

Research Highlights

Prostate News

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After salvage surgery

Patients with persistent prostate cancer after receiving radiotherapy are strong candidates for salvage surgery. Using data from surgeries performed over a 30-year span (1967–2000), John F Ward and colleagues present survival estimates, examine pathological features, and delineate surgical risks in their paper for the *Journal of Urology*. They found that significant survival rates can be expected following salvage surgery for radioresistant prostate cancer, with pathological features of the removed prostate providing a key to outcome predictions.

The authors retrospectively identified patients with biopsy-proven persistent prostate cancer following radiotherapy, thereby generating data on 199 patients, including 138 with retropubic prostatectomy (RP) and 61 with cystoprostatectomies (CP). After surgery, rectal injury rates remained stable (5% for RP and 10% for CP), while transfused units of blood decreased. Surgical risks, including urinary extravasation and bladder neck contracture, were the most common complications. However, urinary continence did improve over time. Overall, the 10-year cancer-specific survival estimate for all patients undergoing salvage surgery was 65%. Patients undergoing RP fared better than those needing CP. The authors further found that tumor policy, percent 4/5 Gleason grade and pathological stage were strong predictors of outcome, while margin status and pre-operative SPA had minimal predictive strength.

Original Research Paper

Ward JF *et al.* Salvage surgery for radio recurrent prostate cancer: contemporary outcomes. *J Urol* 2005;173:1156–1160.

ATBF1: candidate tumor-suppressor gene identified

It is a truism that cancer can be the result of an accumulation of genetic alterations. Although most malignancies are sporadic, only a minority of genes have been shown to undergo frequent mutations in cancers. In human cancers, the long arm of chromosome 16 is frequently deleted, but the target gene for this deletion has not yet been identified. Xiaodong Sun and colleagues writing for *Nature Genetics*, attempt to remedy this lack by proposing a candidate for the 16q22 tumor-suppressor gene.

The authors report that *ATBF1*, which encodes a transcription factor that negatively regulates AFP and MYB but transactivates CDKN1A, might be a plausible candidate gene. To arrive at this conclusion, the authors

narrowed the chromosomal region to that containing *ATBF1*, finding that mRNA specific to this transcription factor was abundant in normal prostates, while more scarce in nearly half of prostate cancers tested. In 36% of cancers examined, the authors identified 22 unique somatic mutations, many of which impair *ATBF1* function. Moreover, *ATBF1* was found to inhibit cell proliferation. The researchers conclude that loss of *ATBF1* is one mechanism that defines the absence of growth control in prostate cancer.

Original Research Paper

Sun X *et al.* Frequent somatic mutations of the transcription factor *ATBF1* in human prostate cancer. *Nat Genet* (Published online 6 March 2005).

Telomerase vaccine clinical trial results

Human telomerase reverse transcriptase (hTERT) is an attractive target for cancer immunotherapy. Silent in normal tissues, hTERT is reactivated and overexpressed in over 85% of human solid tumors, including prostate cancer. Under the aegis of Geron Corporation, senior author Johannes Vieweg and researchers from Duke University Medical Center initiated a Phase 1-2 clinical trial in which hTERT mRNA-transfected dendritic cells were administered to 20 patients with metastatic prostate cancer. The results of this study appeared in *The Journal of Immunology*. In the treatment protocol, patients were partitioned into two treatment groups: a low-dose group comprised of 12 subjects receiving three weekly injections of the vaccine, and a high-dose group of eight patients receiving six weekly injections.

Of the low-dose subjects, 11 responded with significant levels of telomerase-specific CD8+ T cells and nine displayed high levels of Telomerase-specific CD4+ T cells. The high-dose group showed robust CD8+ T-cell responses that peaked two to 4 weeks after the sixth injection, reaching levels of 1–2% of circulating CD8+ T cells exhibiting antitelomerase specificity. This high frequency of antigen-specific T cell response is comparable to that seen after vaccination for infectious diseases. Patients immunized with the vaccine exhibited characteristics consistent with the development of central T-cell memory, a finding with important implications for designing an optimal schedule for continued injections to prolong the duration of vaccine response.

These data show that telomerase vaccination was associated with a significant impact on PSA doubling time. Moreover, a reduction or elimination of circulating prostate cancer cells during the time that a measurable,

telomerase-specific T cell response was detectable in patients' blood was observed. The treatment produced a central T cell memory response, which suggests that continued vaccinations to maintain telomerase-specific T cell response may enhance clinical impact. These findings provide a rationale for further development of hTERT-transfected dendritic cell vaccines in the treatment of prostate and other cancers.

Original Research Paper

Su Z *et al.* Telomerase mRNA-transfected dendritic cells stimulate antigen-specific CD8+ and CD4+ T cell responses in patients with metastatic prostate cancer. *J Immunol* 2005; **174**: 3798–3807.

Genome-wide search for cancer susceptibility

In order to identify genes that generally increase the risk of cancer, Bao-Li Chang and colleagues performed a systematic search of the genome in 188 families primarily associated with prostate cancer, but also including individuals with other cancers. The results of this investigation appeared in *Cancer Letters*. The authors observed significant evidence for linkage between susceptibility to all cancers and markers at 3p24. Among families with either less than three other cancers or prostate cancer only, evidence for linkage at this region was stronger among families with at least three other cancers. This is the first reported example of a genome-wide search for general cancer susceptibility genes among families displaying hereditary prostate cancer.

Original Research Paper

Chang BL *et al.* Evidence for a general cancer susceptibility locus at 3p24 in families with hereditary prostate cancer. *Cancer Lett* 2005; **219**: 177–182.

Cryosurgery for high-risk patients

Some high-risk patients are unwilling to undergo radical surgery or radiation therapy for prostate carcinoma. For these men, cryosurgical ablation of the prostate may represent a viable, minimally invasive alternative. In *Cancer*, Kristofer Prepelica and colleagues from Columbia-Presbyterian Medical Center report their experiences with primary cryosurgery for prostate carcinoma with high-risk features. These features were defined as a PSA level ≥ 10 ng/mL, a Gleason score ≥ 8 , or both. All 65 high-risk patients in the study had biopsy-proven prostate carcinoma with no evidence of metastatic disease. Those who had undergone prior surgery, radiation therapy, or previous cryoablation were excluded from the study. Physical examination and PSA screening, along with radiologic imaging when indicated, were administered every 3 months to monitor patients' progress.

In this study, the median patient age was 72 years, and the median follow-up was 35 months. Although one of eight postcryosurgical biopsies was positive, the overall survival rate after primary cryosurgery was 100%. The authors conclude that cryoablation of the prostate is a

feasible treatment option in patients with organ-confined prostate carcinoma with high-risk features. However, longer follow-up is still necessary to determine the effectiveness of this surgical approach.

Original Research Paper

Prepelica KL *et al.* Cryosurgical ablation of the prostate. *Cancer* **103**, 1625–1630 (Published online 3 March 2005).

ERG1 overexpression in prostate cancer

Epithelial and stromal cells have been shown to play roles in the process of prostate tumorigenesis. Thus, monitoring gene expression changes in these cell types may hold the key to defining genetic alterations that contribute to the development of prostate cancer. Gyorgy Petrovics and colleagues take this as their point of departure in evaluating gene expression signatures via laser microdissection of epithelial cells from benign and malignant glands in radical prostatectomy specimens. In their report for *Oncogene*, the authors identify *ERG*, a member of the *ETS* transcription factor family, as the most frequently overexpressed proto-oncogene in the transcriptome of malignant prostate epithelial cells.

Since only *ERG1* was expressed in the prostate and in PC3 cells, while *ERG2* was not detectable, the authors designed a probe and primers specific to the former splice form. GeneChip analysis identified and real-time QRT-PCR assays verified *ERG1* overexpression in tumor cells. *In situ* hybridization further corroborated the expression data.

Interestingly, when the quantitative features of *ERG1* expression were analyzed in association with clinicopathologic features, the authors found that *ERG1* overexpression in tumor cells is generally higher in less aggressive prostate cancer. There was also a significant correlation of high *ERG1* expression in Caucasian versus African-American patients. Moreover, the authors present results that strongly suggest that *ERG1* expression level in prostate tumor cells relative to benign epithelial cells is an indicator of disease-free survival after radical prostatectomy.

Original Research Paper

Petrovics G *et al.* Frequent overexpression of ETS-related gene-1 (*ERG1*) in prostate cancer transcriptome. *Oncogene* (Published online 7 March 2005).

Role for sentinel lymph node dissection

In the *European Journal of Nuclear Medicine and Molecular Imaging*, Isabelle Brenot-Rossi and colleagues discuss a potential role for the sentinel lymph node (SLN) procedure in patients with apparently localized prostate carcinoma. The study included 27 patients with organ-confined prostate cancer who each received a single radionuclide injection into the peripheral zone of each lobe of the prostate. After the injection, scintigraphy was performed. The first step in this surgery was the detection and dissection of lymph nodes identified as SLNs. Once identified, standard lymphadenectomy consisting of a limited dissection was performed. In

most patients, the authors found the SLN to be located along the hypogastric artery. The second most frequent site of SLNs was in the obturator fossa; in the remaining patients, sentinels were located in the external iliac area. Overall, the SLN procedure revealed individual variability in the lymphatic drainage of the prostate. Of the four patients displaying lymph node metastases, the main site of SLNs was the hypogastric area. The authors conclude that a limited standard pelvic lymphadenectomy would have missed half of the lymph node metastases identified in this study. The results of this pilot study indicate that radionuclide SLN procedures can assist in correctly staging patients with early prostate cancer, and especially when performing limited lymphadenectomy.

Original Research Paper

Brenot-Rossi I *et al.* Limited pelvic lymphadenectomy using the sentinel lymph node procedure in patients with localised prostate carcinoma: a pilot study. *Eur J Nucl Med Mol Imaging* (Published online 4 March 2005).

Prostatitis and benign prostatic hyperplasia

To determine the prevalence and significance of pain at the time of ejaculation (prostatitis-like symptoms) in men with LUTS diagnosed with benign prostatic hyperplasia (BPH). J Curtis Nickel and colleagues evaluated data culled from the ALF-ONE study conducted by general practitioners and urologists throughout Europe, Asia, Latin America, the Middle East and Canada. The results of their analysis appear in *BJU International*.

Of the 5096 men enrolled in the study with LUTS suggestive of BPH, 3700 sexually active men reported assessable answers regarding three symptoms relating to sexual function: rigidity of erection, amount of ejaculate, and pain/discomfort on ejaculation. Approximately 20% of these patients complained of specific prostatitis-like symptoms, and these men clearly differed from those who presented with LUTS only. Of those respondents who reported pain or discomfort on ejaculation, the majority considered it a problem. Patients with BPH and painful ejaculation had more severe LUTS, and also had a higher prevalence of erectile dysfunction and reduced ejaculation than men with LUTS only. Furthermore, a history of urinary tract infection was described by 12% of men in the ejaculatory pain group, compared with 7% in the LUTS-only group. The authors found that men with ejaculatory pain were slightly younger; however, there were no significant differences in duration of LUTS, history of acute urinary retention, PSA concentration, or maximum urinary flow rate compared to the LUTS-only group. Nickel and colleagues conclude that evaluation and treatment strategies should address the population of men with symptoms suggestive of both prostatitis and BPH.

Original Research Paper

Nickel JC *et al.* Benign prostatic hyperplasia (BPH) and prostatitis: prevalence of painful ejaculation in men with clinical BPH. *BJU Int* 2005; 95: 571–574.

Celecoxib: inhibiting tumor growth

It is well-established that selective cyclooxygenase-2 (COX-2) inhibitors are significant and rational targets for anticancer therapy. Andrew Dannenburg and researchers at Weill Medical College of Cornell University have fine-tuned this observation by evaluating whether celecoxib or rofecoxib, two clinically available selective COX-2 inhibitors, possess COX-2 independent antitumor activity.

The authors first established the growth inhibitory effects of selective COX-2 inhibitors *in vitro*, finding only COX-1 detectable in PC3 and LNCaP human prostate cancer cells. Celecoxib inhibited the growth of both cell lines at clinically achievable concentrations, but rofecoxib had no effect over the same concentration range. Celecoxib inhibited cell growth by inducing a G1 cell cycle block and reducing DNA synthesis. By employing animals with grafted human prostate tumors, the authors found that treatment with celecoxib led to a 52% reduction in tumor volume, with an nearly a 50% decrease in both cell proliferation and microvessel density. Rofecoxib had no effect on the transplanted tumors. Celecoxib also caused a marked decrease in amounts of cyclin D1 both *in vitro* and *in vivo*.

This research demonstrates that celecoxib and rofecoxib possess different COX-2 independent anticancer properties. The results, published in *Clinical Cancer Research*, suggest that celecoxib exerts a second mode of action independent of its known anti-inflammatory mechanism that suppresses the proliferation of prostate cancer cells.

Original Research Paper

Patel MI *et al.* Celecoxib inhibits prostate cancer growth: Evidence of a cyclooxygenase-2-independent mechanism. *Clin Cancer Res* 2005; 11: 1999–2007.

Finasteride and the prostate cancer prevention trial

A new analysis of data from the Prostate Cancer Prevention Trial (PCPT) shows that the commonly used drug finasteride could prove effective in preventing prostate cancer. Results from the PCPT indicate that use of finasteride as a chemopreventative reduced the incidence of prostate cancer by 24.8% compared to a placebo. However, a possible increase in the number of high-grade tumors in the trial prompted many to question whether the benefits of the drug would be offset by an increase in mortality related to the higher-grade tumors.

To resolve this question, Joseph Unger and a team of researchers from the Fred Hutchinson Cancer Research Center analyzed Surveillance, Epidemiology and End Results registry data and applied the results from the PCPT. The results showed a net reduction in person-years saved over 10 years using finasteride, even after taking into account an increase in high-grade cancers. Using the PCPT's 24.8% reduction in new cases, the drug would save 316760 person-years over 10 years. An absolute increase in 6.9% of cases with high-grade

disease, as was seen in the trial, would still result in 262 567 person-years saved.

Publishing in *Cancer*, the authors conclude that the results of the PCPT may have a major impact on population mortality from prostate cancer if they are applied clinically. The authors maintain that the potential detrimental effects of an increased rate of patients who have prostate cancer with high-grade Gleason scores would be more than offset by an overall reduc-

tion in the number of prostate cancer cases in the general population.

Original Research Paper

Unger JM *et al.* Estimated impact of the Prostate Cancer Prevention Trial on population mortality. *Cancer* 2005; **103**: 1375–1380 (Published online 28 Feb 2005).