has not improved over the last 20 years. During this time the mainstay of treatment has been single agent chemotherapy, most often with dacarbazine although other alkylating agents, platinum based drugs and vinca alkaloids are also used. Immunotherapies hold some promise, yet phase II studies of interferon and interleukin 2 have not indicated better outcomes for this group of patients than with chemotherapy. A small minority of patients achieve durable complete responses with interleukin 2. Twice in recent years important advances in treatment appear to have been made, but on both occasions large scale studies have failed to confirm earlier results. In the 1980s phase II trials demonstrated greatly enhanced response rates for combination chemotherapy, particularly the Dartmouth regimen of dacarbazine, BCNU, cisplatin and tamoxifen. Multi-centre phase III trials confirmed this increase in responses, but found no impact upon overall survival. The initial, promising results are likely explained by patient selection, for within the grouping of metastatic melanoma there is a wide variation in survival time. The recent AJCC classification highlights this: 29% of patients with M1a disease will be alive at 2 years, compared with 7% with stage M1c. A similar story is being played out with biochemotherapy. Single institution phase II trials suggested a substantial benefit for this approach in patients able to tolerate treatment. Initial interest centred upon the combination of dacarbazine and interferon. However, an ECOG study involving over 250 patients found no advantage to this combination over chemotherapy alone, a finding borne out in a recent meta-analysis. Other groups have tested a variety of combination chemotherapies with varying regimes of interferon and interleukin 2. Phase III trials of the most promising biochemotherapies, involving hundreds of patients, have shown no survival advantage over chemotherapy alone. In 2003 the best treatment option that we can offer patients with metastatic melanoma, outside of clinical trials, is still single agent chemo- or immunotherapy.

350

## Design and testing of chemically–defined melanoma vaccines

J.-C. Cerottini. *Ludwig Institute for Cancer Research, Lausanne Branch, Epalinges, Switzerland*

The molecular identification of melanoma antigens recognized by CD8 and CD4 T cells has paved the way to approaches for the design of therapeutic cancer vaccines that are based on the use of chemically defined antigenic peptides and adjuvants. Most of the trials in progress are focused on the vaccination of melanoma patients with peptides derived from cancer germline gene products, such as the MAGE family, and/or melanocyte lineage-associated proteins, such as the Melan-A/MART-1 antigen. The selection of the antigenic peptides to be incorporated in a given vaccine has to take into account the HLA allele pattern expressed by individual patients as well as the antigenic peptide profile of individual tumors. In some instances, the immunogenicity of peptides can be increased substantially by altering specific aminoacid residues at positions that anchor the peptide to the corresponding HLA molecule and/or confer susceptibility to proteolytic degradation by proteases. As the number of variables to be tested for the optimization of antigen-specific T cell responses is very large, the initial evaluation of vaccine-based strategies cannot rely on usual clinical end points, such as tumor regression or time to recurrence, because of the number of patients and years required to achieve meaningful results. Instead, immunological assays that enable quantitative and qualitative monitoring of antigenic peptide-specific T cell responses are being used to evaluate the immunogenicity of candidate vaccines in phase I clinical trials. Although monitoring methodologies have undergone considerable improvement over the past few years, the complexity of the immune response makes the identification of the most effective immunization procedures quite a challenge. Moreover, application of these assays to the monitoring of specific CD8 T cell responses induced by peptide-based vaccines in melanoma patients has revealed significant interindividual differences, which may reflect the preexistence, or lack thereof, of a spontaneous tumor antigen-induced response in these patients. It is thus necessary to use standardized assays to evaluate the development of immune responses triggered by different vaccine strategies in individual patients. In addition, immunological monitoring should include analyses both in the peripheral circulation and at the tumor site because of possible numerical and functional discrepancies between tumor antigen-specific T cells residing in these compartments

351

## Conformal radiotherapy in prostate cancer: development of the new "standard of care"

D.P. Dearnaley. *The Royal Marsden Hospital, Department of Radiotherapy, Sutton, United Kingdom*

The last decade has seen the widespread implementation of CFRT and dose escalated treatments for prostate cancer. Large "phase I" studies, principally from specialist centres in the USA, have documented the safety of these techniques with reports of apparent improvements in disease control. However, it has recently been appreciated that cohort effects in sequentially treated groups of patients may have led to significant bias due to "stage migration". The results of single centre phase III dose escalation trials (MD Andersen and Institute of Cancer Research/Royal Marsden Hospital) indicate improvements in PSA control for men with advanced localised disease, but benefit for patients with good prognosis disease has not yet been confirmed. Assessment of other clinically meaningful endpoints such as metastases free and overall survival will become possible as other larger multicentre trials, which will in total recruit approximately 4,400 men, reach maturity. Data from these trials and other sources should more clearly define dose-volume-complication relationships and individualisation of treatment based on prognostic features for tumour control and complication probabilities may become realistic.

The role of IMRT is yet to be clearly defined but may offer advantages for some anatomic configurations; complex high dose volumes can be shaped and pelvic lymph node irradiation achieved with a significant reduction in bowel volumes treated to high dose. Modelling studies have shown the potential benefit of intra-prostatic boosts, but improvements in MRI and functional imaging are needed to define such "dominant intraprostatic lesions". Such refinements in treatment require attention to the details of all parts of the "technology chain" in particular to the verification of treatment accuracy taking into account the potential for prostate target movement. A variety of localising devices (fiducial markers, localising catheter, ultrasound, rectal balloons) are being assessed to enable development of guided radiotherapy techniques. These methods of "physical optimisation" will be complementary to "biological optimisation" approaches using both altered fractional or combined modality treatments.

352

## Combination of hormonotherapy (HT) and external irradiation (RT) in prostate cancers. Neo-adjuvant and/ or adjuvant hormonotherapy?

M. Bolla. *Centre Hospitalier de Grenoble, Department of Radiotherapy, Grenoble, France*

Androgen suppression improves the outcome of external irradiation: it possibly eliminates occult systemic disease outside the irradiated volume and has at least an additive effect on local control by inducing apoptosis. RTOG and EORTC trials investigated this combination in locally advanced prostate cancer, cT2c-T4 N0-1 M0 (UICC 1992). Protocol 86-10compared androgen deprivation (flutamide and goserelin) with radiation therapy vs radiation therapy alone in patients with large T2 or T3-4 tumors; androgen deprivation was initiated 2 months prior to starting radiotherapy and stopped at the completion of radiotherapy. Hormonotherapy increased the local control, distant metastases free rate, progression free survival and overall survival in patients with Gleason score 2-6. Protocol 85-31 was devoted to adjuvant androgen suppression with goserelin in T1-2 patients with regional lymph node involvement, T3 regardless of regional lymph node status or pT3 after prostatectomy. Goserelin was started at the end of the radiotherapy and continued indefinitely. There was an increase of the local control, distant metastases free rate, disease free survival; in patients with centrally reviewed tumors with a Gleason score of 8 to 10 there was a difference in survival in favor of the adjuvant goserelin arm. In protocol 92-02, patients with T2c-T4 tumors received goserelin and flutamide two months before and two months during radiation and were randomized to no further therapy or to 24 additional months of goserelin alone (LTAS). The LTAS arm significantly improved the disease free survival, local control, time to distant metastases, time to biochemical failure and showed a favorable trend for disease specific survival. In trial 94-13 the benefits of whole pelvis radiotherapy are manifested when HT is given before and during RT. EORTC trial 22861 has shown that androgen suppression with goserelin given during and for 3 years after external irradiation improves disease free and overall survival whatever the Gleason score is. EORTC trial 22961 closed in 2001, compared surveillance to hormonotherapy with triptoreline for 2·5 years after external irradiation and 6 months of combined androgen blockade. It is now possible to modulate the duration of hormonotherapy

according to prognostic factors. Randomized trials devoted to localized prostate cancers treated with optimized techniques of radiotherapy, plus short term HT, will be rewied.

353

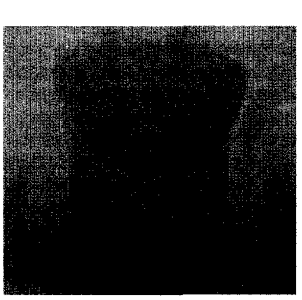
## Brachytherapy of the localized prostate cancer: indications, results and side effects

G. Kovacs. *University Hospital Schleswig-Holstein Campus Kiel, Interdisciplinary Brachytherapy Centre, Kiel, Germany*

**Introduction:** Brachytherapy for prostate cancer could be applied as monotherapy or as a boost in combination with external beam irradiation.

**Methods:** Permanent (seeds) and temporary (remote afterloading) implantations are possible.

**Results:** The most important prognostic factors for disease free survival are initial PSA, Gleason (or WHO) grade and stage. For functional outcome the initial prostate volume and lower urinary tract symptoms best characterised by the IPSS score provide the best guide to outcome. There are no prospective randomised studies proving different types of radiation treatment, but in high/intermediate risk cases the long-term treatment results of combined EBRT and low-dose-rate (LDR) or HDR brachytherapy are favourable. HDR BT alone is not a standard treatment, it represents still subject of clinical experiments. The treatment decision always represents also the effectiveness of the work of a given interdisciplinary group. If a group can offer a bright spectrum of treatment variations, the most effective schedule seems to be as follows: (a) at low-risk patients permanent implants (Fig.1) or radical prostatectomy, (b) at intermediate- or high-risk patients combined external beam treatment and local dose escalation boost using a temporary implant (Fig. 2). Interstitial brachytherapy of the prostate (both seeds and HDR) is not indicated if (a) the patient has a shorter life expectancy than 5 years, (b) the patient has not only local disease, (c) TUR was performed previously, (d) there is a large prostatic defect according to previous TURP, (e) the tumour has a smaller distance to the rectal mucosa than 5 mm, (f) the patient has general contraindications for adequate anaesthesia and/or operative treatment, (g) the treatment is not to complete because of technical problems based on anatomical abnormalities. Long term results in the literature show, that treatment results with permanent implants alone are equal to that of the radical prostatectomy in the case of low-risk patients. The role of additional hormonal deprivation is not yet clear.



**Conclusion:** Patients with higher risk have a clear advantage of combined external beam and interstitial implantation. Thus of medium or high-risk prognostic groups have a clear benefit due to the treatment in terms of results and economics. Patients have the best chance for best possible cure, if the treatment will be coordinated and performed by experienced interdisciplinary teams.

354

## The development and expectations of IMRT in the treatment of prostate cancer

M. Zelefsky. *Memorial Sloan Kettering Cancer Center, Department of Radiation Oncology, New York, USA*

With the recognition that higher doses of irradiation are critical for achieving maximal tumor control among patients with clinically localized prostate cancer, enhanced modes of conformal radiotherapy delivery systems would represent attractive directions to pursue. IMRT is an advanced form of 3-Dimensional Conformal Radiotherapy (3D-CRT) that has been shown to significantly improve the conformality of the dose distribution. Treatment planning is based on the inverse technique and uses an iterative computer-driven optimization method to generate treatment fields with varying intensities over the cross-section of the beam. The combination of multiple intensity-modulated fields produces custom-tailored conformal dose distributions with steep dose gradients at the boundaries between the target and the normal structures.

We have demonstratedthat IMRT improves the conformality of high-dose radiotherapy delivery compared to conventional 3D-CRT. In one study, 20 randomly selected patients were planned concomitantly by both techniques and the resulting plans were compared with DVH analyses for a number of dosimetric parameters. This study indicated that while on average 98 $\pm$ 2% of the clinical target volume would receive 81 Gy with IMRT, only 95 $\pm$ 2% would receive the same dose with 3D-CRT ($p < 0.01$). At the same time, the percentages of the rectal wall (9 $\pm$ 3% vs. 13 $\pm$ 4%) and bladder wall (28.8 $\pm$ 8% vs. 32 $\pm$ 9%) volumes carried to 75 Gy were significantly decreased with IMRT ($p < 0.01$). These data provided evidence supporting the notion that IMRT significantly improves the conformality of radiation treatment in prostate cancer.

The improved conformality and reduction of irradiated rectal tissue with IMRT translated into a decrease in rectal toxicity and provided an opportunity for the safe delivery of radiation doses to as high as 86.4 Gy. To further validate the IMRT approach, the toxicity outcomes of 171 patients treated with IMRT to 81 Gy were compared with 61 patients treated with the 3D-CRT approach to the same dose level. Acute and late urinary toxicities were not significantly different for the two methods. However, the combined rates of acute grade 1 and 2 rectal toxicities and the risk of late grade 2 rectal bleeding was significantly lower in the IMRT patients ($p = 0.05$ and 0.0001, respectively). The 5-year actuarial rates of grade 2 rectal bleeding were 2% for IMRT and 10% for 3D-CRT ($p < 0.001$). We have recently analyzed the outcome of 772 patients treated with IMRT (698 to 81 Gy and 74 to 86.4 Gy. With a median follow-up of 24 months (range, 6 to 60 months), only 11 patients (1.5%) have thus far developed grade 2 rectal bleeding, and four (0.5%) have experienced grade 3 rectal toxicity. The 3-year actuarial rate of $\geq$ grade 2 rectal bleeding was 4%. exhibit rates ofseries ) Thus, the improved conformality and reduction of irradiated rectal tissue with IMRT translated into a decrease in rectal toxicity and provided an opportunity for a safe escalation of dose to 86.4 Gy. As both local control and long-term PSA relapse–free survival are dose-dependent, these data confirm that IMRT represents a noteworthy advancement in the ability to deliver high-dose radiation in prostate cancer.

**(Describe preliminary outcome data and show that it is not worse than 3D)**

The implementation of IMRT requires strong medical physics support and collaboration. The technical aspects of treatment delivery, careful evaluation of treatments plans balancing the normal tissue constraints with the need for optimal target coverage and quality assurance protocols are demanding. Although the margins we routinely use the planning target volume remain the same for 3D-CRT and IMRT, given the enhanced degree of conformality of the dose distribution for the latter, organ motion issues remain important for the clinician to be aware of and address. Yet, despite these technical challenges of IMRT, the reduced toxicity profiles we have observed with this approach which in turn has improved the quality of life of our treated patients is the reason IMRT has become the standard mode of treatment delivery for prostate cancer at Memorial Sloan Kettering Cancer Center.

355

## Cancer gene discovery

M.R. Stratton. *The Wellcome Trust Sanger Institute, Cancer Genome Project, Cambridge, United Kingdom*

A major application for the human genome sequence in elucidating oncogenesis will be as a template subserving genome-wide searches for somatic mutations in cancer cell genomes. A full description of changes at the DNA level in cancer cells will require information on all types of abnormality; copy number changes, rearrangements, point mutations and methylation. Currently, however, there is no single technology that practically can address this diversity of mutation class simultaneously. To begin the process of using a whole genome sequence, we have embarked upon systematic genome-wide searches for small intragenic mutations (base substitutions and small insertions / deletions) and homozygous deletions in cancer cell lines. These searches are beginning to yield fruits in terms of newly identified somatically mutated cancer genes. The first fruit of this process has been the discovery of mutations in the BRAF gene in human cancer. BRAF is a member of a family of three serine / threonine kinases that also includes RAF-1 (also known as CRAF) and ARAF. RAF proteins are recruited to the cell membrane and activated by RAS proteins in the RAS-RAF-MEK-ERK-MAPkinase signal transduction pathway. Mutations of BRAF were found in 70% of melanomas and in a lower proportion of other cancers. Over