مقالات
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Even in the current era of dose-escalated radiotherapy for prostate cancer, biochemical recurrence is not uncommon. Furthermore, biochemical failure is not specific to the site of recurrence. One of the major challenges in the management of prostate cancer patients with biochemical failure after radiotherapy is the early discrimination between those with locoregional recurrence only and those with metastatic disease. While the latter are generally considered incurable, patients with locoregional disease may benefit from emerging treatment options. Ultimately, the objective of salvage therapy is to control disease while ensuring minimal collateral damage, thereby optimizing both cancer and toxicity outcomes. Advances in functional imaging, including multiparametric prostate MRI, abdominopelvic lymphangio-MRI, sentinel node SPECT-CT and/or whole-body PET/CT have paved the way for salvage radiotherapy in patients with local recurrence, microscopic nodal disease limited to the pelvis or oligometastatic
disease. These patients may be considered for salvage reirradiation using different techniques: prostate low-dose or high-dose rate brachytherapy, pelvic and/or lomboaortic image-guided radiotherapy with elective nodal irradiation, focal nodal or bone stereotactic body radiation therapy (SBRT). An individualized approach is recommended. The decision about which treatment, if any, to use will be based on the initial characteristics of the disease, relapse patterns and the natural history of the rising prostate specific antigen (PSA). Preliminary results suggest that more than 50% of patients who have undergone salvage reirradiation are biochemically relapse-free with very low rates of severe toxicity. Large prospective studies with a longer follow-up are needed to confirm the promising benefit/risk ratio observed with salvage brachytherapy and or salvage nodal radiotherapy and/or bone oligometastatic SBRT when compared with life-long palliative hormones.
It has been proposed that the high incidence of prostate cancer in Western countries and the increase in incidence rates over the past 50 years may be partly due to the low content of fiber and whole grains in the Western diet. Animal and experimental studies have shown that whole grain products have beneficial effects on prostate cancer progression, including delayed tumor growth and enhanced tumor cell apoptosis. During the industrial refining process the outer bran layers as well as the germ of the grains are removed, and with them a variety of bioactive substances, including fiber, antioxidants, minerals, vitamins, and phytoestrogens, which may exert cancer-protective effects through multiple and partly overlapping biological mechanisms. Epidemiological studies investigating the association between whole grain or fiber intake and risk of incidence of prostate cancer have not provided strong evidence for a prostate cancer-preventive effect of a diet rich in whole grains or dietary fiber.
Prostate-specific antigen (PSA), the current clinical biomarker for prostate cancer, suffers from high false positive and high false negative rates that leave many men without a conclusive diagnosis. Virtually all clinically approved cancer biomarkers are cell-surface or secreted glycoproteins. We seek to identify more specific clinical biomarkers of prostate cancer by developing an efficient method for specifically labeling and enriching glycoproteins, followed by MS-based analysis of normal and cancerous human prostate tissue. We present a novel biomarker identification strategy where human prostate tissue derived from radical prostatectomies, at varying states of prostatic disease is chemically tagged. To identify cell-surface or secreted glycoproteins from prostate tissue, we employ metabolic labeling, a technique in which unnatural azide or alkyne-functionalized monosaccharides are incorporated, into cell-surface glycoproteins via the cells’ own metabolic machinery. Tissue slices incubated with these labeled sugars are subsequently reacted with a biotin-functionalized probe for the capture of sialylated...
glycoproteins. Analysis of labeled tissue by Western blot confirmed azide or alkyne-dependent labeling. Proteins were then digested with trypsin and the resultant peptides were analyzed on a linear ion trap mass spectrometer with collision-induced dissociation (CID). Greater than 60% of the proteins identified by LC-MS/MS were cell-surface or secreted proteins, indicating that this strategy achieves enrichment of low abundance proteins. Subsequently, we performed a comparative proteomics experiment between diseased and healthy tissue and identified proteins unique to each tissue type, which are undergoing further validation as potential biomarkers. This work extends the application of existing metabolic labeling techniques, while developing new methodologies for cell surface labeling to discover biomarkers associated with prostate cancer.

Resistance to androgen deprivation therapies and increased androgen receptor (AR) activity are major drivers of castrate resistant prostate cancer (CRPC), an advanced and frequently lethal form of this disease. Substantial prior work has focused on targeting AR directly; however, the identification and therapeutic targeting of co-activators of AR signaling remains an underexplored area of potential clinical significance. Here we demonstrate that the MLL complex acts as a co-activator of AR signaling. AR directly interacts with the sub-unit menin
to recruit MLL and its complex to AR target genes. Inhibition of the menin-MLL interaction can block AR signaling and inhibit the formation of castration resistant tumors in vivo. Furthermore, we find that menin is up-regulated in localized and metastatic prostate cancer and high menin expression correlates with poor overall survival. Taken together our study identifies a novel co-activator complex of AR that can be targeted in CRPCs.

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Purpose

We examine the role of body mass index in the assessment of prostate cancer risk.

Materials and Methods

A total of 3,258 participants who underwent biopsy (including 1,902 men with a diagnosis of prostate cancer) were identified from the Selenium and Vitamin E Cancer Prevention Trial. The associations of body mass index with prostate cancer and high grade prostate cancer were examined using logistic regression, adjusting for age, race, body mass index adjusted prostate specific antigen, digital rectal examination, family history of prostate cancer, biopsy history, prostate specific antigen velocity, and time between study entry and the last biopsy. The prediction models were compared with our previously developed body mass index adjusted Prostate Cancer Prevention Trial prostate cancer risk calculator.

Results

Of the study subjects 49.1% were overweight and 29.3% were obese. After adjustment, among men without a known family history of prostate cancer, increased body mass index was not associated with a higher risk of prostate cancer (per one-unit increase in logBMI OR 0.83, p=0.54) but was significantly
associated with a higher risk of high grade prostate cancer (ie Gleason score 7 or greater prostate cancer) (OR 2.31, p=0.03). For men with a known family history of prostate cancer the risks of prostate cancer and high grade prostate cancer increased rapidly as body mass index increased (prostate cancer OR 3.73, p=0.02; high grade prostate cancer OR 7.95, p=0.002). The previously developed risk calculator generally underestimated the risks of prostate cancer and high grade prostate cancer.

Conclusions

Body mass index provided independently predictive information regarding the risks of prostate cancer and high grade prostate cancer after adjusting for other risk factors. Body mass index, especially in men with a known family history of prostate cancer, should be considered for inclusion in any clinical assessment of prostate cancer risk and recommendations regarding prostate biopsy.

6. Integrated CT-perfusion shows no meaningful correlation with PSA and presurgical Gleason score in patients with early prostate cancer

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Objectives

To analyze the correlation of computed tomography (CT) perfusion parameters blood flow (BF), blood volume (BV), and mean transit time (MTT) with presurgical prostate cancer data.

Methods

Ninety-eight patients with biopsy-proven prostate cancer underwent a CT-perfusion scan of the prostate. MTT, BF, and BV were determined and correlated with prostate-specific antigen (PSA) level, tumor load and Gleason score of transrectal ultrasonography-guided biopsy specimens.

Results
Mean BF was 41.3 ml/100 ml*min-1, BV 5.2 ml/100 ml, MTT 8.7 s. Moderate correlations were observed between Gleason score and BF (0.35) and between PSA and BF (0.33) and BV (0.30).

Conclusions

CT-perfusion shows no valuable correlation with presurgical prostate cancer data.

7. Hormone and Radiotherapy versus Hormone or Radiotherapy Alone for Non-metastatic Prostate Cancer: A Systematic Review with Meta-analyses

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Aims

Radiotherapy is standard treatment for localised prostate cancer and is often combined with hormone treatment to prevent androgen stimulation of prostate cancer. Hormone therapy carries significant morbidity and can only be justified in the radical treatment of localised disease if it can be balanced against a significant gain in disease control and survival.
Materials and methods

We searched Medline, Premedline, Embase, Cochrane Library, Web of Science (SCI & SSCI) and Biomed Central for randomised controlled trials published in English comparing radiotherapy or hormone therapy alone with radiotherapy and hormone therapy in combination as first-line treatment in patients with non-metastatic prostate cancer reporting overall survival, disease-free survival, distant metastases-free survival, biochemical survival, adverse events (including cardiovascular) and/or health-related quality of life.

Results

Fourteen trials were included and showed that combination therapy was associated with better or similar survival and disease-free outcomes compared with single-modality treatment, and that this may particularly be the case for patients with higher risk disease. The results also suggested that combination therapy is associated with more and worse adverse events and quality of life, although this was not always the case. Some of the results are at risk of reporting bias.

Conclusion

The published data support the use of combined treatment with androgen deprivation and radiotherapy for intermediate- and high-risk localised and locally advanced prostate cancer. Optimal timing, duration, formulation and the management of side-effects remain important questions for further research.
INTRODUCTION AND OBJECTIVE: Hyaluronic acid (HA) and HYAL-1 hyaluronidase (HAase) family molecules are potential markers for BCa diagnosis and prognosis and promote tumor growth and metastasis. 4-Methylumbelliferone (4-MU) is an orally bioavailable dietary supplement that inhibits HA synthesis. Epithelial-to-mesenchymal transition (EMT) is the hallmark of invasion and metastasis. Since HA promotes tumor metastasis and EMT, we evaluated the expression of EMT markers in bladder tissues and antitumor effects of 4-MU in BCa models.

METHODS: Quantitative PCR was used to measure mRNA expression of EMT genes (β-catenin, Twist, and Snail) in 66 bladder tissue specimens (27 normal; 39 tumor); follow-up: 26±4.3 months; median 20 months. The effect of 4-MU (40 - 120 µg/ml) on cell proliferation, apoptosis, intracellular signaling, and the expression of HA receptors and EMT genes were examined in BCa cell lines, 253J-Lung and HT1376. Effect of 4-MU on tumor growth was analyzed in subcutaneous xenografts.

RESULTS: Among the EMT genes, Snail and Twist were differentially expressed in BCa tissues when compared to normal bladder (P<0.001). Furthermore, elevated Twist expression significantly correlated with metastasis (2-fold increase; P=0.028). β-catenin expression negatively correlated with survival (chi
At IC50 for HA synthesis, 4-MU inhibited proliferation (~2.5-fold) and induced apoptosis (3-fold) in BCa cells. 4-MU induced caspase-8, -9 and -3 activation and up-regulation of Fas and FADD. 4-MU caused 4-10-fold downregulation of HA-receptors (CD44, RHAMM), and EMT promoters - β-catenin, Snail and Twist, but increased E-cadherin expression by 2-fold. In xenograft studies, 4-MU significantly decreased tumor growth (> 3-fold) when treatment was started either on the day of tumor cell injection or after tumors became palpable. No weight loss or serum or organ toxicity was observed in treated mice. Tumors showed reduced microvessel density (~3-fold) and HA expression but increased TURNEL positive cells.

CONCLUSION: This study shows that expression of EMT determinants correlates with clinical outcome. Furthermore, the non-toxic dietary supplement 4-MU has potent antitumor activity and reverses EMT.

Bladder cancer is the fifth most diagnosed cancer in the US. In 2013 there were approximately 72,570 newly diagnosed cases and 15,210 deaths attributing to this disease where the average age of onset for this disease is 65 and remains one of the most expensive cancers to treat due to lifelong surveillance and invasive procedures. Bladder cancer is defined by two distinct pathways which result in either low grade non-invasive or high grade invasive cancer. Although these are marked by distinct mutations, it has been observed that both
display mTORC1 activation. This suggests that activated mTORC1 may be an early contributing factor in bladder tumorigenesis. Additionally, rapamycin, an inhibitor of mTORC1, inhibited tumorigenesis in a mouse model of bladder cancer further implicating mTORC1 as an essential pathway in tumorigenesis.

To elucidate the mechanism of mTORC1 activation in bladder cancer, AMP-activated protein kinase (AMPK), a negative regulator of mTORC1, was investigated. AMPK is a critical metabolic regulator that suppresses cellular growth in response to metabolic stress. Additionally it has been observed that AMPK activation is suppressed in breast and hepatocellular carcinoma and the AMPKα2 isoform is suppressed in breast and gastric cancer. To investigate whether levels or activation of AMPK are altered in bladder cancer a pilot cohort of adjacent non-tumor and bladder tumor human samples was obtained as was a human bladder cancer tissue array. In both the pilot cohort and the array, the levels of AMPKα1 and AMPKα2 were suppressed at statistically significant levels in low and high grade bladder cancer when compared to adjacent non-tumor tissue. Messenger RNA expression for both isoforms in bladder tumors revealed that AMPKα2 may be selectively suppressed at the mRNA level. However AMPKα1 suppression appeared to be due to translational or post translational regulatory mechanisms. It was also observed that AMPKα1 was located predominately in the cytoplasm while AMPKα2 was located in both the nuclear and cytoplasmic compartments. This suggests that AMPKα isoforms may have distinct roles in the bladder and may be suppressed by different mechanisms.

To test the relevance of AMPK in bladder tumorigenesis the mouse BBN bladder carcinogenesis model was employed. BBN was supplemented in the drinking water of wild-type and AMPKα2-/- mice at a concentration of .05% over the course of 20 weeks. AMPKα2-/- mice displayed a significant increase in bladder
weight indicating the presence of larger tumors. There was also an increase in KI67 positive cells in the tumors of AMPKα2-/- mice indicating increased proliferation with no appreciable apoptosis observed in any tumors. Ongoing studies in which BBN is supplemented for 16 weeks and then removed for the duration aim to validate the role of AMPKα2 in bladder tumor initiation and/or progression. In summary, loss of AMPK activity, especially AMPKα2, can promote bladder tumorigenesis through increased proliferation via mTORC1 activity.

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Aims
To evaluate the safety and efficacy of robot-assisted radical cystectomy (RARC) compared with open radical cystectomy (ORC) in the treatment of bladder cancer.

Methods
A systematic search of Medline, Embase databases and the Cochrane Library was performed to identify studies that compared RARC and ORC and were published up to December 2012. Outcomes of interest included demographic and clinical characteristics, perioperative, pathologic variables and complications.

Results
Although there was a significant difference in the operating time in favor of ORC (WMD: 70.69 min; p < 0.001), patients having RARC might benefit from significantly fewer total complications (OR: 0.54; p < 0.001), less blood loss (WMD: −599.03 ml; p < 0.001), shorter length of hospital stay (WMD: −4.56 d; p < 0.001), lower blood transfusion rate (OR: 0.13; p = 0.002), less transfusion needs (WMD: −2.14 units; p < 0.001), shorter time to regular diet (WMD: −1.57 d; p = 0.002), more lymph node yield (WMD: 2.18 n; p = 0.001) and fewer positive lymph node (OR: 0.64; p = 0.03). There was no significant difference between the RARC and ORC regarding positive surgical margins.

Conclusions
In early experience, our data suggest that RARC appears to be a safe, feasible and minimally invasive alternative to its open counterpart when performed by experienced surgeons in selected patients.
مرکز رادیوتراپی و انکولوزی پرتو

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