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MP-04.01

The Perioperative Mortality is Significantly Higher in Septuagenarian and Octogenarian Patients Treated with Radical Cystectomy for Urothelial Carcinoma of the Bladder

Liberman D [1], Sun M [2], Alasker A [1], Thuret R [3], Badaus L [4], Widmer H [1], Graefen M [4], Shariat S [2], Perrotte P [1], Karakiewicz P [2]
[1]Department of Urology, University of Montréal Health Centre, Montréal, QC; [2]University of Montréal Health Centre, Cancer Prognostics and Health Outcomes Unit, Montréal, QC; [3]Department of Urology, Centre Hospitalier Universitaire De Montpellier, Montpellier, France; [4]Martini-Clinic, Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction and Objective: Data from tertiary care centres suggest that the perioperative mortality (POM) after radical cystectomy (RC) is not different in septuagenarian and octogenarian patients compared to younger individuals. Conversely, population-based data state otherwise. We revisited this topic in a large contemporary population-based cohort.

Materials and Methods: Between 1988 and 2006, 12722 underwent radical cystectomy for urothelial carcinoma of the urinary bladder (UCUB) in 17 Surveillance, Epidemiology and End Results (SEER) registries. Of those, 4480 were aged 70-79 and 1439 were 80 and over. Univariable and multivariable logistic regression models tested 90-day mortality after radical cystectomy. Covariates consisted of gender, race, year of surgery, SEER registry, histological grade and stage.

Results: Of all 12722 patients, 4480 (35.2%) were septuagenarian and 1439 (11.3%) were octogenarian. The overall 90-day mortality rate was 4% for the entire population, 2% for patients aged 69 years or younger, 5.4% for septuagenarian patients and 9.2% for octogenarian patients. In multivariable logistic regression analyses, septuagenarian (2.80; <0.001) and octogenarian (5.02; <0.001) age increased the risk of 90-day mortality after RC.

Conclusions: In this population-based analysis, POM was between 3 and 5-fold higher in respectively septuagenarian and octogenarian patients. This information needs to be included in informed consent considerations.

MP-04.02

Intravesically Administered Combination Treatment with Antisense Oligonucleotides Targeting Heat-Shock Protein 27 and Clusterin in a Model of Superficial Bladder Cancer

Gust K, Awrey S, Matsui Y, Gleave M, So A
The Vancouver Prostate Centre, Vancouver, BC

Introduction and Objective: The cytoprotective chaperone heat-shock protein 27 (HSP27) and clusterin, as an inhibitor of apoptotic cell death, are shown to have an important role in progression, drug resistance and therapy response in various kinds of cancer. Single targeting was shown to increase chemo sensitivity and to have tumour inhibitory effects. The objective of this study was to show that the intravesically administered combination of the antisense oligonucleotides (ASO) OGX-011 and OGX-427, which is currently in early phase I clinical trial development for non-muscle invasive bladder cancer, may have additive or synergistic tumour inhibitory effects compared to a single treatment.

Methods: The human bladder tumour cell line KU7 luc that stably expresses luciferase was used in all experiments. *In vitro*, KU7 luc cells were transfected with ASO targeting HSP27 (OGX-427) and clusterin (OGX-011) in doses between 25-100nM and 100-400nM. Cell growth inhibition, cell cycle as well as protein and gene expression were analyzed. *In vivo*, using an established orthotopic bladder tumour model, KU7 luc cells were transurethral instilled into the urinary bladders of female nude mice. ASO was administered intravesically every other day for a period of 2 weeks. Monotherapy OGX-011 and OGX-427 was used in a concentration of 50uM each, as well as combination therapy at same doses each and non-targeting ASO (ScrB) as control. Tumour growth was observed by bioluminescence and mice were sacrificed on day 28.

Results: *In vitro*, protein levels of clusterin and HSP27 were significantly decreased after single treatment with OGX-011 or OGX-427, as well as after the combination of both ASO. While both single treatments showed a dose-dependent growth inhibition, the combination of both treatments was superior to each of the single treatments. Cell cycle analysis showed a significant increase of the $SubG_o$ fraction for the combination treatment compared to single treatment. *In vivo*, intravesical treatment with the combination of OGX-011 and OGX-427 showed a significant inhibition of tumour growth ($P < .05$) compared to non-targeting ASO treatment.

Conclusions: The intravesical application of a combination of ASO targeting HSP27 and clusterin showed promising antitumour activity, providing pre-clinical proof of tumour inhibitory effects by an intravesical administered ASO combination treatment. Collectively, this data shows that further study of this combination is warranted in bladder cancer.

MP-04.03

The FGFR3 Mutation is Related to Favorable pT1 Bladder Cancer

Van Rhijn B[1], Bapat B[2], Van der Kwast T[3], Liu L[2], Fleshner N[1], Van der Aa M[4], Bangma C[4], Zwarthoff E[5], Jewett M[1], Zlotta A[1]
[1]Urology, UHN, Toronto, ON; [2]Molecular Medicine, Mount Sinai Hospital, Toronto, ON; [3]Pathology, UHN, Toronto, ON; [4]Urology, Erasmus Mc, Rotterdam, The Netherlands; [5]Exp. Pathology, Erasmus Mc, Rotterdam, The Netherlands

Introduction and Objective: *Fibroblast growth factor receptor 3 (FGFR3)* mutations have been recently reported at a very high frequency in pTa bladder cancer (BC) whereas these mutations are rare in high grade muscle-invasive BC. pT1-BC comprises a heterogeneous group of tumours for which different management options are advocated depending on the risk of progression to muscle-invasive disease. We have determined the frequency of *FGFR3* mutations in a group of primary pT1-BC and correlated the *FGFR3* mutation to various histo-pathological variables and clinical outcome.

Methods: We included 132 patients from two academic centres (N=60 in Rotterdam / 72 in Toronto) with primary (first diagnosis) pT1-BC. Mean age was 68.7 years (SD: 9.9 y). An experienced uro-pathologist reviewed the slides for grade (1973 and 2004 classification systems) and determined if the tumour was micro-invasive (<0.5 mm; pT1m) or extensive invasive (multiple spots with invasion and/or >0.5 mm; pT1e). The *FGFR3* mutation status was examined by SNaPshot analysis and correlated to pathological parameters. Kaplan-Meier statistics were used to analyze progression to >= pT2 disease.

Results: Median follow-up was 6.5 years (range: 0.3-21.6 years). *FGFR3* mutations were detected in 37/132 (28%) pT1-BC. The most frequent mutation in the *FGFR3* gene (S249C) was observed 24 times whereas other *FGFR3* mutations, R248C, G372C, Y375C, G382R were observed 5, 2, 5 and 1 time(s), respectively. The table shows that presence of a *FGFR3* mutation was highly correlated with favourable disease characteristics in pT1-BC. Thirty-eight (29%) patients progressed. The *FGFR3* mutation was associated with favourable clinical outcome, i.e., less progression (*p*-logrank = 0.041).

Table 1. MP-04.03

		FGFR3 mutant	FGFR3 wild type	*p*-value (chi-square)
Grade 1973	G2	25	31	< 0.001
	G3	12	64	
Grade 2004	Low-grade	15	11	< 0.001
	High-grade	22	84	
Sub-stage	pT1m	18	22	= 0.004
	pT1e	19	73	
Total		37	95	

Conclusion: The *FGFR3* mutation selectively identifies pT1-BC patients with favourable disease characteristics. Further study may confirm that this molecular marker is able to select patients who will benefit from a conservative approach to their disease.

5-STAR

MP-04.04

Molecular Markers Show Differences in Biological Potential per Grade Category for the WHO 1973 and 2004 Classification Systems: A Large Multicentre Study with Central Pathology Review in Non-Muscle Invasive Bladder Cancer

Van Rhijn B[1], Musquera M[1], Bangma C[2], Zwarthoff E[3], Fleshner N[1], Liu L[4], Bapat B[4], Jewett M[1], Zlotta A[1], Van der Kwast T[5]
[1]Urology, UHN, Toronto, ON; [2]Urology, Erasmus Mc, Rotterdam, The Netherlands; [3]Exp. Pathology, Erasmus Mc, Rotterdam, The Netherlands; [4]Molecular Medicine, Mount Sinai Hospital, Toronto, ON; [5]Pathology, UHN, Toronto, ON

Introduction and Objective: Currently, two classification systems for grade are advocated by our guidelines because the new WHO2004 classification system for grade has not been sufficiently validated against the old WHO1973 system with biological markers. We chose to evaluate the FGFR3 mutation as a marker for genetically stable non-muscle invasive (NMI) bladder cancer (BC) and aberrant expression of MIB-1, P53 and P27 as markers for genetically unstable NMI-BC.

Material and Methods: The slides of 327 primary (first diagnosis) NMI-BC from two university hospitals (Rotterdam, the Netherlands and Toronto, Canada) were reviewed by one uro-pathologist for the WHO 1973 (G1, G2 and G3) and 2004 (low malignant potential (LMP), low-grade (LG) and high grade (HG)) classifications systems. *FGFR3* status was examined by multiplex PCR-SNaPshot analysis. Expression levels of MIB-1, P53 and P27 were determined with standard immunohisto-chemistry. Cut-off-values for MIB-1, P53 and P27 were 25%, 10% and 50%, respectively.

Results: Grade review resulted in 88 G1, 148 G2 and 91 G3 lesions (WHO1973) and 79 LMP, 102 LG and 146 HG lesions (WHO2004). *FGFR3* mutations were detected in 187/327 (57%) of NMI-BC. Aberrant expression of MIB-1, P53 and P27 was found in 126, 99 and 72 NMI-BC, respectively. Stage pTa-BC had a *FGFR3* mutation in 134/171 (78%) cases as opposed to 53/156 (34%) *FGFR3* mutations in pT1-BC (Chi-square, $p < .001$). The table shows the relation of the 4 molecular markers with the 2 grading systems. In general, the FGFR3 mutation was associated with lower grades whereas MIB-1, P53 and P27 were associated with higher grades (Chi-square, $p < .0001$ for all). Moreover, the table shows that the WHO1973 G3 and G2 categories have a more aggressive biological potential than the WHO 2004 HG and LG categories. The G1 and LMP categories have a similar molecular profile.

Conclusions: Our results show that the introduction of the WHO2004 leads to higher grading implying a Will Rogers effect. Biological differences between the G3/HG and G2/LG categories were evident and support the continued joint use of both grading systems to guide clinical management of NMI-BC.

Table 1. MP-04.04

		FGFR3 mt (% of total)	MIB-1>25% (% of total)	P53>10% (% of total)	P27<50% (% of total)	Total
WHO1973	G1	78 (89)	5 (6)	2 (2)	3 (3)	88
	G2	92 (62)	53 (36)	37 (25)	33 (22)	148
	G3	17 (18)	68 (75)	60 (66)	36 (40)	91
WHO2004	LMP	67 (85)	5 (7)	2 (2)	3 (4)	79
	LG	80 (78)	23 (23)	15 (15)	18 (17)	102
	HG	40 (38)	98 (65)	82 (56)	51 (35)	146

MP-04.05

In vivo Evaluation of Mucoadhesive Docetaxel for Intravesical Treatment of Nonmuscle-Invasive Bladder Cancer

So A[1,2], Mugabe C[3], Matsui Y[1,2], Gleave M[1,2], Brooks D[3], Burt H[3]
[1]The Prostate Centre, Vancouver, BC; [2]University of British Columbia, Vancouver, BC; [3]Department of Pharmacology, University of British Columbia, Vancouver, BC

Introduction and Objective: Current treatment options for nonmuscle-invasive bladder cancer following transurethral resection are of limited efficacy since up to 80% of patients develop recurrent tumours. Microtubules are one of the most successful targets in cancer therapy to date and the recent Phase I trial of intravesical docetaxel for treatment of nonmuscle-invasive bladder cancer refractory to BCG therapy has shown this to be a promising intravesical agent with minimal toxicity and no systemic absorption. The present work describes the development and *in vivo* evaluation of a mucoadhesive docetaxel formulation for intravesical bladder cancer therapy.

Methods: Mucoadhesive formulations based on hydrophobically derivatized hyperbranched polyglycerols (dHPGs) were synthesized and docetaxel was loaded into these by a solvent evaporation method. Four bladder cancer cell lines were treated with various concentrations of docetaxel formulations *in vitro*. Human KU7 bladder tumour cells that stably express firefly luciferase (KU7-luc) were inoculated in female nude mice by intravesical instillation and quantified using bioluminescence imaging. Mice with established KU7-luc tumours were given a single intravesical instillation with PBS, Taxotere® (docetaxel from Sanofi-Aventis) or mucoadhesive docetaxel.

Results: dHPGs are nanoparticles with hydrodynamic radii of less than 10nm and incorporation of docetaxel did not affect their size. The release profiles of docetaxel from these nanoparticles were characterized by a rapid release phase (55% drug release during the first 24 hours) followed by a slower sustained release phase. *In vitro*, all docetaxel formulations potently decrease bladder cancer proliferation. However, *in vivo*, mucoadhesive docetaxel was the most effective formulation to inhibit tumour growth in an orthotopic model of high-grade nonmuscle-invasive bladder cancer.

Conclusions: Our data show promising *in vivo* antitumour efficacy and provide preclinical proof-of-principle for the intravesical application of

mucoadhesive docetaxel in the treatment of high-grade nonmuscle-invasive bladder cancer. Further research is warranted to evaluate its safety and efficacy in early phase clinical trials in patients refractory to standard therapy.

MP-04.06

Increasing Rates of Metastatic Seminoma and Nonseminoma Testicular Cancer: A Cause for Concern?

Liberman D[1], Badaus L[2], Jeldres C[3], Morgan M[1], Schmitges J[2], Perrotte P[1], Shariat S[3], Hartmann M[2], Graefen M[2], Karakiewicz P[3]
[1]Department of Urology, University of Montréal Health Centre, Montréal, QC; [2]Martini-Clinic, Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]University of Montréal Health Centre, Cancer Prognostics and Health Outcomes Unit, Montréal, QC

Introduction and Objective: Elevated rate of metastatic stage at presentation may be indicative of delays in diagnosis and is usually considered as an adverse predictor of cancer control outcome. We examined the annual rates of diagnosis of metastatic germ cell tumours as well as the associated 5-year survival rates, in a large population-based cohort over a period of 20 years.

Methods: Between 1988 and 2006, 17080 and 12984 patients were identified with respectively seminoma and nonseminoma of the testis within the 17 SEER registries. Rates and proportions as well as 5-year overall survivals were recorded and analyzed.

Results: Metastatic seminoma and nonseminoma was found in 2373 patients (7.8%). Of those, 500 (21%) and 1595 (79%) were metastatic at diagnosis. The rate of metastatic seminoma increased from 1.2 to 4.8% (Chi-square trend: $p < 0.001$) over the study span vs. 12.7 to 18.4% for nonseminoma (Chi-Square trend: $p < 0.001$). The median 5-year survival rate was 98% for both seminoma and nonseminoma. No differences were recorded in temporal 5-year survival rates ($p = 0.08$).

Conclusions: The rates of metastatic seminoma and nonseminoma at diagnosis increased over the study period. Therefore better detection strategies might require consideration. Nonetheless despite higher rates of metastatic disease at diagnosis the survival has not changed, which indicates excellent cancer control outcome.

MP-04.07

Tumour Grade Improves the Ability of the Prognostic Ability of AJCC Stages in Patients with Penile Carcinoma

Alasker A[1], Liberman D[1, 2], Jeldres C[1, 2], Ismail S[2], Morgan M[1, 2], Lughezzani G[2], Kassouf W[3], Widmer H[1], Perrotte P[1, 2], Karakiewicz P[1, 2]
[1]Department of Urology, University of Montréal Health Centre, Montréal, QC; [2]Cancer Prognostics and Health Outcomes Unit, University of Montréal Health Centre, Montréal, QC; [3]Department of Urology, McGill University, Montréal, QC

Introduction and Objective: The AJCC or TNM staging of penile carcinoma represents a standard and is widely used in clinical practice. We examined the ability of tumour grade that currently is not considered in the AJCC or TNM staging, to improve the prognostic ability of these two established staging schemes.

Methods: We relied on a population of 1577 penile carcinoma patients stages T1-4 N0-3 M0 who underwent an excision biopsy or partial or radical penectomy with or without a lymph node dissection. Separate Cox regression models were fitted for AJCC stages I to II (stage 0 not considered), T and N stages, as well as for T and N stages with tumour grade (grades I vs. II vs. III-IV). Harrell's concordance index was quantified for each of the three tested schemes.

Results: Overall, 194 patients died of penile carcinomas and the 5-year cancer-specific mortality rate was 16.1% (95% CI = 14.0 to 18.4%). The accuracy of AJCC staging in the prediction of cancer-specific mortality-free survival was 68.3% versus 70.0% for TN-based prediction (Mantel-Haenszel test, $p < 0.001$) versus 72.0% for T and N and grade-based prediction (Mantel-Haenszel test, $p < 0.001$).

Conclusions: The AJCC staging stratified non-metastatic penile cancer patients into three distinct categories versus 16 categories for the combination of T1-4 and N0-3 stages versus 48 categories for the combination of T1-4, N0-3 and grade 1-3 stage and grade combination. The prognostic accuracy of the AJCC staging schemes was the lowest versus an intermediate value for the TN-based scheme versus the highest for the TN and grade-based scheme. The superior prognostic ability of the TN and grade-based scheme suggests that grade should be routinely considered when the T and N stages are used for prediction of prognosis.

MP-04.08

Retroperitoneal Lymph Node Dissection of Post Chemotherapy Residual Masses for Metastatic Germ Cell Testicular Cancer

Luz M[1], Aldousari S[1], Brimo F[2], Kotb A[1], Tanguay S[1], Kassouf W[1], Aprikian A[1]
[1]Urology; [2]Pathology, McGill University, Montréal, QC

Introduction and Objective: Testicular cancer has become the model for a curable neoplasm. Nearly 80% of the patients can be cured by surgery removing the residual masses after the cisplatin-based chemotherapy. However, there is continued controversy regarding the optimal treatment of patients with nodal metastases. While some investigators have reported relapse rates as low as 6.3% in patients with low-volume nodal disease managed expectantly, others have reported rates as high as 45%.

Methods: Between 1994 and 2008, three surgeons had operated 73 cases of post chemotherapy retroperitoneal lymph node dissection (PC-RPLND) for metastatic residual germ cell testicular cancer. Our purpose was to analyze the indications, clinical features, patterns of recurrence, surgical complications, final pathology diagnosis in residual masses and clinical predictors of complications and viable cancer after chemotherapy. We have included patients with nonseminomatous histology, clinical stage II or III and residual masses post-chemotherapy treatment. To an objective analysis of surgical complications, we have used the Clavien classification ranging from I to V.

Results: The majority of our cases were between 20 and 40 years old. Lymphovascular invasion was present in 32% of cases and 12% of cases had associated carcinoma in situ. Mixed germ cell tumour was the histology of orchiectomy in 59% of patients. The mean size of retroperitoneal metastasis before and after chemotherapy was 6.3 and 4.0 cm, respectively ($p < 0.001$). All patients received cisplatin-based chemotherapy. Ninety-two percent of patients were submitted to a complete bilateral dissection. Nerve-sparing procedure was not possible in 43% of cases. The complication rate was 38% but only 3 patients (4%) had grade IV complications and no one died. After review, 22% of patients had viable non-teratoma cancer on retroperitoneum and 41% had teratoma. Size of residual disease and the presence of fibrosis were predictors of surgical complications and non nerve-sparing procedures ($p < 0.05$). The mean follow-up was 47 months. After RPLND, we had only 2% of recurrence in retroperitoneum site and 8% of overall recurrence rate. The 5-year overall survival rate was 91%.

Conclusions: the PC-RPLND for testicular cancer is a relatively safe procedure. It is less likely to perform a nerve sparing surgery post chemotherapy than in primary procedures. There are still a large number of patients with viable cancer after chemotherapy, justifying surgical treatment of residual masses. The residual mass size and the presence of fibrosis are predictors to surgical complications and non nerve-sparing procedures.