of the combined modality treatment. The local treatment varies depending on the staing of the disease, but also by country. In stage III technically resectable, the addition of neoadjuvant chemotherapy has been showed to improve survival in 3 small randomized trials. However, whether radical radiotherapy can achieve results similar to surgery is still a matter of debate. A large EORTC randomized trial is addressing this question in patients with histologically verified stage IIIaN2 disease who respond to platinum-based chemotherapy. The study has now accrued over 400 patients and randomized over 200 of them; the response rate to the newest combination chemotherapy (e.g. cisplatin-gemcitabine or carboplatin-paclitaxel) is well over 50% in this patient population. Other similar studies are running the the US. However, in the US chemotherapy is usually given concomitant to radiation. This leads to an improved response rate, with over 20% pathological complete response rates (it is less than 10% in chemotherapy only treatments), but also increased toxicity and morbidity of operation. For inoperable stage III (usually stage IIIb) radiation therapy has been standard treatment in several institutions. The combination of chemotherapy and radiation has now become standard in many centers. However, the optimal way of combining these modalities still needs further investigation. In particular the timing of the treatments, the radiation dose and volume, the type of chemotherapy are still under evaluation.

Recently combined modality treatment has been evaluated also in early stage (stage I, II, IIIa) resectable NSCLC, and promising results have been recently reported. Neoadjuvant chemotherapy seems feasible in this patient category with very few progressions before surgery. Response rates are very high and the only randomized study so far presented appears to be positive for some subgroups of patients. Tolerability of the chemotherapy, together with its effectiveness are major issues in this type of studies. It is however clear that the compliance to neoadjuvant chemotherapy is higher than that to post-operative chemotherapy.

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Post-operative treatments in resected NSCLC

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Five-year survival rate of patients (pts) with non-small cell lung cancer (NSCLC) who undergo complete surgical resection is only 40–69%, depending on the stage. It is well known that distant metastatic disease is the dominant site of recurrence in such patients and this observation served as the basis for trials of postoperative systemic therapy. The earliest trials of adjuvant chemotherapy, which consisted of single alkylating agents, could not achieve this goal or, even worse, showed a detrimental effect of chemotherapy on survival. The introduction of more active drags, such as cisplatin and vinca alkaloids, made it possible to obtain more promising results in terms of delayed recurrence of the disease. A recent meta-analysis including all randomized trials with accrual from January 1965 to December 1991 showed that the absolute risk of death was reduced by 3% at two years and by 5% at 5 years for pts who were treated with postoperative cisplatin-con-