مقالات
از تورنال های انکولوزی
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کانسر های اورولوزی
The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has been revolutionized by the arrival of multiple novel agents in the past 2 years. Immunotherapy in the form of sipuleucel-T, androgen axis inhibitors, including abiraterone acetate and enzalutamide, a chemotherapeutic agent, cabazitaxel, and a radiopharmaceutical, radium-223, have all yielded incremental extensions of survival and have been recently approved. A number of other agents appear promising in early studies, suggesting that the armamentarium against castrate-resistant prostate cancer is likely to continue to expand. Emerging androgen pathway inhibitors include androgen synthesis inhibitors (TAK700), androgen receptor inhibitors (ARN-509, ODM-201), AR DNA binding domain inhibitors (EPI-001), selective AR downregulators or SARDs (AZD-3514), and agents that inhibit both androgen synthesis and receptor binding (TOK-001/galeterone). Promising immunotherapeutic agents include poxvirus vaccines and CTLA-4 inhibitor (ipilimumab). Biologic agents targeting the molecular drivers of disease are also being investigated as single agents, including cabozantinib (Met and VEGFR2...
inhibitor) and tasquinimod (angiogenesis and immune modulatory agent). Despite the disappointing results seen from studies evaluating docetaxel in combination with other agents, including GVAX, anti-angiogenic agents (bevacizumab, aflibercept, lenalidomide), a SRC kinase inhibitor (dasatinib), endothelin receptor antagonists (atrasentan, zibotentan), and high-dose calcitriol (DN-101), the results from the trial evaluating docetaxel in combination with the clusterin antagonist, custirsen, are eagerly awaited. New therapeutic hurdles consist of discovering new targets, understanding resistance mechanisms, the optimal sequencing and combinations of available agents, as well as biomarkers predictive for benefit. Novel agents targeting bone metastases are being developed following the success of zoledronic acid and denosumab. Finally, all of these modalities do not appear curative, suggesting that clinical trial enrollment and a better understanding of biology remain of paramount importance.


2. Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

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Radical prostatectomy reduces mortality among men with localized prostate cancer; however, important questions regarding long-term benefit remain.

Between 1989 and 1999, we randomly assigned 695 men with early prostate cancer to watchful waiting or radical prostatectomy and followed them through the end of 2012. The primary end points in the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) were death from any cause, death from prostate cancer, and the risk of metastases. Secondary end points included the initiation of androgen-deprivation therapy.

During 23.2 years of follow-up, 200 of 347 men in the surgery group and 247 of the 348 men in the watchful-waiting group died. Of the deaths, 63 in the surgery group and 99 in the watchful-
waiting group were due to prostate cancer; the relative risk was 0.56 (95% confidence interval [CI], 0.41 to 0.77; P=0.001), and the absolute difference was 11.0 percentage points (95% CI, 4.5 to 17.5). The number needed to treat to prevent one death was 8. One man died after surgery in the radical-prostatectomy group. Androgen-deprivation therapy was used in fewer patients who underwent prostatectomy (a difference of 25.0 percentage points; 95% CI, 17.7 to 32.3). The benefit of surgery with respect to death from prostate cancer was largest in men younger than 65 years of age (relative risk, 0.45) and in those with intermediate-risk prostate cancer (relative risk, 0.38). However, radical prostatectomy was associated with a reduced risk of metastases among older men (relative risk, 0.68; P=0.04).

Extended follow-up confirmed a substantial reduction in mortality after radical prostatectomy; the number needed to treat to prevent one death continued to decrease when the treatment was modified according to age at diagnosis and tumor risk. A large proportion of long-term survivors in the watchful-waiting group have not required any palliative treatment. (Funded by the Swedish Cancer Society and others.)
BACKGROUND
Emerging evidence shows that nanomechanical phenotypes of circulating tumor cells (CTC) could become potential biomarkers for metastatic castration resistant prostate cancer (mCRPC).

METHODS
To determine the nanomechanical phenotypes of CTCs we applied atomic force microscopy (AFM) employing the PeakForce quantitative nanomechanical (QNM) imaging. We assessed biophysical parameters (elasticity, deformation, and adhesion) of 130 CTCs isolated from blood samples from five castration sensitive (CS) and 12 castration resistant prostate cancer (CRPCa) patients.

RESULTS
We found that CTCs from CRPCa patients are three times softer, three times more deformable, and seven times more adhesive than counterparts from CSPCa patients. Both nonsupervised hierarchical clustering and principle component analysis show that three combined nanomechanical parameters could constitute a valuable set to distinguish between CSPCa and CRPCa.

CONCLUSIONS
Our study indicates that nanomechanical phenotypes of CTCs may serve as novel and effective biomarkers for mCRPC.

4. A phase I study of cabozantinib (XL184) in patients with renal cell cancer

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Background Cabozantinib targets tyrosine kinases including the hepatocyte growth factor receptor (MET) and vascular endothelial growth factor (VEGF) receptor 2, which are important drug targets in renal cell carcinoma (RCC).

Patients and methods This single-arm open-label phase I trial evaluated the safety and tolerability of cabozantinib in heavily pretreated patients with metastatic clear cell RCC.

Results The study enrolled 25 RCC patients for whom standard therapy had failed. Patients received a median of two prior systemic agents, and most patients had previously received at least one VEGF pathway inhibiting therapy (22 patients [88%]). Common adverse events included fatigue, diarrhea, nausea, proteinuria, appetite decreased, palmar–plantar erythrodysesthesia, and vomiting. Partial response was reported in seven patients (28%). Median progression-free survival was 12.9 months, and median overall survival was 15.0 months.

Conclusion Cabozantinib demonstrates preliminary anti-tumor activity and a safety profile similar to that seen with other multitargeted VEGFR tyrosine kinase inhibitors in advanced RCC patients. Further evaluation of cabozantinib in RCC is warranted.


5. Genome-wide interaction study of smoking and bladder cancer risk

Bladder cancer is a complex disease with known environmental and genetic risk factors. We performed a genome-wide interaction study (GWAS) of smoking and bladder cancer risk based on primary scan data from 3002 cases and 4411 controls from the National Cancer Institute Bladder Cancer GWAS. Alternative methods were used to evaluate both additive and multiplicative interactions between
individual single nucleotide polymorphisms (SNPs) and smoking exposure. SNPs with interaction \( P \) values < \( 5 \times 10^{-5} \) were evaluated further in an independent dataset of 2422 bladder cancer cases and 5751 controls. We identified 10 SNPs that showed association in a consistent manner with the initial dataset and in the combined dataset, providing evidence of interaction with tobacco use. Further, two of these novel SNPs showed strong evidence of association with bladder cancer in tobacco use subgroups that approached genome-wide significance. Specifically, rs1711973 (FOXF2) on 6p25.3 was a susceptibility SNP for never smokers [combined odds ratio (OR) = 1.34, 95% confidence interval (CI) = 1.20–1.50, \( P \) value = \( 5.18 \times 10^{-7} \)]; and rs12216499 (RSPH3-TAGAP-EZR) on 6q25.3 was a susceptibility SNP for never smokers (combined OR = 0.75, 95% CI = 0.67–0.84, \( P \) value = \( 6.35 \times 10^{-7} \)). In our analysis of smoking and bladder cancer, the tests for multiplicative interaction seemed to more commonly identify susceptibility loci with associations in never smokers, whereas the additive interaction analysis identified more loci with associations among smokers—including the known smoking and NAT2 acetylation interaction. Our findings provide additional evidence of gene–environment interactions for tobacco and bladder cancer.

**6. Obesity and the Odds of Weight Gain following Androgen Deprivation Therapy for Prostate Cancer**

**Background:** Increasing body mass index (BMI) is associated with increased risk of mortality; however, quantifying weight gain in men undergoing androgen deprivation therapy (ADT) for prostate cancer (PC) remains unexplored. **Methods.** Between 1995 and 2001, 206 men were enrolled in a randomized trial evaluating the survival difference of adding 6 months of ADT to radiation therapy (RT). BMI measurements were available in 171 men comprising the study cohort. The primary endpoint was weight gain of ≥10 lbs by 6-month followup. Logistic regression analysis was performed to assess whether baseline BMI or treatment received was associated with this endpoint adjusting for known prognostic factors. **Results.** By the 6-month followup, 12 men gained ≥10 lbs, of which 10 (83%) received RT + ADT and, of these, 7 (70%) were obese at randomization. Men treated with RT as compared to RT + ADT were less likely to gain ≥10 lbs (adjusted odds ratio (AOR): 0.18 [95% CI: 0.04–0.89]; \( P = 0.04 \)), whereas this risk increased with increasing BMI (AOR: 1.15 [95% CI: 1.01–1.31]; \( P = 0.04 \)). **Conclusions.** Consideration should be given to avoid ADT in obese men with low- or favorable-intermediate risk PC where improved cancer control has not been observed, but shortened life expectancy from weight gain is expected.

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BACKGROUND:

Lymph node dissection (LND) in prostate cancer patients may increase complications. An association of LND with thromboembolic events has been suggested. We compared the incidence and investigated predictors of deep venous thrombosis (DVT) and pulmonary embolism (PE) among other complications in patients undergoing or not undergoing LND during open (ORP) and robot-assisted laparoscopic radical prostatectomy (RARP) METHODS: 3544 patients were included between 2008-2011. The cohort derives from LAPPRO, a multi-center, prospective controlled trial. Data concerning adverse events were extracted from patient-completed questionnaires. Our primary outcome was prevalence of DVT and/or PE. Secondary outcomes were other types of 90-day adverse events and re-admission causes.

RESULTS:

547 (15.4%) patients underwent LND. LND was associated with an 8-fold and 6-fold higher risk of DVT and PE events, respectively, compared to the no-LND patients [RR 95%CI: 7.80 (3.51-17.32) and 6.29 (2.11-18.73)]. Predictive factors for thromboembolic events included a previous history of thrombosis, pT4 stage, Gleason score ≥8. ORP and LND had a higher risk of DVT and/or PE [RR 95%CI: 12.67 (5.05-31.77) versus 7.52 (2.84-19.88) in RARP]. In no-LND patients, ORP increased 3.8-fold the thromboembolic risk compared to RARP.
(95%CI 1.42-9.99). LND induced more wound, respiratory, cardiovascular and neuromusculoskeletal events. LND caused more re-admissions compared to no-LND (14.6% vs. 6.3%).

CONCLUSIONS:

Among other adverse events, we found that LND during radical prostatectomy increased the occurrence of DVT and PE. Open surgery increased the above risk more than robot-assisted surgery; this was most prominent in patients not undergoing LND.

Prostate cancer is the second leading cause of cancer deaths in men in the United States. There is a major need for less toxic but yet effective therapies to treat prostate cancer. Pomegranate fruit from the tree Punica granatum has been used for centuries for medicinal purposes and is described as "nature's power fruit". Recent research has shown that pomegranate juice (PJ) and/or pomegranate extracts (PE) significantly inhibit the growth of prostate cancer cells in culture. In preclinical murine models, PJ and/or PE inhibit growth and angiogenesis of prostate tumors. More recently, we have shown that three components of PJ, luteolin, ellagic acid and punicic acid together, have similar inhibitory effects on prostate cancer growth, angiogenesis and metastasis. Results from clinical trials are also promising. PJ and/or PE significantly prolonged the prostatespecific antigen (PSA) doubling time in patients with prostate cancer. In this review we discuss data on the effects of PJ and PE on prostate cancer. We also discuss the effects of specific components of the pomegranate fruit and how they have been used to study the mechanisms involved in prostate cancer progression and their potential to be used in deterring prostate cancer metastasis.

Chemopreventive effects of the essential trace element selenium against prostate cancer have been shown in preclinical models and human observational studies, but results from clinical trials have been disappointing. It appears that there is a threshold selenium (Se) status below which improvement will decrease prostate cancer risk, but above which supplemental Se may be deleterious. Different forms of selenium have different effects, and genetic and other factors modify selenium's chemopreventive potential. Identification of men most likely to benefit from Se status improvement could have significant public health benefits.

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