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出國報告（出國類別：參加國際會議發表論文）

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參加國際泌尿病理學會腎臟腫瘤共識研討會暨美國加拿大病理醫學會 2012 年年會心得報告

③

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出國期間：3/16 ~ 3/22
報告日期： 4/9

一、 目的：

參加於加拿大溫哥華舉行之國際泌尿病理學會腎臟腫瘤共識研討會暨美國加拿大病理醫學會 2012 年年會，並發表論文「建立預測非肌肉侵襲性膀胱癌惡化之預後模型」及「非肌肉侵襲性膀胱泌尿上皮癌之 Her2 擴增與腫瘤惡化顯著相關」二篇。

關鍵字：泌尿上皮癌、膀胱

二、 過程

本次行程之第一部份為十七日舉行之國際泌尿病理學會腎臟腫瘤共識研討會。國際泌尿病理學會（International Society of Urological Pathology）為一跨國際之學會，登錄之會員約二百名。筆者為其中之一。國際泌尿病理學會定期會針對泌尿病理學中有爭議之主題召開共識研討會，迄今已完成攝護腺腫瘤之共識研討會。本年度即針對腎臟腫瘤之議題進行交流溝通。與會之會員約 130 名。總計之議題共分腫瘤分類、組織學預後因子、分期與檢體處理、生物標記等四大項。會前先請會員就上百題題目進行問卷調查。會中則由負責人報告文獻背景並進行討論。討論後則請與會會員以電子投票器進行無記名投票。若投票一致率超過 66%則識為有共識。經討論後大約八成以上之議題均能獲得共識。會議結果將寫成論文發表於 American Journal of Surgical Pathology。

值得一提的是，國際泌尿病理學會雖為跨國之學會，參加會議者各國皆有。當日會議主持人分屬義大利籍（會長）、瑞典籍（秘書長）及紐西蘭籍（召集人），但與會者美國籍佔居大多數，經常上台發表意見者不超過五位，全為美國之專家。可見在泌尿病理學美國專家仍保有難以撼動之地位。

第二部份為美國加拿大病理醫學會。美國加拿大病理醫學會雖本為美加地區之病理學年會，但由於內容豐富，規模宏大，已經成為國際性之病理學大會。與會者涵蓋全球各地。筆者每隔數年便會參加，發表論文，獲取新知，並與國際知名學者進行交流。此次會議於溫哥華召開，為期一週。協同之次專科學會有神經病理、眼科病理、內分泌病理、泌尿病理、細胞病理、肺臟病理、傳染病病理、血液病理、腎臟病理、

心血管病理、超顯微病理、皮膚病理、消化道病理、骨軟組織病理、婦產科病理、頭頸病理、分子病理、乳房病理等數十學會。每個學會均會安排專科會議（Specialty conference）、教育課程、口頭與壁報論文發表。全部會議其間總共有 26 場協同會議（Companion meeting）、19 場專科會議、6 場特別課程（Special course）、6 場短期課程（Short course），及 1 場長課程（Long course）。口頭與壁報論文發表總計 2176 篇。與會者可依其專業興趣，選擇適當之會議與課程。此次會議本人共發表壁報論文二篇，摘要如附件。

三、 心得

筆者雖非第一次參加美國加拿大病理醫學會年會，但每次參加均獲益匪淺。不僅可以觀摩學習其他病理學者之研究，對掌握新知與了解最新發展趨勢均有難以取代之貢獻。此外，在會議期間也可藉機認識國際知名學者，對進行跨國際之合作研究並與世界接軌，都是很好的管道。筆者即是在類似之國際會議（第七屆亞太病理學會年會）中認識期刊 *Pathology*（Impact Factor: 2.168）之主編 Prof. Brett Delahunt，相談甚歡，從而獲邀擔任該期刊之編輯委員（Editorial Board）。筆者近期亦參與四個於美國、加拿大、義大利與瑞典主持之跨國病理研究計劃（其中二個已發表），並在 Jonathan Epstein、George Netto、Ming Zhou 主編之病理教科書「High Yield Pathology: Genitourinary Pathology」（已出版）中撰寫部份章節，均是藉由國際會議認識多位專家之故。

四、 建議事項（包括改進作法）

筆者在次會議中，遇到耕莘醫院主治醫師一名、和信醫院主治醫師一名、高雄長庚部主任與科主任、成大科主任、奇美科主任及大林慈濟之科主任前來，各自均有發表論文。本部前往紐約 Sloan-Kettering 進修之葉奕成醫師亦有發表壁報論文。據悉尚有台大二名住院醫師與會（未實際面見），實屬難能可貴。筆者認為，出國參加國

際會議對培訓專業人才甚有助益。然而出國一次，報名費、機票與住宿生活費總共多達十數萬元，經濟負擔不小。本人幸獲國科會表助 100,210 元，個人所費不多。惟年輕主治醫師申請院外補助不易。若是院方能有管道提供部份補助（如耕莘醫院對發表論文者補助機票費），應能減輕與會者經濟負擔，從而有效鼓勵醫師出國與會，增長國際視野。

were used for univariate analysis and logistic regression for multivariate analysis.
Results: A total of 55 patients had SVI. Mean serum prostate-specific antigen (PSA) was 8.36 in SVI vs 5.16 in NSVI with high incidence of PSA >10 ng/ml in SVI (16/55) vs NSVI (4/110). Clinical T stage above cT2a was seen in 60% of SVI vs 18.6% of NSVI ($p<0.001$). SVI group showed higher number of positive biopsy cores (6.45 in SVI vs. 3.11 in NSVI, $p<.0001$). The frequency of SVI was high when highest Gleason score on 12 core biopsy was ≥437 (67.3% in SVI vs 18.2% in NSVI, $p<.0001$). Base biopsy was positive in 53/55 (94.5%) patients with SVI, compared with 67/110 (60.9%) patients without seminal vesicle invasion (NSVI) ($p<0.0001$). SVI was frequently seen with either medial or lateral base involvement, highest Gleason score of ≥437 at the base, high tumor volume in base biopsy and bilateral base involvement ($p<.0001$). However, on multivariate analysis, only serum PSA, medial base tumor volume and high Gleason score in base were independent predictors of SVI.

Base involvement on biopsy

	B + ≥G437	MB + ≥G437	LB+ ≥G437	MB+ TV,%	LB+ TV,%	B+ Bilateral	B+ Unilateral
SVI +	30/52 (57.7%)	24/47 (51.1%)	24/47 (51.1%)	48.5%	52.1%	29/52 (55.8%)	23/52 (44.2%)
SVI -	7/67 (10.4%)	2/32 (6.2%)	6/60 (10%)	7.1%	16.9%	16/67 (23.9%)	51/67 (76.1%)

B:base, MB: Medial base, LB: Lateral base, TV: Tumor volume

Conclusions: Our results show that serum PSA, medial base tumor volume and high Gleason score on base biopsy may be useful predictors of SVI based on 12 core needle biopsy protocol.

1068 Correlation of Urine *TMPRSS2: ERG* and *PCA3* to ERG+ and Total Prostate Cancer Burden

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Background: *ERG* rearrangement, (most commonly resulting in *TMPRSS2:ERG* (*T2:ERG*) gene fusions), have been identified in approximately 50% of prostate cancers (PCa) and to date is the most specific prostate cancer biomarker. Quantification of *T2:ERG* in post-DRE urine, in combination with PCA3, improves the serum PSA performance for PCa prediction on biopsy. Previously, we have shown significant correlation between urine *T2:ERG* and maximum index tumor nodule dimension at prostatectomy.
Here we compared urine *T2:ERG* and *PCA3* to both ERG+ and overall tumor burden at prostatectomy to assess the cancer specificity of these urine biomarkers.
Design: Of 301 men presenting for biopsy assessed by transcription mediated amplification (TMA) for *T2:ERG* and *PCA3*, 41 (14%) underwent prostatectomy. All prostatectomies were mapped and all tumor nodules (including suspicious foci) were immmunostained with an ERG antibody shown to be sensitive and specific for ERG rearranged cancer (EPR3864). For each prostatectomy, the total number, greatest linear dimension, Gleason score and ERG IHC status of all tumor nodules was documented. Correlations between clinicopathological data and urine *T2:ERG* and *PCA3* were determined.
Results: The 41 prostatectomies had a median of 3 tumor nodules (1-15) and 2.7 cm of total linear tumor dimension (0.5-7.1 cm). There was no significant difference between the number ($p=0.59$) or linear tumor dimension (1.2 cm vs. 0.9 cm, $p=0.36$) of ERG+ and ERG- nodules ($p=0.59$). Urine *T2:ERG* most correlated with the number of ERG+ foci and total ERG+ linear tumor dimension (both $r_s=0.67$, $p<0.0001$). Of patients with 0 cm, >0.1 to 1.0 cm, and >1.0 cm of total ERG+ linear tumor dimension, 1/8 (13%), 4/10 (40%) and 21/23 (91%) had urine *T2: ERG* >30. Urine *PCA3* showed weaker correlation with both tumor nodule number ($r_s=0.37$, $p=0.02$) and total linear tumor dimension ($r_s=0.27$, $p=0.08$).
Conclusions: We demonstrate a strong correlation between urine *T2:ERG* and total ERG+ tumor burden at prostatectomy. The weaker correlation between urine *PCA3* and total tumor volume suggests that this biomarker may be less cancer specific than *T2:ERG*. Hence, urine *T2: ERG* may be useful for risk stratifying men with elevated serum PSA, prior negative biopsy, or those considering active surveillance.

1069 Construction of Prognostic Model Incorporating Biological Markers To Predict Progression of Non-Muscle-Invasive Bladder Cancer

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Background: Non-muscle invasive bladder cancers (NMIBC) run a variable course. The study was conducted to construct a robust multivariate model incorporating clinicopathologic factors and biological markers to predict the risk of progression.
Design: Immunohistochemistry for a series of biological markers (cyclin D1, *p27*Kip1, p21WAF1, EpCam, E-cadherin, Ki67, p53, *neu*, Cox2, p16, EGFR, PTEN, HSP27) were performed on 616 cases of NMIBC. Multivariate competing risk analyses including clinicopathologic variables (grade, stage, multiplicity, tumor size, prior history of bladder cancer) and expression of markers were performed. Prognostic model was constructed to predict progression based on the variables showing independent significance. Concordance index was calculated with internal validation using 200 bootstrapped resamplings.
Results: For patients without receiving intravesical instillation, the significant factors. associated with progression were grade-stage, multiplicity, p53, *neu* and HSP-27. For patients receiving intravesical instillation, the significant factors were grade-stage, prior history of bladder cancer, Ki-67, *neu* and HSP-27. The concordance indices were 0.785 and 0.749 for patients without and with intravesical instillation, respectively. The accuracy was better than the models without including biological markers for the 2 groups (0.732 and 0.695), respectively.
Conclusions: Inclusion of relevant biological markers enhances the prognostication of NMIBC. Based on the multivariate models incorporating both clinicopathologic variables biological markers, NMIBC could be stratified satisfactorily into 3 distinctive groups of high, intermediate and low risk for progression.

1070 PSA and NKX3.1: A Comparative IHC Study of Sensitivity and Specificity in Prostate Cancer

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Background: Adenocarcinoma of the prostate can present as metastatic carcinoma, which typically can be confirmed in most metastatic sites by immunohistochemistry with PSA antibodies. A new anti-PSA rabbit monoclonal (RM) antibody has been developed, which theoretically combines the advantages of high affinity, due to its rabbit origin, and high specificity, resulting from its monoclonal nature. Additionally, NKX3.1 protein has recently been shown to be a superior and sensitive marker in the majority of primary and metastatic prostatic adenocarcinomas. This study compared the staining sensitivity of a mouse monoclonal PSA (M) cocktail, a new PSA (RM), and NKX3.1 rabbit polyclonal (P). The PSA (RM) was also tested for specificity in over 600 cases of various normal and neoplastic tissues.
Design: Formalin-fixed paraffin-embedded tissue microarrays (TMA) were deparaffinized in the usual manner, followed by antigen retrieval. PSA (M), PSA (RM) and NKX3.1 (P) were optimized for staining prostate cancers, using an HRP micro-polymer detection system and visualization with DAB.
Results: The PSA (RM) stained 163/167 (98%) cases of prostate cancer, including 94/94 cases with a Gleason score of 3 to 8, and 55/58 (95%) cases with a Gleason score of 9 or 10. All other cancers and normal tissues were 100% negative. Both PSA antibodies stained 67 of 70 (95%) cases and were negative in the same cases (Gleason score 9 and 10). A comparison of PSA (M) and NKX3.1 on 71 cases of prostate adenocarcinoma (Grade II-IV) is summarized in Table 1:

Table 1

Tumor Grade	PSA (M)	NKX3.1
II	21/22	21/22
III	26/27	26/27
IV	19/22	20/22

Conclusions: The newly developed PSA (RM) was 100% specific and demonstrated equivalent staining to PSA (M), but in some cases provided sharper staining. The NKX3.1 (P) was slightly superior to PSA (M) in grade IV tumors. The strong nuclear staining of NKX3.1 results in easier interpretation of low expression cases, compared to the cytoplasmic staining of PSA, which can be ambiguous in these cases. PSA (RM) and NKX3.1 may be suitable for differential diagnosis, work-ups of tumors of unknown origin and multiplex stains.

1071 CD44 Full-Thickness Immunoreactivity Is More Sensitive Than CK5/6 for the Diagnosis of Flat Urothelial Lesions with Atypia

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Background: Flat urothelial lesions with atypia can pose a diagnostic dilemma when attempting to make the distinction between reactive urothelial atypia (RUA) and carcinoma in situ (CIS). A recent study suggested that CK5/6 may be a useful biomarker to help in this differential diagnosis. The aim of this study is to determine the diagnostic utility of CK5/6 in comparison to CD44 immunostain in the evaluation of flat urothelial lesions with atypia, since both immunostains demonstrate similar immunoreactive patterns.
Design: Thirty-seven transurethral resection of bladder (TURB) biopsies were evaluated. Twenty-eight (76%) cases comprised RUA with benign clinical follow-up and 9 (24%) CIS cases with classic histomorphologic features. All cases were evaluated by immunohistochemistry for CK5/6 (DAKO, RTU) and CD44 (DAKO, 1:25) using the LSAB method. Intensity and staining patterns were determined for each marker. Sensitivity and specificity for the diagnosis of RUA was determined.
Results: Full-thickness staining for CK5/6 was observed in 20 RUA cases. Negative or weak basal staining for CK5/6 was observed in 8 RUA cases and in all 9 CIS cases. Full-thickness staining for CD44 was observed in all 28 RUA cases and in 1 case of CIS. Negative or weak basal staining for CD44 was observed in 8 CIS cases. Sensitivity and specificity for the diagnosis of RUA were 71% and 100% for CK5/6 immunostain, and 100% and 89% for CD44, respectively.
Conclusions: Full-thickness staining for CD44 is more sensitive than full-thickness staining for CK5/6 for the diagnosis of RUA. CK5/6 does not add diagnostic value in this setting, and therefore should not be used as a substitute for CD44 in the traditional triple stain panel (CD44, CK20 and p53) employed in the differential diagnoses of flat urothelial lesions with atypia.

1072 Depth of Invasion of Urinary Bladder Cancer: Comparison of Direct Measurement Versus 2010 American Joint Committee on Cancer (AJCC) pT2 and 3 Classification

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Background: The clinical significance of sub-staging muscle invasive (AJCC pT2a and pT2b) and perivesical fat invasive (AJCC pT3a and pT3b) urinary bladder cancer remains uncertain. The objective of this study was to compare the cancer-specific (CS) outcome of pT2 and pT3 sub-staging and to compare the current AJCC staging system to a direct measurement of depth of invasion into muscularis propria and into perivesical fat.

969 Microvascular Pericyte Density Predicts Prostate Cancer Progression

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Background: The progression of tumor neovascularization is critical to continued tumor progression. It is critical to note that the walls of neovascular blood vessel capillaries are composed of two principal cell types: vascular endothelial cells and pericytes. Pericytes form an outer sheath surrounding the endothelial cells. Nascent pericytes express PDGF receptor-beta while nascent blood vessels and lymphatic endothelial cells express CD34. This investigation deals with establishing a quantitative analysis of PDGF receptor-beta and CD34 expression in prostate cancer as a tangible prognostic tool.

Design: We used a tissue microarray, which represented 49 patients with Gleason scores 0 (normal prostate tissue), 6, 7, 8, 9, and 10. These prostate cancer samples represented prognostic stages II, III, and IV (AJCC Manual 2010, p. 457). Tissue microarray slides were immunostained with PDGF receptor-beta and CD34. Immunostained slides were imaged with a high resolution digital camera. Digital images were analyzed by using NIH ImageJ1.44 image analysis software to quantify PDGF receptor-beta and CD34 expression. Microvascular density was measured for each patient as a percentage of the area covered by pericytes or endothelial cells to the area of the microarray spot. Statistical analyses were performed using Graphpad Prism. The microvascular pericyte density (MVPD) or microvascular endothelial density (MVED) scores in each position of tissue microarray were compared across each prognostic group.

Results: The mean MVPD score was 0.70%, 0.98%, 2.00%, 2.87%, 3.79%, and 4.33% in patients with Gleason scores 0, 6, 7, 8, 9, and 10, respectively. MVPD was significantly different between patients with different Gleason scores ($p<0.001$). The mean MVPD score was 2.05%, 3.02%, and 3.30% in patients with stage II, III, and IV prostate cancer, respectively ($p<0.05$). The mean MVED score was 0.74%, 1.19%, 2.04%, 3.02%, 3.97%, and 4.44% in patients with Gleason scores 0, 6, 7, 8, 9, and 10, respectively. MVED was significantly different between patients with different Gleason scores ($p<0.001$). Mean MVED was 2.31%, 3.23%, and 3.29% for patients with stage II, III, and IV prostate cancer, respectively ($p<0.05$).

Conclusions: MVPD and MVED scores can easily be utilized as practical prognostic tools in prostate cancer. Potentially, MVPD and MVED scores can be used to identify the patients who would benefit from targeted anti-pericyte, anti-endothelium, and anti-lymphangiogenesis therapies. *This project has been supported by an institutional research grant.*

970 Gleason Score at Surgical Margin Is Not an Independent Predictor of Biochemical Recurrence after Radical Prostatectomy

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Background: A positive surgical margin is known to increase the risk of prostatic adenocarcinoma (PA) recurrence after surgery. Gleason score at surgical resection margin (GSM) may independently affect postoperative outcome; this association however has not been confirmed. The objective of this study is to retrospectively analyze the association between GSM and biochemical recurrence (BCR) after radical prostatectomy (RP).

Design: We identified 154 RPs with positive surgical resection margin (SRM) and different Gleason patterns amounting to scores of 7 (3+4, 4+3) and 8 (3+5 and 5+3). Since GSM may impact BCR, these cases were selected for their disparate Gleason patterns. All slides with positive margins were reviewed and the GSM was recorded for each case. The BCR-free survival in patients with same overall Gleason score (GS) and different GSM was estimated using the Kaplan-Meier method and results were compared with the log-rank test. To determine if the GSM has independent predictive value with regards to biochemical outcome, we also compared the predictive performance of two multivariate Cox regression models. One model comprised traditional pathologic and clinical variables, including pathologic stage and GS, lymph nodes status, visually estimated percent of carcinoma, length of surgical margin and preoperative PSA. The other model added GSM to the first model variables. The predictive performance of these two models was quantified using the Harrell's c-index.

Results: Thirteen (12%) of 109 patients with PA GS 7 (3+4) and GS 8 (3+5) had GSM of 7 (4+3) or 8 (5+3). Twenty-eight (62%) of 45 patients with PA GS 7 (4+3) and GS 8 (5+3) had GSM of 7 (3+4). Over a median follow-up of 4.2 years, 52 (34%) patients had BCR. No difference in BCR-free survival was found between the two models. GSM was not significantly associated with BCR-free survival in the multivariate analysis ($p=0.285$). A marginal increase in predictive performance of the multivariate model was noted after inclusion of GSM (c-index changed from 0.689 to 0.691).

Conclusions: GSM is not associated with biochemical outcome after radical prostatectomy in both univariate and multivariate analyses. GSM does not add predictive accuracy to the standard model containing established prognostic factors. We found no evidence to support the inclusion of GSM in routine pathologic reporting of radical prostatectomy specimens.

971 Her2 Amplification Is Associated with a High Risk of Progression in Non-Muscle-Invasive Bladder Cancer

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Background: Her2/*neu* amplification and overexpression have been studied mainly in invasive and metastatic bladder cancers, but its significance in non-muscle invasive bladder cancer (NMIBC) has not been substantially investigated. The study was conducted to evaluate the prognostic value of Her2 amplification in NMIBC.

Design: Immunohistochemistry for *neu* and fluorescence in situ hybridization (FISH) using Her2/CEP17 probe (PathVysion) were performed on 8 cases of papillary urothelial neoplasm of low malignant potential (PUNLMP), 108 cases of low-grade papillary urothelial carcinoma (LPUC) and 169 cases of high-grade papillary urothelial carcinoma (HPUC). The immunoreactivity for neu was assessed by the percentage of tumor cells showing complete membranous positivity. Amplification was defined following the ASCO/CAP guideline (Her2/CEP 17 ratio >2.2). The status of Her2 amplification was correlated to progression of detrusor muscle invasion (progression from Ta/T1 to T2-4, metastasis or cancer-specific mortality).

Results: None of the PUNLMPs and LPUCs showed Her2 amplification. Fifteen (8.9%) of HPUCs showed Her2 amplification. Eleven (73.3%) of Her2-positive HPUCs progressed into muscle-invasive or metastatic disease. The cumulative incidence of progression at 5 years was 80.9% in Her2-positive HPUCs, as opposed to 40.1%, 14.8% and 2.2% in T1 Her2-negative HPUC, Ta Her2-negative HPUC, and LPUC/PUNLMP, respectively ($p<0.0001$). When overexpression of *neu* was defined using a cut-point of 50%, the concordance rate between immunohistochemistry and FISH was 100%.

Conclusions: Her2 amplification and overexpression can discern a subset of NMIBC with high risk for progression. These patients may be eligible for target therapy if the tumor progressed.

972 Pseudoangiosarcomatous (Acantholytic) Variant of Urothelial Carcinoma of the Urinary Bladder

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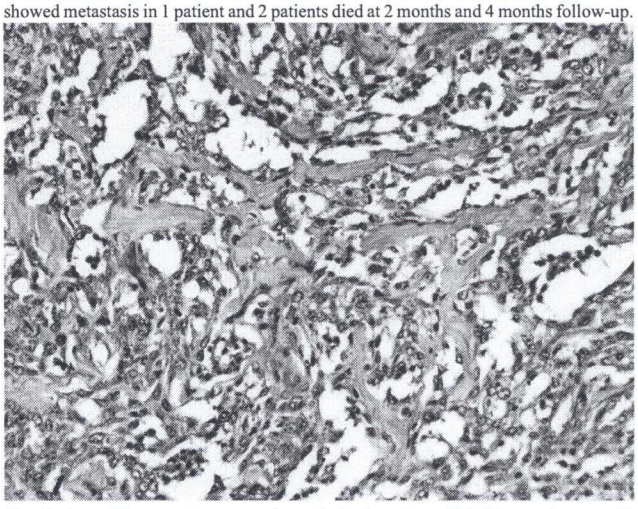
Background: We present an unusual morphologic pattern of urothelial carcinoma of the bladder. Although rare instances of this morphology had been reported in other organ carcinomas, only one example in the bladder has been previously described in the literature.

Design: Six radical cystectomies obtained from the surgical pathology files of two institutions formed the basis of this study.

Results: Patients included 5 males and 1 female ranging from 47 to 78 years old (mean 63 years). Histologically, the tumor was characterized by florid vascular-like formations of invasive carcinoma cells. There were elongated jagged and larger nests of cells with abundant central acantholysis and dyscohesion. Complete cell loss imparted an appearance of interanastomosing network of vascular-like channels lined by residual plump hobnailing cells reminiscent of epithelioid angiosarcoma. In addition, dyscohesion or cracking in smaller elongated nests formed slit-like spaces and occasionally, intracytoplasmic vacuoles were also seen. When in the muscle, the tumor tended to infiltrate in between and wrapped around smaller muscle bundles. The acantholytic areas were often accompanied by abundant acute inflammatory cells. Other admixed morphologies included squamous (3/6, 20-40% of tumor), small cell neuroendocrine (1/6, 15% of tumor) and sarcomatoid (1/6, 50% of tumor) differentiations. Pseudoangiosarcomatous pattern was similarly seen in the squamous component. Immunohistochemical stains in 3 tumors for Fli-1, CD31 and CD34 were all negative. AJCC pT stages were as follows: pT3a (2), pT3b (2) and pT4a (2) and 2/6 had lymph nodal metastasis at time of surgery. 1 patient had concomitant Gleason score 9 and pT3 prostate adenocarcinoma. Follow-up available in 4 patients (mean 6.7 months) showed metastasis in 1 patient and 2 patients died at 2 months and 4 months follow-up.



Conclusions: We present an unusual morphologic pattern of bladder carcinoma with striking resemblance to a malignant vasoformative tumor. Knowledge of this pattern is important to avoid misdiagnosis particularly in smaller TURBT samples. It appears that this morphology is associated with higher tumor stage and suggests a poorer outcome.

973 Application of ERG/TFF3/HMWCK Triple Immunostain: A Novel Diagnostic Biomarker in Prostate Needle Biopsies

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Background: Trefoil factor 3 (TFF3) expression is associated with various cancers and found to be over-expressed in a subset of prostate cancer (PCa). Functional studies suggest that *TMPRSS2-ERG* fusion down-regulates TFF3 expression in hormone-naïve prostate cancer. Through these *cis* interactions on chromosome 21, we posit a mutually exclusive expression of ERG and TFF3. Given this inverse relationship in

Her2 Amplification is Associated with a High Risk of Progression in Non-Muscle-Invasive Bladder Cancer

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Background: Her2/neu amplification and overexpression have been studied mainly in invasive and metastatic bladder cancers, but its significance in non-muscle invasive bladder cancer (NMIBC) has not been substantially investigated. The study was conducted to evaluate the prognostic value of Her2 amplification in NMIBC.

Design: Immunohistochemistry for neu and fluorescence in situ hybridization (FISH) using Her2/CEP17 probe (PathVysion) were performed on 10 cases of papillary urothelial neoplasm of low malignant potential (PUNLMP), 102 cases of low-grade papillary urothelial carcinoma (LPUC) and 178 cases of high-grade papillary urothelial carcinoma (HPUC). The immunoreactivity for neu was assessed by the percentage of tumor cells showing complete membranous positivity. Amplification was defined following the ASCO/CAP guideline (Her2/CEP 17 ratio >2.2). The average chromosome 17 copy number was 1.74 (±0.13). Polysomy 17 was defined as a chromosome 17 copy number greater than 2.13 (1.74+3×0.13). The status of Her2 amplification was correlated to progression of detrusor muscle invasion (progression from Ta/T1 to T2-4, metastasis or cancer-specific mortality).

Results: Table 1 lists the chromosome alteration in NIMBC. HPUC showed polysomy more frequently than LPUC and PUNLMP. None of the PUNLMPs and LPUCs showed Her2 amplification. Sixteen (9%) of HPUCs showed Her2 amplification. Figure 1 demonstrates the typical examples of amplification and polysomy. Thirteen (76.5%) of Her2-positive HPUCs progressed into muscle-invasive or metastatic disease. The cumulative incidence of progression at 5 years was 84.1% in Her2-positive HPUCs, as opposed to 30.7%, 11.5% and 1.1% in T1 Her2-negative HPUC, Ta Her2-negative HPUC, and LPUC/PUNLMP, respectively ($p<0.0001$) (Figure 2). When overexpression of neu was defined using a cut-point of 50%, the concordance rate between immunohistochemistry and FISH was 100%.

When the NMIBCs were stratified into HPUC and LPUC/PUNLMP groups, the polysomy did not correlate with progression (Figure3).

Conclusion: Her2 amplification and overexpression can discern a subset of NMIBC with high risk for progression. These patients may be eligible for target therapy if the tumor progresses.

Table 1. Her2 alterations in NMBC

	PUNLMP	LGUC	HGUC	pTa	pT1
Disomy	8 (80.0%)	88 (86.3%)	95 (53.4%)	111 (74.0%)	80 (57.2%)
Polysomy	2 (20.0%)	14 (14.7%)	67 (38.6%)	33 (22.0%)	50 (35.7%)
Amplification	0	0	16 (9.0%)	6 (4.0%)	10 (7.1%)
Total	10	102	178	150	140

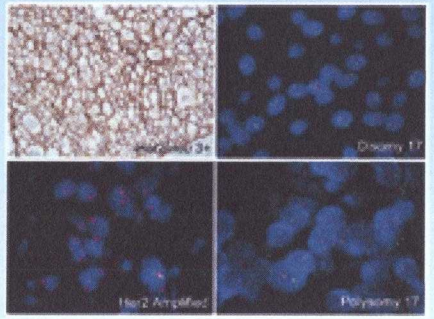


Figure 1

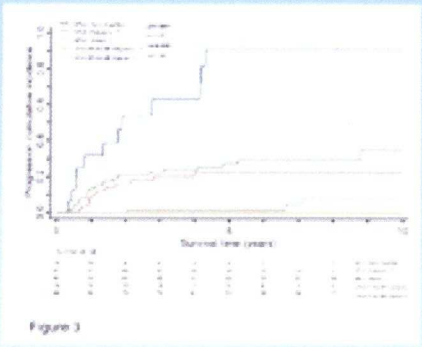


Figure 3

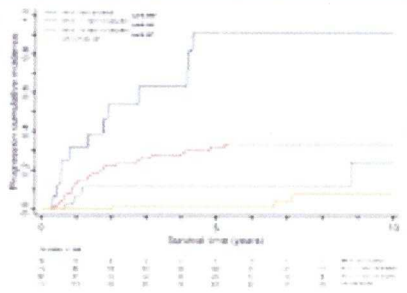
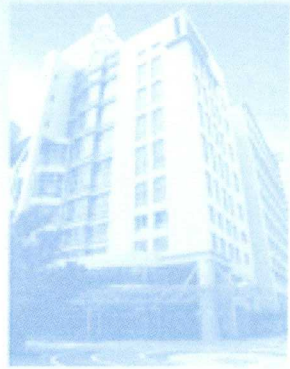


Figure 2



Construction of Prognostic Model Incorporating Biological Markers to Predict Progression of Non-Muscle-Invasive Bladder Cancer

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Institutions:[1]Cardinal Tien Hospital, Pathology, New Taipei City, Taiwan; [2]Taipei Veterans General Hospital, Pathology, Taipei, Taiwan

Background: Non-muscle invasive bladder cancers (NMIBC) run a variable course. The study was conducted to construct a robust multivariate model incorporating clinicopathologic factors and biological markers to predict the risk of progression.

Design: Immunohistochemistry for a series of biological markers (cyclin D1, *p27*Kip1, p21WAF1, EpCam, E-cadherin, Ki67, p53, neu, Cox2, p16, EGFR, PTEN, HSP27) were performed on 616 cases of NMIBC (Figure 1). Multivariate competing risk analyses including clinicopathologic variables (grade, stage, multiplicity, tumor size, prior history of bladder cancer) and expression of markers were performed. Prognostic model was constructed to predict progression based on the variables showing independent significance. Concordance index was calculated with internal validation using 200 bootstrapped resamplings.

Results: For patients without receiving intravesical instillation, the significant factors associated with progression were grade-stage (low-grade papillary urothelial carcinoma versus Ta high-grade papillary urothelial carcinoma versus T1 high-grade papillary urothelial carcinoma), multiplicity, p53, *neu* and HSP-27 (Table 1, Figure 2A). For patients receiving intravesical instillation, the significant factors were grade-stage, prior history of bladder cancer,Ki-67, *neu* and HSP-27 (Table 2, Figure 2B). The concordance indices were 0.785 and 0.749 for patients without and with intravesical instillation, respectively. The accuracy was better than the models without including biological markers for the 2 groups (0.732 and 0.695), respectively.

Conclusion: Inclusion of relevant biological markers enhances the prognostication of NMIBC. Based on the multivariate models incorporating both clinicopathologic variables biological markers, NMIBC could be stratified satisfactorily into 3 distinctive groups of high, intermediate and low risk for progression.

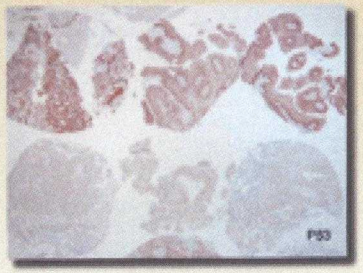

Figure 1A

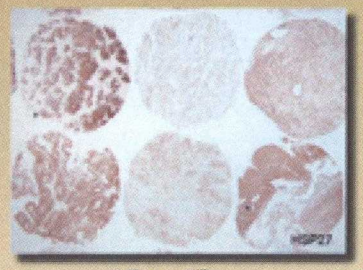

Figure 1B

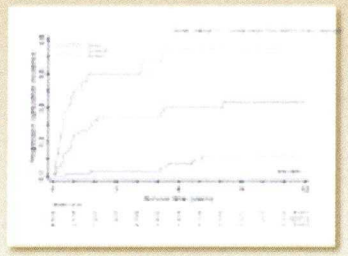

Figure 2A

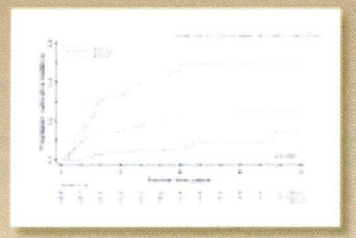

Figure 2B