maps to the *Alpha-1,3-mannosyl-glycoprotein 4-beta-N-acetylglucosami-nyltransferase C* (*MGAT4C*) gene on 12q21.31. *In vitro* cell line assays found this gene to significantly modulate cell proliferation and migration in both benign and cancer prostate cells. Further, *MGAT4C* was significantly overexpressed in metastatic *versus* localized prostate cancer. These two risk associations were replicated in an independent PSA-screened cohort of 800 men (15q21.3, combined p=0.006; 12q21.31, combined p=0.026). *Discussion:* These findings establish non-coding and coding germline CNVs as significant risk factors for prostate cancer susceptibility and implicate their role in disease development and progression. In summary, this is the first large scale, unbiased study using this patient population to study the contribution of germline CNVs towards prostate cancer risk. *Conclusion:* We envision that CNVs can eventually be used to assess patient risk for aggressive prostate cancer at time of diagnosis.

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RADICAL NEPHRECTOMY AND CAVOATRIAL THROMBECTOMY ON NORMOTHERMIC CARDIOPULMONARY BY-PASS AND BEATING HEART: A CASE REPORT AND DESCRIPTION OF THE TECHNIQUE

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Objectives: Usually, cavoatrial kidney cancer is managed with cardiopulmonary by-pass (CBP) with deep hypothermia circulatory arrest (DHCA). In this study, we report the feasibility, safety and effectiveness of radical nephrectomy with cavoatrial thrombectomy on normothermic CPB and beating heart. *Patients:* A 71 years old healthy woman presented with lumbar pain. Abdomen US and following CT scan detected an 8 cm right renal tumor with a neoplastic thrombus (NT) extended from the right renal vein to all inferior vena cava (IVC) and to the right atrium (RA). The thrombus partially involved the right supra hepatic veins and the left renal vein. Distant metastases were not detected. *Results:* Through a laparotomic median incision, the urological equipe mobilised the right colon and exposed the right kidney. The renal vascular pedicle was exposed and the radical nephrectomy with adrenalectomy was performed. The right and left renal veins, that were obstructed by NT, were isolated. The liver was mobilized to allow the exposition of the intra and supra hepatic VCI, completely occupied by the NT. Sternotomy and pericardiotomy were performed by the heart surgery equipe. Aortic arch, superior VC and the VCI just above iliac veins were cannulated. On normothermic CBP and beating heart, right atriotomy and a "J" incision on VCI were simultaneously performed. At the same time, the urologists and heart surgeons removed the NT from the RA, the left VR and the VCI. Part of the VCI wall was infiltrated by the thrombus and was resected. RA and VCI were closed and the patient was weaned from CBP. CPB time: 91 min; Surgical time: 6 hrs. Estimated blood loss 500 ml. Autologous blood transfusion: 700 ml. Pathological report: clear cell RCC pT3c Fuhrman G3 pN1. Intensive care stay: 5 days. Post operative in-hospital stay: 7 days. A post-surgical transthoracal echocardiography demonstrated regular parameters without any residual thrombus in RA and normal cardiac function. One month later, total body CT showed a regular VCI with no signs of persistent disease. *Conclusion:* In our experience, management of T3c kidney cancer with a beating heart normothermic CBP appears a feasible, safe and effective technique. As neither hypothermia nor heart arrest are needed, our technique improves patient recovery and diminishes risks of complications. Furthermore, with cannulation of lower IVC, other vascular access for lower venous return are not necessary.

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HORMONAL THERAPY PROMOTES HORMONE-RESISTANT PHENOTYPE BY INCREASING DNMT ACTIVITY AND EXPRESSION IN PROSTATE CANCER MODELS

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We hypothesized that hormonal therapy favors the development of the hormone-resistant phenotype through epigenetic mechanisms. Human prostate cancer tissues and *in vitro* and *in vivo* models were used to verify this hypothesis. We demonstrated that tumor cells continuously treated with bicalutamide (BCLT) or cultured in androgen-depleted medium progressively acquire higher DNA methyltransferase (DNMT) activity and expression than cells cultured in standard condition. Increased DNMT expression and activity also paralleled the up-regulation of truncated AR isoforms, which favors the development of the hormone-resistant phenotype. After androgen stimulation with 12 10− M dihydrotestosterone, DNMT activity was significantly reduced in comparison with hormonal therapy. Consistent with these observations, the silencing of DNMT3a and DNMT3b significantly decreased the DNMT activity levels. These findings were also directly correlated with PTEN downregulation and activation of ERK and PI3K/Akt pathways. The use of a pan-DNMT inhibitor (5Azacitidine) greatly reduced the development of the hormone-resistant phenotype induced by longterm BCLT treatment, and this finding correlated with low DNMT activity. The regulation of DNMT activity was, in some measure, dependent on the androgen receptor, as small interfering RNA treatment targeting the androgen receptor greatly decreased the modulation of DNMT activity under androgenic and antiandrogenic stimulation. These observations were correlated *in vivo* in patients, as demonstrated by immunohistochemistry. Patients treated by BCLT before surgery had higher DNMT3a and DNMT3b expression than patients who had not undergone this treatment. Our findings provide evidence of a relationship between the castration-resistant phenotype and DNMT expression and activity in human prostate cancer.

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THE VALUE OF BIOPSY LATERALITY IN ASSOCIATION WITH PSA AND GLEASON SCORE FOR THE IDENTIFICATION OF SUBJECTS AT HIGH RISK OF RECURRENCE IN PROSTATE CANCER

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Background: Predicting patients with prostate cancer (Pca) at high risk of recurrence (HRR) is a major challenge for clinicians. Clinical T-stage poorly predicts the pathological stage and understaging occurs in up to 60% of cases. Here we determine if needle biopsy parameters improve the value of NCCN criteria for predicting men at HRR. *Methods:* A retrospective survey of 488 men who underwent RP was undertaken. Univariate and multivariate logistic regression with receiver operating characteristic (ROC) curves were generated to test which parameters were able to best individulize men at HRR when histopathologic findings were used as the reference standard. The parameters were: PSA, biopsy laterality, total number of positive biopsy cores, clinical T stage, and Gleason score. The combination of best predictors then was compared with the standard NCCN criteria in terms of ability to predict HRR. *Results:* At univariate analysis all clinical parameters [biopsy laterality (OR=2.389; 95%CI 1.49 to 3.82; $p<0.0001$); Gleason score (OR=1.678; 95%CI 1.37 to 2.046; $p<0.0001$), total number of positive biopsy cores (OR=1.488; 95%CI 1.27 to 1.74; $p<0.0001$) and PSA (OR=1.329; 95%CI 1.26 to 1.53; $p<0.0001$)] except the clinical T-stage (OR=1.136; 95%CI 0.86 to 1.49; $p=0.343$) significantly predicted men at HRR. At multivariate analysis only biopsy laterality (OR=2.453; 95%CI 1.07 to 5.61; $p=0.033$), Gleason score (OR=1.847; 95%CI 1.38 to 2.46; $p<0.0001$) and PSA (OR=1.490; 95%CI 1.29 to 1.71; $p<0.0001$) were predictors of HRR. The association of PSA, Gleason score and biopsy laterality achieved a significant larger AUC (AUC=0.835; 95%CI 0.791 to 0.873; $p<0.0001$) than the association of standard parameters used in the NCCN criteria

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