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Expression of Bcl-2 and androgen receptors in carcinoma of the prostate.

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The bcl-2 proto-oncogene is said to contribute to malignant cell expansion primarily by prolonging cell survival rather than by increasing the rate of cellular proliferation, in other words by delaying or blocking apoptosis. It has been studied in a number of malignancies including breast, thyroid, neuroblastoma and lung where loss of bcl-2 expression would appear to correlate with poor prognosis. In contrast, some studies in prostate cancer have suggested that high levels of expression are associated with disease progression following androgen ablation. We set out to examine bcl-2 and androgen receptor (AR) expression in prostate cancer with a view to relating expression to clinical outcome.

We studied 10 cases of benign prostatic, 7 androgen- dependent cancers and 8 cases of progressive cancer following androgen ablation. Using immunohistochemistry, paraffin tissue sections from transurethral prostatectomy specimens were stained for bcl-2 and AR using mouse monoclonal antibodies. Antibody specificity was confirmed by Western blotting. The benign cases all stained similarly for bcl-2 with basal glandular cells and lymphocytes positive. For AR there was good nuclear staining in the glands with weak nuclear/cytoplasmic staining in the epithelium of the prostatic ducts and urethra. Smooth muscle from prostate stained better than smooth muscle from bladder neck.

In the cancers, only areas of malignant disease were studied. Of the 7 androgen-dependent cancers, 2 showed moderate staining for bcl-2, 3 were weak and 2 negative. In the 8 androgen-independent cases, 1 showed moderate staining, 1 was weak and 6 negative. In regard to AR, only 1 of the androgen-dependent group was negative, in contrast to half of the androgen-independent group. In general, the solid, poorly differentiated cancers were negative but AR expression did not correlate well with bcl-2 expression.

Our results suggest that in prostate cancer, as in other cancers, loss of bcl-2 expression correlates with disease which is less responsive to treatment. We are currently examining larger numbers of both treated and untreated patients and are correlating our findings with the number of apoptotic cells in each case. (supported by Royal College of Surgeons of Edinburgh and by the Prostate Cancer Research Campaign).

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PREDICTING PROSTATE CANCER STAGE UTILIZING ANGIOGENESIS, GLEASON SCORE AND PSA

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A preoperative method of predicting tumor stage has been shown. The method incorporates digital imaging and analysis to characterize an area of carcinogenic prostate tissue taken from a needle biopsy. A retrospective, blinded, multivariate study involving 550 cases was conducted. Radical Prostatectomy samples at 3-5mm sections, were independently reviewed by blinded referee pathologists to verify pathologic stage. Five (5) staging classes were defined: 1) Tumor Organ Confined, 2) Capsular Involvement, 3) Extra Capsular Extension, 4) Lymphnode metastases and, 5) Bone metastases. Seminal Vesicle involvement was also recorded for each stage. One H & E and two unstained slides from each positive needle core were supplied for image analysis. Each 5 um thick sample was formalin fixed and paraffin embedded and then stained for Factor VIII related antigen. At least 3 fields of cancer were required for analysis. Microvessels were counted at 400x magnification by two independent technicians. Microvessel density (MVD) was calculated as the number of microvessels per square millimeter of tissue. 100,000 fields were measured. MVD was shown to be an independent predictor of tumor stage. A statistical model combining MVD, Gleason Score and pre-operative PSA was used to produce a quantitative result that was strongly predictive of tumor stage. The result significantly enhanced the accuracy of tumor stage prediction over Gleason Score and PSA alone.

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A RETROSPECTIVE STUDY OF HIGH MOBILITY GROUP PROTEIN I(Y) AS PROGRESSION MARKER IN PROSTATIC CANCER DETERMINED BY IN-SITU HYBRIDIZATION

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In a previous study using RNA in-situ hybridization, we found a significant correlation between high mobility group protein I(Y), (HMG I(Y)) mRNA expression and tumor stage and grade in prostate cancer patients, suggesting that HMG-I(Y) might be a potential prognostic marker in prostate cancer. However, our clinical follow up was limited because cryopreserved material was used. Assessing the potential prognostic value of this molecule is of importance because the clinical course of prostate cancer patients remains unpredictable. Here we describe our results on paraffin embedded archival material from a group of 102 patients undergoing radical prostatectomy. These were evaluated for the presence of HMG-I(Y) using RNA in situ hybridization and a follow up of 12-92 months (average 53 months), was available. In 2 of 14 prostate cancers of Gleason grade 1-2 a high HMG-I(Y) expression was observed, whereas in 19 of 23 Gleason grade 3, and 34 of 35 Gleason grade 4-5 tumors, high HMG-I(Y) mRNA levels were detected (chi-square= 38.78, P < 0.0001). Moreover, of tumors that expressed high HMG-I(Y) levels, 25% were organ confined (T1-2) in contrast to 74.5% of the invading tumors (T3, chi-square = 15.8, p < 0.001). Furthermore, 87% of recurrent tumors showed high HMG-I(Y) expression. However, a multivariate regression analysis including Gleason grade, tumor stage, HMG-I(Y) expression, and PSA levels showed Gleason grade as the most accurate predictor of progression. These results, confirm our previous findings in a cohort of radical prostatectomy patients. High HMG-I(Y) levels measured by RISH were indicative for a worse prognosis, albeit that additional value over the more subjective grading methods was not evident.

6B Miscellaneous

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PRENATAL ENDOSCOPIC INTRATERNIE THERAPY: A MONKEY MODEL

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Prenatal endoscopy was performed in a model for experimental surgery in primates. In the rhesus monkey midtrimester endoscopic intratereine access with 3 canulae could be successfully achieved in 8 rhesus monkeys (macaca mulatta). Timing was controlled by physical examination and ultrasonographic biometry by which intratereine growth curves could be obtained. Using a sediing technique and a 1.2 mm introduction sheet with fibertopic endoscope, intratereine inspection could be performed and a second and third operative 4.5 mm port could be introduced under optical control. Fetal conditions were monitored by ultrasonography, doppler investigations of the umbilical cord and arterial uterine bloodflow measurements. After partial amniotic fluid exchange, adequate fetoscopy was always possible. Two monkeys aborted in the 2nd and 6th postoperative day respectively. Measurements of electrical uterine activity 24 hours postoperatively in the first 5 animals showed no uterine contractions. Prenatal endoscopy and microsphetic tolysis has been abandoned since then. Serial ultrasonographic investigations for fetal biometry showed no disturbance of the intratereine growth patterns. We currently conclude that the rhesus monkey model for experimental intratereine endoscopic surgery seems to be a suitable model in which developmental abnormalities of the genitourinary tract can be studied.