PROSTATE CANCER HOT SHEET

US TOO! INTERNATIONAL JUNE 2003

AUA 2003 ROUNDUP

TREATMENT OPTIONS - PART 1

Following are selected clinical abstracts from the 2003 Annual Meeting of the American Urological Association (AUA) held in Chicago, April 26 - May 1, 2003. This selection focuses on treatment options including Brachytherapy, Chemotherapy, Cryotherapy/ Cryoablation, Hormonal Therpay and Watchful Waiting. (Note: Title is preceeded by abstract number) To access the complete abstract on these and other selections from AUA 2003 visit the ***Us Too!*** website: http://www.ustoo.org/AUA2003.html

BRACHYTHERAPY

1720: 10-YEAR BIOCHEMICAL AND LOCAL CONTROL FOLLOWING REAL-TIME I-125 PROSTATE BRACHYTHERAPY

Nelson N Stone, et al

Introduction and Objective: We determined the 10-year biochemical and local control results for I-125 prostate brachytherapy in men implanted by the real-time technique who have been followed a minimum of 4 years.

Conclusions: These data demonstrate high biochemical and local control in men with T1-T2 prostate cancer treated with I-125 brachytherapy. Delivered radiation dose and risk category are important predictors of success. The risk of biochemical and local failure are high if the delivered dose is less than 120 Gy. Patients receiving a dose of at least 160 Gy have a 93% chance of FFF and a 95.4% likelihood of local control.

Univariate Analysis for 10 year Biochemical Freedom From Failure

Variable	PSA≤10 vs >10	Stage ≤T2a vs ≥T2b	Low vs high risk	HT vs no HT	D90≥160 vs <160 Gy
% FFF	86 vs 63	88 vs 61	91 vs 66	94 vs 75	93 vs 70
P Value	0.001	0.0002	<0.001	0.013	<0.001

699: PROSTATE SPECIFIC ANTIGEN NADIR AFTER BRACHYTHERAPY FOR PROSTATE CANCER CORRELATES WITH PROGNOSIS OF MEN WHO RECUR

Frank A Critz, et al

Introduction and Objective: Clinical factors associated with prognosis after failure are evaluated in this study of men with recurrent prostate cancer treated five or more years ago by brachytherapy.

Conclusions: The PSA nadir achieved after treatment with brachytherapy is the single most important factor associated with subsequent prognosis for non-surgically staged men who have recurrent prostate cancer.

Nadir group	No. (%)	Time to recurrence (mos.)	Hormones	Hormone Resistant
≤0.2	37 (25%)	54	11%	0%
0.3-0.5	35 (24%)	30	20%	3%
0.6-1.0	34 (23%)	18	56%	24%
1.1-2.0	34 (15%)	24	61%	17%
>2.0	20 (13%)	12	85%	45%

With administration of hormones as an end-point, on multivariate analysis the PSA nadir is highly significant (p=0.001), Gleason score is of lower significance (p=0.04), but pretreatment PSA and stage are not significant factors. With hormone resistant disease as an end-point, only PSA nadir achieved (p=0.003) has significant prognostic value relative to these same factors.

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CAN LIFESTYLE CHANGES STOP PROSTATE CANCER?

Ed Edelson / HealthScoutNews

Changes in lifestyle can reverse the progress of prostate cancer, a leading proponent of alternative medicine says in a claim met with interested skepticism by medical experts.

The claim was made in a presentation by Dr. Dean Ornish, founder and director of the Preventive Medicine Research Institute in Sausalito, Calif., at the annual meeting of the American Urological Association in Chicago.

Ornish has been preaching lifestyle change as a way to reverse heart disease for years, in medical journals and five best-selling books.

His prescription calls for a low-fat vegan diet supplemented with soy and oxidants, moderate aerobic exercise, stress management and psychosocial group support. Now he says the same regimen lowered levels of prostate-specific antigen (PSA), a marker of the cancer, in a one-year study.

The study included 87 men with diagnosed prostate cancer at an early stage, when doctors often choose to do nothing while they check on the progress of the tumor — "watchful waiting," in medical terms. In the study, 41 of the men were assigned to observe the Ornish regimen carefully, under supervision. The others were allowed to follow the regimen if they chose, with no supervision.

At the end of three months, PSA levels dropped by 5 percent in the group following the regimen but rose by 1 percent in the control group, Ornish says. The difference in PSA levels was greater after one year: down by 3 percent in the regimen group, up 7 percent in the control group.

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1665: RELATIONSHIP OF BIOCHEMICAL OUTCOME TO PERCENT POSITIVE PROSTATE BIOPSIES IN CLINICALLY LOCALIZED PROSTATE CANCER TREATED WITH PERMANENT INTERSTITIAL BRACHYTHERAPY

Richard Lee, et al

Introduction and Objective: Recent studies have demonstrated that the percent of positive prostate needle biopsy cores can predict biochemical outcome after radical prostatectomy or external beam radiotherapy. Conclusive corresponding data for permanent interstitial brachytherapy however are lacking. We have conducted an analysis to determine the clinical utility of the percent of positive prostate biopsies (PPB) in predicting PSA outcome following interstitial brachytherapy for prostate cancer.

Conclusions: Our results suggest that the percent of PPB is positively but not significantly associated with biochemical outcome for patients undergoing permanent interstitial brachytherapy. Gleason score, preimplant PSA, and age were significant predictors of biochemical failure; the first two were also significant in predicting time to failure. Our data suggest that the ability to aggressively treat and dose-escalate the periprostatic region with interstitial brachytherapy may obviate the clinical utility of percentage of PPB in predicting biochemical failure.

277: SECONDARY BLADDER CANCER AFTER BRACHYTHERAPY FOR PROSTATE CANCER

Lee R Schachter, et al

Introduction and Objective: Several studies have documented an increased incidence of bladder cancer after radiation to the pelvis. Most reports have involved radiation for cervical cancer, although cases secondary to radiation for prostate cancer have also been reported.

Conclusions: We report the largest series of secondary bladder cancers after brachytherapy with or without external beam radiation therapy (EBRT) for prostate cancer, and at a rate significantly higher than expected. While most previous reports suggest that the majority of cases occur more than five years after radiation therapy, nine of our ten cases occurred within five years. A high index of suspicion is important to appropriately diagnose and treat this subset of patients, and we routinely work up all episodes of hematuria after one year.

692: TEN YEAR DISEASE FREE SURVIVAL RATE CALCULATED WITH PSA CUTPOINT 0.2 NG/ML IN MEN AFTER BRACHYTHERAPY FOR PROSTATE CANCER

Frank A Critz, et al

Introduction and Objective: Recent reports have documented that it is misleading to compare irradiation disease free survival (DFS) rates calculated by the American Society of Therapeutic Radiation Oncology definition with radical prostatectomy DFS rates calculated by an undetectable prostate specific antigen (PSA). Instead, the same definition of disease freedom should be used to calculate results after surgery or irradiation for localized prostate cancer and PSA cutpoint 0.2 ng/ml has been recommended as the standard. The DFS rates of this brachytherapy program calculated by this standard are documented for men treated five or more years ago.

Conclusions: To be fair when comparing irradiation results with radical prostatectomy, a standard definition of disease freedom must be used and, since PSA falls slowly after irradiation, men should have minimum five-year followup to allow time for recurrence and also time to achieve PSA 0.2 ng/ml (99% of men who achieve PSA 0.2 ng/ml after irradiation do so by five-year followup). These 10-year DFS rates can be reasonably compared with radical prostatectomy results from the PSA era.

1846: THE IMPORTANCE OF IMPLANT QUALITY FOR PATIENTS UNDERGOING PROSTATE BRACHYTHERAPY

Louis Potters, et al

Introduction and Objective: To evaluate disease and treatment related factors for predicting the 7-year biochemical freedom from survival (BFS) in patients undergoing permanent prostate brachytherapy (PPB) for clinically localized prostate cancer.

Conclusions: PPB quality as measured by the D90 dose was the most significant predictor for BFS in this study cohort. Further, the addition of EBT and/or NAAD did not independently predictor BFS. While the reported 5 and 7-year BFS rates in this study are favorable, the importance of implant quality remains paramount to assess outcome. All efforts to maximize implant quality should be performed. When reporting brachytherapy outcomes, implant quality should also be reported.

1841: URINARY AND RECTAL COMPLICATIONS OF CONTEMPORARY PROSTATE BRACHYTHERAPY (PB) FOR PROSTATE CANCER (PC)

Michael F Sarosdy

Introduction and Objective: PB is a popular treatment for PC alone or with external beam therapy (PB+EBT) for high risk disease. Most reports on PB do not detail complications. This review assesses urinary and rectal complications requiring intervention after contemporary PB.

Conclusions: Complications of PB occur, and increase significantly in nature, frequency, severity, and permanency for PB+EBT. These may limit the use of PB+EBT. Importantly, high implant quality (v100 > 95%) does not appear to protect against complications when EBT is added to PB.

Invasive Procedures for Complications

Procedure	Overall	PB	PB+EBT
Catheter Required	20%	24%	16%
TURP	9%	5%	15%
Colonoscopy +/- fulg.	20%	16%	35%
fecal diversion	2.6%	0	6.6%
urinary diversion or CIC	3.2%	0	8.2%

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CHEMOTHERAPY

822: CHEMOSENSITISATION OF HUMAN PROSTATE CANCER USING ANTISENSE AGENTS TARGETING THE TYPE 1 INSULIN-LIKE GROWTH FACTOR RECEPTOR

Giles O Hellawell, et al

Introduction and Objective: The type 1 insulin-like growth factor receptor (IGF1R) is important for tumour growth and apoptosis protection. We have recently shown that the IGF1R is overexpressed by prostate cancer compared with benign prostatic epithelium, and IGF1R expression commonly persists in androgen-independent metastatic disease at levels comparable to those in the primary (Cancer Res 62:2942-50, 2002). The importance of this receptor has been reinforced by a recent report of IGF1R upregulation in prostate cancer cells during the development of androgen-independence. The objective of this study was to determine whether antisense mediated IGF1R downregulation could enhance the chemosensitivity of androgen-independent prostate cancer cells in vitro.

Conclusions: These results indicate that IGF1R downregulation can enhance chemosensitivity of androgen-independent prostate cancer in part via enhanced susceptibility to apoptosis. In a clinical setting, targeted suppression of the IGF1R using ASO technology may enhance the effects of conventional chemotherapy and therefore offers promise as novel therapy for patients with androgen-independent disease.

1491: DOCETAXEL AND MITOXANTRON IN THE MANAGEMENT OF HORMONE REFRACTORY PROSTATE CANCER: RESULTS OF A PROSPECTIVE PHASE-II TRIAL

Axel Heidenreich, et al

Introduction and Objective: Taxanes are the most active cytotoxic drugs in hormone refractory prostate cancer (HRPCA). The combination of docetaxel (DOC) and mitoxantron (MIT) has been shown to be highly active as first or second line chemotherapy in metastatic breast cancer. It was the purpose of this trial to determine the response rate of DOC/MIT in patients with asymptomatic HRPCA.

Conclusions: Combination of DOC and MIT is well tolerated, has a limited spectrum of therapy associated side effects, does not interfere with QoL, and results in a high objective response rate in HRPCA with asymptomatic PSA progression. DOC/MIT will serve as control arm for further prospective randomised phase-III-trials.

840: SAFETY AND EFFICACY OF ELECTROPERMEABILIZATION AFTER ADMINISTRATION OF BLEOMYCIN ON PROSTATE CANCER IN SCID MICE

Yoko Kubota, et al

Introduction and Objective: Cell electropermeabilization allows non-permeating drugs, such as bleomycin, to enter cells. Electric pulses permeate cell membrane and deliver the drug inside the cells (electrochemotherapy). We evaluated the safety and efficacy of electropermeabilization after administration of bleomycin on prostate cancer in SCID mice.

Conclusions: The safety and efficacy of electrochemotherapy using bleomycin on prostate cancer were demonstrated.

339: SELECTIVE CHEMOSENSITIZATION OF ANDROGEN-INDEPENDENT PROSTATE CANCER USING NEUTRAL ENDOPEPTIDASE

Makoto Sumitomo, et al

Introduction and Objective: In prostate cancer (PC) conventional chemotherapy has had very limited success especially in the control of androgen-independent prostate cancer (AIPC). We have recently reported that in PC cells neutral endopeptidase (NEP) has a novel function to stabilize protein kinase C (PKC) which has been implicated in anticancer drug-induced mitochondrial apoptosis. We investigated whether NEP could augment chemosensitivity by promoting PKC-mediated mitochondrial apoptosis in AIPC cells.

Conclusions: These results suggest that NEP enzyme activity contributes to anticancer drug-induced PC cell apoptosis dependent on PKC-mediated mitochondrial events. More importantly, our findings may provide a promising therapeutic modality to augment chemosensitivity selectively in AIPC with minimal toxicity in the normal tissue.

1662: WEEKLY DOCETAXEL AND MITOXANTRONE PRIOR TO PROSTATECTOMY IN PATIENTS WITH HIGH RISK LOCALIZED PROSTATE CANCER

Tomasz M Beer, et al

Introduction and Objective: While combined modality therapy has improved survival in high-risk breast and colon cancer, this approach has been sparsely investigated in the management of prostate cancer. Docetaxel and mitoxantrone have substantial single-agent activity in advanced prostate cancer but have not been combined in this disease. We report the development of a new regimen that combines these drugs in high-risk patients undergoing prostatectomy.

Conclusions: Weekly docetaxel and mitoxantrone is a well-tolerated regimen in the treatment of high risk prostate cancer prior to prostatectomy. Direct anti-tumor activity of this regimen is suggested by PSA reductions in the absence of change in testosterone levels.

CRYOABLATION / CRYOTHERAPY

DP23: QUALITY OF LIFE AFTER PRIMARY OR SALVAGE CRYOTHERAPY FOR CLINICALLY LOCALIZED PROSTATE CANCER

Aristotelis G Anastasiadis, et al

Introduction and Objective: Recent modifications in the technique of cryosurgery of the prostate have led to the ability to treat tumors successfully with decreased morbidity. The patients' perspectives of this relatively new technique, however, have not yet been addressed. The purpose of this study was to evaluate health-related Quality of Life (QoL) in patients after cryoablation for clinically localized prostate cancer using a validated and reliable, self-administered questionnaire.

Conclusions: Previous studies have already demonstrated safety and feasibility of prostate cryosurgery. This report underlines that the procedure, in appropriately selected cases, is well tolerated and contributes to preservation of quality of life in this patient group.

DP15: SALVAGE CRYOSURGERY FOR RECURRENT PROSTATE CANCER AFTER RADIATION THERAPY: A 7-YEAR FOLLOW-UP

Duke K Bahn, et al

Introduction and Objective: Up to 30% of patients who receive radiation therapy for prostate cancer will have a recurrent disease. Salvage radical prostatectomy for radioresistent disease is associated with high morbidity, and long recovery time. Cryosurgery has been investigated as a salvage therapy following failed radiation therapy and was found to have acceptable morbidity although its long term efficacy

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was unknown. Presented are seven year actuarial outcomes of salvage cryoablation.

Conclusions: We have found that salvage cryosurgery is a promising form of treatment for radioresistent prostate cancer. 7-year retrospective analysis shows a success rate comparable to a virgin group if salvage cryosurgery is performed when PSA <10 ng/mL. Minimal morbidity rates and no known latent complications further validate cryoablation as a viable option for recurrent prostate cancer following failed radiation therapy.

1486: SALVAGE CRYOSURGERY USING 3RD GENERATION CRYO "NEEDLES"

Ken-Ryu Han, et al

Introduction and Objective: Increasing numbers of patients are presenting with rising PSA and local cancer recurrence following radiation therapy (XRT)- either brachytherapy and/or external beam radiation therapy (EBRT) for the treatment of localized prostate cancer (CaP). Salvage prostatectomy in these cases is associated with significant morbidities, leaving the patient with watchful waiting, hormone deprivation therapy, or cryosurgery as alternative therapeutic options. We reviewed the preliminary experience using 17-gauge (1.47mm), 3rd generation cryo "needles" in the treatment of recurrent CaP after XRT.

Conclusions: Salvage cryosurgery using minimally invasive 17-gauge cryo "needles" can be performed through a brachytherapy template. It offers an attractive alternative to salvage prostatectomy for patients who fail XRT. Preliminary complications rates suggest decreased morbidity compared to earlier generations of cryosurgery. Long-term follow-up of PSA values and survival is necessary before any comment on efficacy can be made.

Complications rates after salvage cryosurgery

Complication	
Urinary retention	2/18 (11.1%)
Urge Incontinence	1/18 (5.6%)
Incontinence (Pads)	2/18 (11.1%)
Penile paresthesia	1/17 (5.9%)
Impotence	16/18 (89%)
Pelvic pain	1/18 (5.6%)
Scrotal swelling	2/18 (11%)

1488: SERIAL BIOPSY AND PROSTASTE SPECIFIC ANTIGEN (PSA) RESULTS ON SALVAGE CRYOABLATON FOR PROSTATE CANCER: 5 YEAR RESULTS ON 142 PATIENTS (PTS)

Joseph L Chin, et al

Introduction and Objective: Cryoablation (Cab) is now approved first-line therapy in the U.S. in previously untreated prostate cancer. However, aside from short-term biopsy results, there has been a paucity of long-term results on prostate primary Cab and no reports on histologic and prostate specific antigen (PSA) long-term results from salvage Cab. Serial biopsy and PSA results up to 5 years (yrs) are reported herein on 142 pts who underwent salvage Cab after radiation failure.

Conclusions: Cab has a role in radiation-failure pts. who have few remaining therapeutic options. Satisfactory long-term results with acceptable morbidity can be achieved thereby obviating or deferring long-term endocrine therapy, provided rigid selection criteria are used. Findings of residual viable benign glandular and stromal tissue mandates vigilant long-term follow-up.

1722: CRYOABLATION OF THE PROSTATE FOR LOCALIZED PROSTATE CANCER. 8 YEAR EXPERIENCE WITH 215 CASES

Fletcher C Derrick, et al

Introduction and Objective: Between Jan 1994 and Aug 2002, 215 cases of Cryoablation of the Prostate (CryoP) procedures were performed. The objective was to determine the efficacy of this treatment modality in cases of primary cancer of the prostate and in cases of radiation failure. 90% of the cases treated had primary cancer (T-1 and T-2 disease) and 10% had radiation failure (both from brachytherapy and external beam). Gleason's numbers varied from 5-9.

Conclusions: It is our opinion that Cryoablation of the prostate is a minimally invasive, alternative treatment of primary cancer of the prostate. CryoP is also a treatment choice for radiation failure patients, when it can be determined that the cancer is still confined to the prostate gland.

861: IMMUNO-CRYOTHERAPY OF PROSTATE CANCER: APPLICATION IN A MOUSE MODEL

Michael Cohen, et al

Introduction and Objective: Cryoablation of prostate cancer is gaining increasing popularity, especially as a treatment modality for radiation therapy failures. We propose to combine Cryoablation of prostate cancer with both local and systemic immuno-modulatory techniques (Adenoviral murine Granulocyte-Macrophage Colony Stimulating Factor {AdmGMCSF} And Cytotoxic T Lymphocyte-Associated Antigen 4 {CTLA-4}Blockade, respectively). We suggest that this approach may enhance local tumor eradication and synergistically augment anti-tumor immunity through an *in-vivo* paradigm.

Conclusions: The presented data supports tumor immunity in both the CR and re-challenged mice. Our Cryo-immunotherapy paradigm for treatment of established tumors uses a multi-factorial approach. Since cryoablation is already in clinical use, this combined approach may augment its activity in locally recurrent disease after radiation therapy. Further efforts are underway to study the immune mechanisms underlying the observed outcomes as well as modes for enhancing its efficacy.

HORMONAL THERAPY

834: BETA-CATENIN SWITCH IN APOPTOSIS-RESISTANT AND HORMONE-REFRACTORY PROSTATE CANCER CELLS

Luis Quires, et al

Introduction and Objective: beta-catenin is a critical end component of the wnt-signaling pathway that regulates cell growth, apoptosis and migratory behavior in response to intercellular adhesion. The study aim was to evaluate abnormalities of beta-catenin protein expression in an in vitro model of acquired apoptosis-resistance in cultured PC cells and in primary human prostate cancer (PC).

Conclusions: These data suggest that anomalies of beta-catenin expression occur in PC and that these anomalies are associated with disease progression, especially to the therapeutic-resistant state.

1481: CAN INTERMITTENT ANDROGEN DEPRIVATION BE AN ALTERNATIVE TO CONTINUOUS ANDROGEN WITHDRAWAL IN PATIENTS WITH PSA-RELAPSE? FIRST RESULTS OF THE RANDOMIZED PROSPECTIVE PHASE-III CLINICAL TRIAL EC 507

Ulf W Tunn, et al

Introduction and Objective: This is the first randomized prospective trial

comparing intermittent (IAD) to continuous androgen deprivation (CAD) in patients with PSA-Relapse after radical prostatectomy (RP). Aim of the study was to evaluate efficacy and tolerability in both treatments.

Conclusions: These results of this first randomized phase III trial comparing IAD to CAD in patients with PSA-relapse after RP suggest a benefit for IAD with regard to the quality of life during OTT. More than 90 % of patients in the IAD-group regained normal T values. OTT were 62 % and 51 % in IAD cycles 1 and 2 respectively. Time to progression showed no difference in either treatment. IAD would seem to be an attractive alternative in high risk patients who need androgen deprivation after RP and PSA-relapse.

943: CHROMOGRANIN A SERUM LEVELS DURING INTERMITTENT VERSUS CONTINUOUS ANDROGEN DEPRIVATION THERAPY FOR PROSTATE ADENOCARCINOMA

Alessandro Sciarra, et al

Introduction and Objective: Continuous androgen suppression therapy produces a hyperactivation of NE cells and an increase in chormogranin A (CgA) levels in the prostate carcinoma (PC).We verified whether the intermittent administration (IAD) reduces the risk of CgA increase and NE hyperactivation in PC cases treated with hormone therapy.

Conclusions: IAD produces no significant increase in serum CgA levels whereas the continuous administration of CAD, despite stable low PSA levels, produces significant increase in CgA. IAD therapy may reduce the risk of NE hyperactivation in prostate cancer during hormone-treatment.

637: CYCLOOXYGENASE 2, C-JUN/C-FOS [AP-I] EXPRESSION IN HORMONE SENSITIVE AND HORMONE REFRACTORY PROSTATE CANCER

Sarath K Nalagatla, et al

Introduction and Objective: Although most patients with advanced prostate cancer respond to hormonal therapies, the majority relapse and eventually die of their disease. Hence alternative approaches for the treatment of advanced prostate cancer are needed. COX 2 activity has been implicated in cancer angiogenesis, cellular proliferation, apoptosis, and differentiation. Activator Protein I [AP1] is a transcription factor activated by Protein Kinase C and is a complex of c-Jun protein homo-dimers or c-Jun & c-Fos protein hetero-dimers. Experimental studies have shown COX 2 up-regulation by Protein Kinase C through induction of c-Jun. Selective COX 2 inhibitors suppress LNCaP & PC3 cell tumour growth by inducing apoptosis and down regulating tumour VEGF with decreased angiogenesis. We have therefore investigated the role of AP-1 in modulating COX 2 expression during hormone relapse in prostate cancer tissue specimens.

Conclusions: Marked differences in COX 2 expression were observed as hormone sensitive prostate cancer progressed to hormone refractory disease. There was no apparent link between AP I expression and COX 2 expression. Possibly other mechanisms could be mediating COX 2 expression. Therefore Since COX2 inhibitors suppress proliferation and induce apoptosis in prostate cancer cells, they may have a potential role not only in hormone sensitive prostate cancer but also in hormone refractory disease.

342: DOES AP-1 UPREGULATION IN ANDROGEN REFRACTORY PROSTATE CANCER IDENTIFY A SUBSET OF PATIENTS SUITABLE FOR AP-1 SPECIFIC TARGETTED THERAPY?

Sarath K Nalagatla, et al

Introduction and Objective: Hormonal therapy remains the treatment of choice for metastatic prostate cancer. Development of androgen refractory disease is a serious clinical problem, as there is no effective therapy.AP-1 is a complex of transcription factors c-Jun & c-Fos proteins,activated by Protein Kinase C. These proteins are up-regulated in prostate cancer cell lines in the absence of androgens & there is evidence that PKC activity is required for the survival and growth of androgen independent prostate cancer cell line. We investigated this using human prostate cancer tissue. Objective-1. To investigate the levels of expression of c-Jun, c-Fos & AR protein levels in paired pre & post androgen refractory prostate cancer tissue. 2. To identify patients in whose tumours up-regulation of AP-1 may be mediating androgen refractory disease.

Conclusions: We have demonstrated up-regulation and activation [via phosphorylation of c-Jun]AP-1 transcription factor in a significant subset [32%] of patients who have progressed to androgen refractory disease, independent of changes in AR expression. In this subset of patients, AP-1 may have a dominant effect in cancer progression via activation of androgen regulated genes by an AR independent mechanism. AP-1 could be a potential target for future therapies against androgen refractory disease in a selected group of patients.

1487: EARLY VERSUS DELAYED ENDOCRINE TREATMENT IN PN1-3 M0 PROSTATE CANCER WITHOUT LOCAL TREATMENT OF THE PRIMARY TUMOR - RESULTS OF EORTC 30846 - A PHASE III STUDY

Fritz H Schröder, et al

Introduction and Objective: The timing of endocrine treatment of prostate cancer remains controversial in spite of an increasing amount of information from recent randomised studies. The issue is addressed in protocol 30846 of the European Organisation for Research and Treatment of Cancer (EORTC) for patients with lymph node positive cancer without local treatment of the primary tumor.

Conclusions: This study, while it suggests an advantage for early treatment, does not show equivalence nor superiority for either the early or delayed approach. Even if all patients had died the study would not reveal the 23% difference in favour of endocrine treatment as being statistically significant.

1707: HOW DO PROSTATE CANCER SURVIVORS PERCEIVE TREATMENT TRADE-OFFS FOR HYPOTHETICAL CLINICAL SITUATIONS?

Neil H Love, et al

Introduction and Objective: The most common information source guiding prostate cancer (PCA) treatment decisions is verbal consultation with physicians. This pilot study assessed prostate cancer survivors (PCAS) treatment preferences based on a presentation by a urologist (MS) during a day-long town meeting (TM). The objectives were to learn how PCAS perceive treatment trade-offs and to evaluate the effectiveness of a TM to gather such data.

Conclusions: After verbal education/ counseling by a urologist, considerable heterogeneity was observed in PCAS perceptions of treatment trade-offs for hypothetical situations. The TM was an effective method to obtain preliminary,

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hypothesis-generating data on these issues. Health care professionals, advocacy groups, and policy-makers should be informed about the spectrum of patient perceptions of treatment trade-offs and the need for information on a broader variety of treatment options.

Preferred initial therapy for theoretical low-risk PCA cases

Age in theoretical case	RP	EBRT	BT	WW	HT
45	51%	9%	15%	22%	3%
60	31%	12%	22%	24%	11%
72	14%	9%	21%	49%	7%
85	1%	2%	4%	85%	8%

50: NATIONAL PRACTICE PATTERNS AND TIME TRENDS IN PRIMARY AND NEOADJUVANT ANDROGEN ABLATION FOR PROSTATE CANCER: DATA FROM CAPSURE

Matthew R Cooperberg, et al

Introduction and Objective: Androgen deprivation therapy is one treatment option for men with prostate cancer. While it has been used for men with advanced disease, either as monotherapy or before radiation therapy, recent reports have suggested that its use may be growing in men with lower stages of disease. The intent of this study was to describe national trends over time in the use of androgen deprivation therapy, and to identify any sociodemographic variables which predict increased use of such therapy.

Conclusions: Rates of both PADT and NADT are increasing across risk groups and treatment types. Additional clinical trials must define more clearly the appropriate role of hormonal therapy in localized prostate cancer, and future results should shape updated practice guidelines.

1480: IMMEDIATE HORMONAL THERAPY COMPARED WITH OBSERVATION AFTER RADICAL PROSTATECTOMY AND PELVIC LYMPHADENECTOMY IN MEN WITH NODE POSITIVE PROSTATE CANCER: RESULTS AT 10 YEARS OF EST 3886

Edward Messing, et al

Introduction and Objective: We have previously reported 7 year follow-up of a study in which men with clinically localized prostate cancer, who underwent radical prostatectomy (RP) and pelvic lymphadenectomy (PLD) and were found to have nodal metastases (N+), had significantly improved survival and disease-specific survival when they received immediate (within 3 months of surgery) and continuous androgen ablative monotherapy compared with those who had this treatment withheld until distant metastases were identified (NEJM 341:1781,1999). To determine the durability of this effect, we now update results.

Conclusions: At this time median survival in the deferred arm has been reached, and early androgen ablative therapy in patients with N+ disease following RP+PLD continues to be associated with highly significant improvements in overall and disease-specific survival. The treatment has been generally well tolerated. Early androgen ablative therapy's role in other disease scenarios warrants testing in prospective randomized studies.

1483: INTERMITTENT ANDROGEN SUPPRESSION FOR THE TREATMENT OF ADVANCED PROSTATE CANCER

Edith Schasfoort, et al

Introduction and Objective: An international, prospective, randomized clinical trial was initiated in 1998 to obtain more data on intermittent androgen suppression (IAS). The primary objective of this study was evaluation of time to clinical tumor progression and/or PSA escape (defined as PSA concentrations over 50 mg/mL). The major secondary objective was evaluation of patients' quality of life.

Conclusions: This trial showed that both treatments were well tolerated, although quality of life may be higher in the IAS arm. The time to progression/PSA escape was longer in the CAS arm, indicating that continuous therapy may be more effective than intermittent therapy.

DP11: PROSTATE CANCER CELLS BECOME ANDROGEN-HYPERSENSITIVE BY INCREASE OF NUCLEAR ANDROGEN RECEPTOR AND OF ANDROGEN RECEPTOR COACTIVATORS

Naohiro Fujimoto, et al

Introduction and Objective: Hormone-resistance is one of the biggest problems in the treatment of prostate cancer. One of the possible mechanisms of hormone-resistance is androgen-hypersensitivity of cancer cells. If cancer cells become androgen-hypersensitive, they can grow in the situation of low concentration of androgen, such as during androgen ablation therapy. We established androgen-hypersensitive cell line LN-TR2. Using this cell line, we investigated the mechanisms by which prostate cancer cells become hypersensitive to androgen.

Conclusions: LN-TR2 cells were hypersensitive to androgen compared to LNCaP cells. Possible mechanisms of androgen-hypersensitivity of LN-TR2 cells were 1) increased nuclear AR, 2) increased expression of AR coactivators such as ARA55 and TIF2. Prostate cancer cells could become androgen-hypersensitive by those mechanisms and survive under the situation of low concentration of androgen.

1173: QUANTIFYING THE CHANGE IN ENDORECTAL MAGNETIC RESONANCE IMAGING DEFINED TUMOR VOLUME DURING NEOADJUVANT ANDROGREN SUPPRESSION THERAPY IN PATIENTS WITH PROSTATE CANCER

Mona V Sanghani, et al

Introduction and Objective: To quantify the changes seen in endorectal MRI (erMRI)-defined prostate volume, and predominant and second most predominant tumor volumes, during two months of neoadjuvant androgen suppression therapy.

Conclusions: While the erMRI-defined tumor volumes generally decreased in the study population during neoadjuvant TAS, 15% of all patients had an increase in their primary tumor volume. The clinical significance of this increase in erMRI-defined tumor volume during neoadjuvant TAS awaits the results of CALGB 9682. This study will clarify whether erMRI tumor volume changes can be used to predict for biochemical failure and possibly the presence of intraprostatic hormone-insensitive disease.

690: RANDOMIZED COMPARATIVE STUDY OF 3 VS 8 MONTHS OF NEOADJUVANT HORMONAL THERAPY PRIOR TO RADICAL PROSTATECTOMY: 3 YEAR PSA RECURRENCE RATES

Martin E Gleave, et al

Introduction and Objective: A prospective, Phase III trial was initiated by the Canadian Uro-Oncology Group to determine whether 8 months of neoadjuvant hormone therapy (NHT) reduces PSA recurrence rates after radical prostatectomy compared to 3 months of

NHT.

Conclusions: Although the Kaplan-Meier analysis shows a trend towards delay in time to biochemical recurrence in the 8 month group (p=0.0511), no significant differences in PSA recurrence rates was apparent with longer duration NHT by 3 year post-surgery.

350: THE IMPACT OF ANDROGEN ABLATION ON LIPID PEROXIDATION AND ANTIOXIDANT SYSTEMS IN METASTATIC PROSTATE CANCER

Hacer A Iynem, et al

Introduction and Objective: Evidence suggests that free radicals have a role in initiation of cancer. It has also been suggested that free radicals accumulate within the cell during the process of aging and may act as endogenous genotoxins leading to the development of prostate cancer. In addition, it has been reported that androgens may play a role in carginogenesis through increasing reactive oxygen derivatives (ROD) in tissue. We assessed the status of lipid peroxidation and antioxidant systems in metastatic prostate cancer as well as the impact of hormonal treatment on these systems.

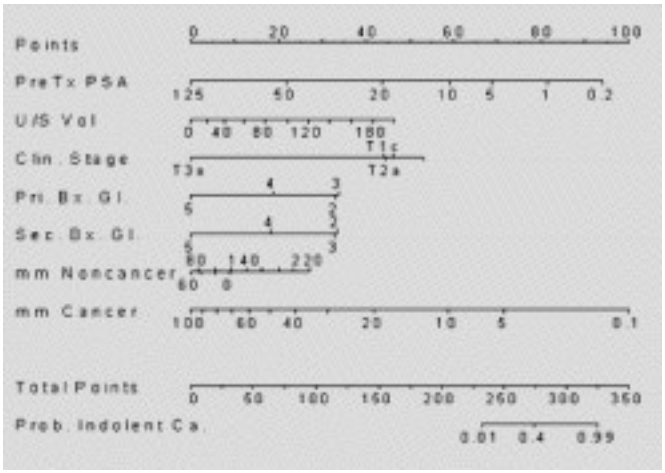
Conclusions: Our results reveal that there is an increase in the production of free radicals and a decrease in the activities of antioxidant enzymes in metastatic prostate cancer. This suggests a shift towards the oxidative state in the oxidant—antioxidant equilibrium. An increase in GST activity and a decrease in lipid peroxidation following 3 months of hormonal treatment imply that androgen blockade could result in a decrease in oxidative stress, and thus help restore the equilibrium.

WATCHFUL WAITING

1593: COUNSELING MEN WITH PROSTATE CANCER (PCA): A NOMOGRAM FOR PREDICTING THE PRESENCE OF INDOLENT (SMALL, WELL-MODERATELY DIFFERENTIATED, CONFINED) TUMORS

Makoto Ohori, et al

Introduction and Objective: With serum PSA testing, PCa are being diagnosed at an earlier point in their natural history. Many small cancers pose little risk to the life or health of the patient, at least in the short-term. To better counsel men diagnosed with PCa, we developed a statistical model that accurately predicts the presence of indolent cancer based on clinical variables including systematic biopsy results.



Conclusions: Nomograms incorporating pretreatment variables (clinical stage, Gleason grade, PSA, and the amount of cancer in systematic biopsies) can predict the probability that a man with PCa has an indolent tumor. These nomograms have excellent discriminatory ability and good calibration and may benefit both patient and clinician when the various treatment options for PCa are being considered.

1844: DELAYED CURATIVE THERAPY IN PATIENTS WHO INITIALLY CHOOSE WATCHFUL WAITING FOR PROSTATE CANCER IN THE PSA ERA

Tomasz M Beer, et al

Introduction and Objective: Preliminary data suggest prostate-specific antigen (PSA) monitoring in watchful waiting patients has increased the proportion of patients subsequently electing delayed therapy with curative intent. Prospective identification and treatment of this patient subset could reduce the number experiencing cancer progression on watchful waiting. The goals of this study were to determine the incidence of delayed curative intervention and to identify independent risk factors for curative intervention in patients who initially chose watchful waiting.

Conclusions: Curative intervention is common in contemporary patients who initially choose watchful waiting for prostate cancer. Age, initial serum PSA, and %positive biopsy cores are independent predictors of curative intervention. When PSADT is added to the model, it replaces initial PSA as a significant predictor.

1648: OUTCOME MODEL OF PROSTATE CANCER PROGRESSION FOLLOWING RADICAL PROSTATECTOMY

Anthony Y Smith, et al

Introduction and Objective: A new model of prostate cancer progression following radical prostatectomy (RP) has been developed in order to predict which men might derive life expectancy benefit from surgery. The program computes a tumor doubling time (DT) from prostate specific antigen (PSA) data and forecasts outcome based on the assumption of minimal retained disease. The model computes an expected time of death for watchful waiting (WW) and surgery which are compared to life expectancy (LE) to determine a net gain or loss of life years (NGLY). We then compared the theoretical NGLY to patients' actual NGLY.

Conclusions: As expected, PSA doubling times were rapid for this early mortality group. The model proved useful to predict death as an outcome. Even in the face of minimal retained disease and aggressive cancer and in spite of positive margins or PSA recurrence, the study suggests that a majority of men should gain life years over WW after RP. Because of the assumption of minimal retained disease for all patients, the model predictions tend to be conservative.

1642: PREDICTORS OF ACTIVE TREATMENT IN MEN WITH LOCALIZED PROSTATE CANCER WHO SELECT WATCHFUL WAITING: RESULTS FROM CAPSURE

Susan L Rider, et al

Introduction and Objective: Watchful waiting (WW) is one of many options for men with clinically localized prostate cancer. Some individuals who initially choose WW may progress clinically and be treated at a later date. We wished to identify clinical and/or sociodemographic predictors of eventual treatment in those who chose WW.

Conclusions: For those who choose WW,

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baseline clinical and sociodemographic variables predict eventual treatment. This information may help identify those most likely to benefit from this approach as initial treatment.

1724: PREDICTORS OF DELAYED PROSTATE CANCER-DIRECTED INTERVENTION IN WATCHFUL WAITING PATIENTS IN THE PSA ERA

Mark Garzotto, et al

Introduction and Objective: The outcome of watchful waiting as a strategy for clinically localized prostate cancer has primarily been described on the basis of data collected prior to the introduction of PSA. The use of the PSA in prostate cancer diagnosis and its availability during observation would be expected to alter the outcome of watchful waiting. The goals of this study were to define the incidence of delayed cancer-directed intervention and to identify independent risk-factors for delayed intervention in patients who chose watchful waiting for initial management of prostate cancer.

Conclusions: Cancer-directed intervention is common in modern patients who choose watchful waiting as initial management of clinically localized prostate cancer. Gleason score and percent-positive biopsy cores are independent predictors of intervention. When available, PSADT becomes the most important predictor of intervention.

1677: VALIDITY OF REPEAT PROSTATIC BIOPSIES IN UNTREATED PATIENTS WITH LOCALIZED PROSTATE CANCER

Phillip L Ross, et al

Introduction and Objective: Early detection of prostate cancer has lead to a stage migration that may contribute to increased detection of insignificant prostate cancer. Many patients will consider watchful waiting as a way to delay treatment. The safety of observation is based mainly on clinical assessment of PSA measurements and digital rectal examination. The objective of this study was to evaluate the utility of PSA and repeat systematic prostate biopsy as reliable markers of prostate cancer progression in patients who elected for watchful waiting.

Conclusions: PSA doubling time less than 120 months correlated with disease progression. Standardized criteria for expectant management of localized prostate cancer are yet to be defined. Repeat prostatic biopsies may be a useful tool to help determine disease progression in patients with stable PSA.

1847: WATCHFUL WAITING AND PREDICTING FACTORS FOR SECONDARY TREATMENT IN PROSTATE CANCER

Hongyan Wu, et al

Introduction and Objective: We attempted to verify and document the demographic, clinical and outcome features of watchful waiting and to understand what leads men to choose "watchful waiting", rather than active treatment and what are the predicting factor of secondary treatment.

Conclusions: Men who elected watchful waiting for prostate cancer tend to be older with lower serum PSA and lower Gleason score. The age at diagnosis, diagnostic PSA and clinical T stage are the most significant predictors to predict the likelihood of secondary treatment in watchful waiting. The model based on these three factors may benefit the identification on high risk patients as candidates for early clinical intervention.

1635: WATCHFUL WAITING FOR PROSTATE CANCER REEXAMINED: INTERVENTION FREE SURVIVAL WHILE ON SURVEILLANCE IN A CONTEMPORARY COHORT OF PATIENTS

Young M Kang, et al

Introduction and Objective: Clinical outcomes of surveillance or watchful waiting for localized prostate cancer (PC) are traditionally measured in terms of overall survival. If surveillance is considered a treatment option for PC, then intervention free survival (IFS) must be considered a relevant endpoint in outcomes research. Applying this definition of failure, we report our outcomes of surveillance for PC in a contemporary cohort of patients diagnosed and followed in the PSA era.

Conclusions: In a contemporary cohort of patients electing surveillance for PC, no disease specific mortality was observed, but long term IFS occurred in only 2/3 of patients. Only pre-surveillance PSA was predictive of IFS in our experience. Moreover, patients placed on surveillance because of clinically insignificant cancers were as likely to receive treatment as patients whose poor overall health had prompted surveillance. The likelihood of IFS in the PSA era must be considered when counseling patients regarding therapy for localized PC.

LIFESTYLE CHANGES

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The regimen must be followed precisely to achieve its full results, Ornish stresses. Most of the men in the control group tried to follow the regimen, with middling success; their PSA levels rose — but not as much as would have happened if they had not adopted some of the measures, he maintains.

The study's reliance on PSA levels, however, is seen as a major problem by Andrew Vickers, an assistant attending research methodologist at Memorial Sloan-Kettering Cancer Center in New York.

"When you get down to it, no one should care about the PSA level," he says. "It is widely used, but one has to be cautious in interpreting it. It is a marker of cancer growth, but not necessarily a one-to-one marker."

What Vickers would like to see are measurements of how the cancer is affecting the patients' quality of life. "The results they show are highly provocative, but they are not measuring anything that makes a difference in someone's life," he says.

Dr. B. Jay Brooks, chief of hematology/oncology at the Ochsner Clinic in Baton Rouge, La., also looks at the study with a skeptical eye.

"This was an extremely small study, and the endpoint was a rise in PSA, which is not necessarily related to the progress of the cancer," Brooks says. "The difference between the experimental group and the control group was extremely small and barely reached statistical significance."

It is "an interesting concept," Brooks adds, "but this needs to be expanded to a larger group of patients and followed for a long period of time, perhaps five years."

"If it were me or any of my patients, I would certainly not rely on a change in lifestyle to affect a proven diagnosis," Brooks sums up.