Development of a risk calculator of recurrence in inguinal lymph node metastatic (ILNM) patients with surgically resected penile squamous cell carcinoma (PSCC).

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Background: ILNM PSCC patients (pts) have heterogeneous outcomes. We aimed to identify risk factors of early recurrence in order to optimize the selection of pts for adjuvant (adj) therapies (tx).

Methods: In a multicenter database of 924 pts who underwent ILN dissection, we identified 311 ILNM pts. Pts treated with neoadj chemo (CT) and/or radiotherapy (RT) were excluded. Multivariable Cox regression analyses (MVA) tested for predictors of recurrence, after adjusting for adj tx, age, type of surgery of the primary and smoking status. As primary endpoint, a risk calculator predicting early (24-month) risk of recurrence was developed. As secondary endpoint, the overall survival (OS) benefit of adj tx was examined according to the risk calculator-derived tertiles using Kaplan-Meier analysis.

Results: Overall, 159 pts (51.1%) had pN1-2 and 203 (65.3%) pT2-4 disease. Overall, 195 (62.7%) and 78 (25.1%) received partial or total penectomy, whereas 6 (1.9%) local excision and 32 (10.3%) other procedures. Median number of removed and positive ILN were 15 (IQR 9-21) and 2 (IQR 1-3). Pelvic LND was performed in 154 (49.5%) pts, and 39% of them had pelvic LNM. In MVA, ILN ratio (HR: 1.01, p= 0.04), pN3 (HR: 2.53, p=0.002) and positive proximal margin of the primary (HR: 2.13, p=0.02) were significantly associated with recurrence. The c-index of our 3-variable risk calculator was 68%, with a net benefit higher that treat-all option from 20% to 90% threshold-probabilities. Within the cohort of adj CT and/or RT (N=127) pts, intermediate-high tertile had similar median OS (NR vs 107m) compared to pts in the low tertile (p=0.1). Conversely, intermediate-high tertile pts who received observation alone had shorter OS (NR vs 40m) compared to the same pts in the lower tertile (p<0.001). Similar results were obtained for CT and RT separately analyzed.

Conclusions: We developed and internally validated a risk calculator to predict early recurrence in ILNM surgically-resected PSCC pts. According to our risk-calculator, pts with intermediate/higher risk of early recurrence may benefit from adj tx. Our risk calculator can be used for counseling and enrolment in ongoing studies. Research Sponsor: Fondazione IRCCS Istituto Nazionale dei Tumori.
Regression tree analysis to identify the best candidates for neoadjuvant chemotherapy (NAC) in patients with clinically lymph node-positive penile squamous cell carcinoma (PSCC).

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Background: PSCC patients (pts) with palpable inguinal lymph node (ILN) disease have a poor overall survival (OS). For them, use of neoadjuvant chemotherapy (NAC) is recommended in guidelines, but limited data are available to inform pt selection. We aim to identify predictors of poor OS in clinically ILN-positive (ILN+) pts to define the optimal candidates for NAC.

Methods: Within an international, multicenter database of 924 PSCC pts, we identified 334 ILN+ pts with available data. ILN involvement was defined either with the presence of palpable ILN disease or based on preoperative CT-scan. FDG-PET/CT-scan was performed based on clinical judgment of the treating physician. Univariable and multivariable analyses (MVA) assessed predictors of overall mortality (OM). A regression-tree method for censored data was used to generate a risk stratification tool for prediction of 24m OM after diagnosis of ILN+ PSCC. Kaplan-Meier method was used to define the OS benefit related to the use of NAC according to the regression-tree stratified sub-groups.

Results: Median age at diagnosis was 58yrs, and 105 (31.4%) had ECOG 1. Of all, 120 (35.9%), 152 (45.5%), and 62 (18.6%) harbored cN1, cN2, and cN3 disease. Additionally, 152 (45.5%) and 117 (35%) had monolateral vs bilateral clinical ILN involvement. FDG-PET/CT was adopted in 42 (12.2%) pts, and 16 (4.8%) had pelvic LN uptake. Median OS was 107m, with 24m OS = 66%. At MVA, cN2 (HR: 2.28, p=0.006), cN3 (HR: 2.15, p=0.02), PET/CT scan-detected pelvic and ILN involvement (HR: 2.57, p=0.007) were independently associated with higher OM, whether bilateral clinical ILN+ was only univariably significant (HR: 1.56, p=0.02). At regression-tree analysis (AUC 70%), pts with cN3 and cN2 with PET/CT-detected pelvic and ILN involvement had the higher risk of 24m OM (>54%). NAC was associated with improved 24m OS rates (54 vs. 33%) only in this pt subgroup (p=0.002).

Conclusions: NAC improves OS in pts with cN3 or cN2 and pelvic FDG-PET/CT scan-detected disease. Our regression-tree may serve to screen ILN+ pts, to identify the optimal NAC candidates before radical treatments. Research Sponsor: Fondazione IRCCS Istituto Nazionale dei Tumori.
Locally advanced scrotal squamous cell carcinoma: Does chemotherapy affect survival?

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Background: Scrotal squamous cell carcinoma (SSCC) though rare, represents the most common forms of scrotal malignancies. 40-50% of patients present with locally advanced disease, and treatment is extrapolated from penile cancer. Here we report practice trend and overall survival (OS) outcome of locally advanced SSCC patients who underwent surgery with or without chemotherapy. Methods: We performed a retrospective analysis using the national cancer center database (NCDB) (2004-2016). All patients aged ≥ 18 years with locally advanced SSCC who underwent surgery with or without chemotherapy were included. OS is estimated with Kaplan-Meier curves, with an adjusted hazard ratio (aHR) calculated from Cox proportional hazard regression model. Results: 638 patients were identified with SSCC without distant metastasis. Of these 49 underwent surgery with perioperative chemotherapy and 589 underwent surgery alone. At the median follow up of 39.9 months (mo), median OS is 41.4 mo and 145.7 mo for surgery with chemotherapy group versus surgery alone respectively (P-value, 0.0001), with aHR for OS 1.673 (95%CI 0.966-2.897). Patients age ≥ 65 (HR= 3.081, 95% CI=2.107- 4.505, p<0.001), Charlson-Deyo Score (CCI) 2 or more (HR=3.441, 95% CI=2.140-.533, p<0.0001), moderately-poorly differentiated carcinoma (HR=1.713, 95% CI=1.038- 2.829, p=0.0352), and higher clinical nodal status N1,N2 and N3 (HR=2.543, 95% CI=1.42-4.548, p=0.0016) were observed to do worse with surgery and chemotherapy. Patients with CCI of 2 or more, moderate to poorly differentiated carcinoma, higher clinical T and N stage (T2- T4 and N1-N3 respectively) were observed more likely to receive surgery and chemotherapy. Conclusions: No OS improvement was seen in locally advanced SSCC with addition of chemotherapy to surgery. Patients who received chemotherapy along with surgery are observed to have higher risk of mortality vs surgery alone. The study is limited by retrospective nature, lack of randomization, patient selection bias, patient’s choice of therapy, small sample size, and missing information. Research Sponsor: None.
Tumor immune microenvironment alterations in penile squamous cell carcinoma using multiplex immunofluorescence and image analysis approaches.

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Background: Penile Squamous Cell Carcinoma (PSCC) is a rare but often fatal disease. In this study, we characterize the poorly understood immune microenvironment using multiplex immunofluorescence (mIF) and image analysis approaches in 54 patients with PSCC. Methods: Representative blocks of 54 PSCC patients were stained for six immune markers: CD3, CD8, CD68, PD-1, PD-L1, Pancytokeratin and DAPI. Two experienced pathologists using an image analysis system (InForm 2.2.4) divided them into the tumor and stroma compartment and assessed the different densities of cell phenotypes using R studio with results expressed as cells/mm2. The statistical correlations were performed using Fisher's exact test, Pearson and Log-rank test for Kaplan Meyer plots. Results: 54 patients with confirmed diagnosis of PSCC had a median age of 62 (IQR 50-70). All samples were from the primary penile tumor with the majority of cases being HPV(−) (62%). We observed significantly higher stromal cytotoxic T cells in HPV(+) cases compared to HPV(−) (P=0.04). Using the mean macrophage count as cutoff for positivity, high densities of total tumor macrophages CD68+ were associated with significantly improved estimated median cancer specific survival (CSS) (NA, P=0.04), median overall survival (OS) (68mos vs NA P=0.02) and lower risk of regional recurrence (P=0.04). On the other hand, the high densities of stromal cytotoxic T cells antigen-experienced (CD3+CD8+PD-1+), was associated with significantly worse median OS (27 vs 102mos P=0.05) and median disease free survival (DFS) (18.2mos vs NA P= 0.07). Also, high densities of stromal T cells antigen-experienced (CD3+PD-L1+), were associated with significantly better CSS (NA, P=0.06) and better median OS (142.1 vs 68.8mos P=0.14). Conclusions: Using novel multiplex image analysis to assess the immune microenvironment in primary PSCC, we showed that high macrophage levels were associated with lower risk of recurrence and improved survival outcomes. Moreover, a low level of exhausted stromal cytotoxic PD-1+ T cells was associated with improved PSCC survival. Further characterization of T cell subsets in relation to tumor HPV status is ongoing. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.
p16INK4a expression and survival outcomes in patients with penile squamous cell carcinoma: The M.D. Anderson Cancer Center Experience.

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Background: Penile Squamous Cell Carcinoma (PSCC) is associated with high risk human papillomavirus (HR-HPV) in about 50% of cases. The immunohistochemical test for p16INK4a (p16) is highly correlated with HR-HPV expression and used as prognostic marker for squamous cell carcinomas in various sites. The prognostic role of this marker in PSCC remains unclear. We studied whether the expression of HPV or p16INK4a is associated with survival in a large PSCC cohort.

Methods: We conducted a single institution analysis of PSCC patients who received treatment between 1991-2017. Patients with a confirmed diagnosis of PSCC and available tissue were tested for HR-HPV status using the Cobas PCR assay. Histological subtype, tumor grade, LVI and p16 staining patterns were confirmed by an experienced pathologist. Patient characteristics were summarized using descriptive statistics of clinico-pathologic variables. Kaplan-Meier was used to estimate median overall survival (OS) and cancer specific survival (CSS). Log rank test, univariate and multivariate Cox models were applied to identify the prognostic factors for survival. Results: We identified 147 patients with PSCC, with available tissue for testing. The median follow-up was 5.2 years (95% CI; 4.48, 6.68y). Patients with p16(+) tumors showed a significantly longer median OS and CSS in comparison to the p16(-) group (p=0.038 and p=0.012), with respective 5 year OS probability of 73% (95% CI; 0.74, 0.98) in comparison to 56% (95% CI; 0.46, 0.67) and 5 year CSS probability of 89% (95% CI; 0.7, 1) in comparison to 64% (95% CI; 0.54, 0.75). In contrast, HPV status by PCR did not predict survival outcomes, with 5 year CSS probability for HPV(+) of 75% (95% CI; 0.61, 0.91) compared to 65% (95% CI; 0.55, 0.78) for HPV(-) patients. Multivariable analysis to evaluate the association with CSS, showed that p16(+) along with lymph node status was associated with lower risk of death (HR=0.28, 95%CI; 0.09-0.8, p=0.002), and OS (HR=0.49, 95% CI; 0.19-1.24, p=0.13) after adjusting for the covariates. Conclusions: Tumor p16 status was an independent prognostic factor for CSS in our PSCC cohort providing unique information above that of lymph node status alone. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.
Genomic landscape of circulating tumor (ct)-DNA alterations in patients with penile cancer.

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Background: Penile cancer is a rare disease associated with HPV infection and harbors recurrent somatic genomic alterations in the ERBB (HER)-family, CDKN2A, TP53, NOTCH1 and PIK3CA. ctDNA assay allows the noninvasive genomic profiling of malignancies and may assist with understanding molecular evolution. To our knowledge, the genomic alterations observed in ctDNA for penile cancer have not been described before. We report ctDNA profiling of patients with advanced penile cancer.

Methods: Sixteen pts with metastatic penile cancer from multiple institutions in the United States that underwent ctDNA analysis using the Guardant360 platform were eligible. Three patients had at least one serial ctDNA sample. De-identified demographic data were collected. Guardant 360 is CLIA-certified ctDNA panel that assesses single nucleotide variants and copy number alterations in 68 to 73 genes for potentially actionable genomic alterations. Variants seen at least 3 times in the Catalogue of Somatic Mutations in Cancer (COSMIC) database or reported in OncoKB were considered pathogenic.

Results: The median age was 64 years (range 40-77). 4 pts (25%) were documented to be post platinum-based chemotherapy. Among the entire cohort, 51 ctDNA alterations were detected (median=2, range 0-6) in 15/16 patients (94%) across 21 genes (table). Of the 51 alterations, 24 (47%) were actionable and had approved targeted therapies in other cancers. Alterations were most frequently detected in TP53 (9/16, 56%), CDKN2A (5/16, 31%), and TERT promoter (5/16, 31%) (table). In 3 patients with serial samples, 9 novel pathogenic alterations were detected in the second sample including ATM, CDKN2A, ARIDIA, CCND1, CDK6, EGFR, PDGFRA, PIK3CA, and SMAD4.

Conclusions: ctDNA alterations in patients with advanced penile cancer were frequently detected and appeared similar to previously described tumor tissue analyses. New alterations found on serial ctDNA assays shed light on patterns of tumor evolution and may inform drug development for this challenging orphan malignancy. Research Sponsor: None.

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A multicenter phase II study of avelumab in patients with locally advanced or metastatic penile cancer (PC) who are unfit for, or have progressed on or after platinum-based chemotherapy: (ALPACA).

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Background: Squamous cell carcinoma of the penis is a rare and highly aggressive malignancy. Combination platinum-based chemotherapy is the standard of care in the metastatic setting. However, it is poorly tolerated and outcomes are dismal, underscoring an urgent unmet need for novel strategies. Since, penile cancers are often HPV-mediated and frequently overexpress PDL1, there is strong rationale to test the PDL1 inhibitor Avelumab, which is a well-tolerated drug in the setting of metastatic PC. Methods: This is a multicenter, single arm, phase 2 study of Avelumab (10mg/kg IV every 2 weeks) in patients with locally advanced or metastatic PC unfit for or progressed on platinum-based chemotherapy. A Simon’s two-stage design will be used where 9 patients will be enrolled in stage 1. If there is at least 1 response defined by iRECIST (complete response [iCR], partial response [iPR], or stable disease [iSD]) the study will proceed to stage 2, where an additional 15 patients will be enrolled. The primary objective is to demonstrate the anti-tumor activity of avelumab by objective response rate (ORR) according to (iRECIST). Secondary endpoints include: PFS, OS in patients determined to have PD-L1 positive tumors (including infiltrating immune cells) by the GMP verified Dako PD-L1 IHC 22C3 pharmDx test with thresholds of <1%, 1-49%, and ≥ 50% to define PD-L1 positivity, and in all enrolled patients. Secondary objectives also include assessing pathologic complete response rate (pCR) for patients undergoing surgery in the treatment time course, evaluation of safety and immunogenicity profile of Avelumab. The study is now open and actively accruing with further centres opening imminently. Funding Source: Pfizer. Clinical trial information: 03391479. Research Sponsor: Pfizer.