1438 POSTER

Claudin-4/E-cadherin Index to Predict Prognosis in Breast Cancer

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Background: Different expression of claudins and E-cadherin was described in pathologic processes including cancer. Elevated expression of claudin-4 was found to correlate with poor prognostic features in adenocarcinomas of different origin.
Patients and Methods: Expression of claudin-1, -3, -4, -5, -7, -8, -10, -15, -18 and E-cadherin at mRNA level was evaluated for correlation with survival in datasets containing expression measurements of 1809 breast cancer patients. Another training set of breast cancer tissues of 197 patients were evaluated with tissue microarray technique and immunohistochemical method for claudin-1, -2, -3, -4, -5, -7 and E-cadherin protein expression. 387 independent samples were used to evaluate the performance of the claudin-4/E-cadherin (CC) index.
Results: Expression of certain claudins bears prognostic information in itself. The meta-gene of claudin-3, -4, -7 and E-cadherin has shown the most powerful predictive power for survival analyses in silico. An immunohistochemical protein profile consisting of claudin-2, -4 and E-cadherin was able to predict outcome in the most effective manner in the tissue based training set. Combining the overlapping members of the distinct methods resulted in the CC index, which was able to accurately predict relapse-free survival in the validation cohort ($p = 0.029$) in a more efficient way than its components (claudin-4, E-cadherin).
Conclusion: The defined claudin-cadherin index provides additional prognostic information besides the routinely utilized diagnostic approaches and factors.
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Treatment-related Changes in Systemic Inflammatory Status, Measured by Neutrophil-to-lymphocyte Ratio, is Predictive of Outcome in Metastatic Colorectal Cancer Patients

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Background: Systemic and local tumour-associated inflammatory status plays a key role in tumour growth and progression in colorectal cancer. Experimental evidences suggest that different myeloid derived cells associated with inflammation, such as neutrophils and macrophages, activate different cytokine/chemokine networks which in turn are able to promote tumour-escape from host's adaptive immunity, tumour growth and neo-angiogenesis. In this contest, we investigated, in metastatic colorectal cancer (mCRC) patients, the prognostic role of several clinical, laboratory and inflammatory-related parameters.
Material and Methods: In this retrospective multicentric study, including 247 mCRC patients who had received at least a line of chemo/bio-chemotherapy, we evaluated possible correlations among overall survival (OS), progression-free survival (PFS) and multiple parameters including sex, age, performance status, grading, serum CEA, CA19.9, LDH and CRP concentrations, ESR, lymphocyte, neutrophil and monocyte counts and neutrophil-to-lymphocyte ratio (NLR) at baseline and after six chemo/bio-chemotherapy courses. Kaplan Meier curves, Log-Rank test and Cox's regression analysis were used to perform statistical analysis.
Results: Median PFS and OS in the whole group were 9.0 (95% CI 7.794–10.206) months and 22.3 (95% CI 19.932–24.668) months respectively. Multivariate analysis revealed a significant prognostic value only for performance status (HR: 1.604; $p = 0.045$), serum CEA concentration (HR: 2.284; $p = 0.001$) and NLR (HR: 1.767; $p = 0.004$). Furthermore, in our statistical analysis the reduction of NLR under 3 during the treatment, predicted a significantly longer time to event when compared with those who did not show such reduction [21.5 (95% CI 19.171–23.763) vs 11.0 (95% CI 6.063–15.937) months; $p = 0.004$; HR: 2.009 vs 4.262, $p < 0.001$]. In the whole patient population, we were not able to find any correlation among PFS and treatment-related changes in NLR; however, those patients who presented NLR >3 at baseline, showed the worse treatment-related outcome. These events were independent by the kind of treatment regimen adopted for these patients.
Conclusions: These results suggest that possible treatment-related changes in systemic inflammatory status, indirectly measured throughout NLR, may affect prognosis of mCRC patients.

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Comparison of Prognostic Impact of Circulating Tumour Cells, Tumour Markers, and Radiological Tumour Assessment in Patients With Small-cell Lung Cancer

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Background: Little is known about the prognostic impact of circulating tumour cells (CTCs), tumour markers, and radiological tumour assessment in patients with small-cell lung cancer (SCLC).
Materials and Methods: In total, 51 consecutive patients with newly diagnosed SCLC, starting chemotherapy or chemoradiotherapy, were prospectively enrolled. Blood samples were drawn at baseline and after 1st-line chemotherapy. CTCs were isolated using the CellSearch System (Veridex LLC). Tumour response was assessed by RECIST criteria.
Results: Two or more baseline-CTCs were detected in 35 patients (68.6%). Area under the receiver operating curve (AUROC) for predicting 1-year survival was 0.8 (0.6−0.9) for baseline-CTC, 0.7 (0.5−0.8) for NSE, 0.5 (0.3−0.7) for Pro-GRP, and 0.7 (0.5−0.8) for radiological staging ($P = 0.018$). The Cox proportional-hazards ratios (HR) were 10.0 (3.3–37.2), 2.9 (0.9−7.9), 1.7 (0.4−5.4), and 3.6 (1.4–10.5), respectively. At post-treatment period, AUROC for predicting 6-months post-treatment survival was 0.7 (0.4−0.9) for post-treatment CTC, 0.8 (0.6−0.9) for NSE, 0.7 (0.4−0.9) for ProGRP, and 0.8 (0.6−0.9) for radiological tumour response ($P = 0.580$). HRs were 3.2 (1.0−8.9), 7.3 (2.5–26.4), 3.4 (1.2−9.8), and 7.0 (2.4–25.2), respectively.
Conclusions: CTC-count is sensitive and specific prognostic factor especially for the baseline measurement when compared with tumour markers and radiological tumour assessment.

1441 POSTER

Prognostic Factors and Patterns of Recurrence After Resection of Primary Desmoids − a Single-institution Experience Over 10 Years

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Background: Local control of desmoids remains a significant problem, with the average recurrence rate of 24−77% no matter what therapeutic modality used. The aim of this study was to analize the prognostic factors for recurrence after macroscopically radical resection of desmoid tumours.
Material and Methods: From 2000 to 2010 40 patients (12 males, 28 females; mean age 37.6 years, range 16−69 years) underwent macroscopically radical removal of a primary desmoid tumour at the European Institute of Oncology, Milan. Tumour arose from the trunk wall in 27 cases (68%), from lower extremity in 5 (12%), from head and neck in 4 (10%), and was intrabdominal in another 4 (10%). Kaplan-Maier curves were employed to calculate actuarial disease-free survival (DFS) with comparison between groups using the log-rank test.
Results: In 32 patients pathological examination revealed a R0 situation and R1 in the remaining 8 (20%). Six patients developed tumour recurrence after a median 48 months follow-up period but no deaths caused by disease progression were registered. In 2 cases recurrence was at the surgical site and in 4 patients within the same anatomical region but not immediately near the surgical site. Five-years DFS was 76% for the whole group of patients. At univariate analysis only R0 vs R1 surgery (89% vs 45% 5-years DFS respectively; $p = 0.025$) and maximum tumour diameter $\geqslant$10 cm vs <10 cm (85% vs 33% 5-years DFS respectively; $p = 0.025$) were significantly correlated to DFS. According to desmoid location 5-years DFS rates were 81% for trunk vs 60% lower extremity vs 100% head and neck vs 66% intrabdominal ($p = 0.52$).

Conclusions: R0 surgery still represent the milestone of treatment for primary desmoids no matter where the tumour is localized. This is particularly important for huge tumours, where an higher incidence of recurrence is expected.

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Mina53, a Target Gene of C-Myc, is a Favorable Prognostic Marker in Early Stage Lung Cancer

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Background: Mina53, a novel target gene of c-Myc, is overexpressed in various malignancies. Overexpression of Mina53 has been associated with poor prognosis in esophageal cancer, renal cell carcinoma, and neuroblastoma. We previously demonstrated that Mina53 is overexpressed in lung cancer patients from the early clinical stages. In addition, the enforced expression of Mina53 in NIH/3T3 cells, a mouse fibroblast cell line, induces cell transformation, and Mina53 transfected NIH/3T3 clones produce tumours in nude mice. In this study, we examined the association between disease prognosis and Mina53 expression in lung cancer patients.
Materials and Methods: Mina53 expression was determined by immunohistochemistry and western blotting using lung cancer cell lines and lung cancer tissues. The survival rate was calculated according to the Kaplan–Meier method and the logrank test was used for assessing differences. Biological effects of Mina53 were evaluated by cell proliferation assay, cell cycle analysis, apoptosis assay, and *in vitro* cell invasion assay using Mina53 transfected A549 and H226B cells.
Results: Patients with negative staining for Mina53 had significantly shorter survival than patients with positive staining for Mina53, especially in stage I or with squamous cell carcinoma. We hypothesized that Mina53 exerts different effects according to cancer cell type, inhibiting tumour progression in lung cancer cells. Growth of A549 transfected with pCAGGS/*mina53* (expression plasmid) was inhibited. After transfection of pCAGGS/*mina53* into A549, pre-G0/G1 phase cells increased in a time-dependent manner. In addition, early apoptotic cells were more frequently observed among cells transfected with pCAGGS/*mina53* than those with pCAGGS. Because cell growth inhibition associated with apoptosis was not observed in H226B, we examined the possibility of an effect of Mina53 on cancer cell invasion. The number of invading cells transfected with pCAGGS/*mina53* significantly decreased compared with those with pCAGGS, whereas transfection with *mina53* shRNA increased the number of invading cells.
Conclusions: Mina53 could be a possible favorable prognostic marker, especially in squamous cell carcinoma. Considering the results of biological effects of Mina53, is may play a role on inhibition of cancer progression.

1443 POSTER

High Blood Neutrophil-to-lymphocyte Ratio as an Indicator of Poor Prognosis in Advanced Non Small Cell Lung Cancer

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Background: The neutrophil-to-lymphocyte ratio (NLR) is an index of inflammatory status and in malignant tumours an elevated NLR has been considered as a negative prognostic factor. The aim of this study is to evaluate the clinical significance of the NLR in patients with advanced non-small cell lung cancer (NSCLC) treated with chemotherapy.
Methods: One hundred and seventy one stage IV NSCLC patients diagnosed in our institution between April 2004 and March 2009 were retrospectively reviewed. NRL $\geqslant$5 was considered elevated. Baseline factors analyzed were histology, gender and NLR. Overall survival (OS) and progression-free survival (PFS) were calculated by the Kaplan–Meier method.
Results: Baseline patients characteristics: median age 63 (30−82 years), males 83.6%; adenocarcinoma 40%, large cell carcinoma 21.1%, squamous carcinoma 18.1% and undifferentiated carcinoma 3.5%. All patients were treated with chemotherapy and 36.3% had partial response. NLR was elevated in 60 (35.1%) patients and no differences were detected according clinical characteristics (histology, sex or tumour size). After a median follow-up of 9.1 months, 164 patients relapsed and 159 patients had died. PFS and OS in patients with normal and elevated NLR were 5.6 vs 3.2 months ($p = 0.09$) and 9.1 vs 5.6 months ($p = 0.032$) respectively. Thirty five (60.3%) patients with an elevated basal NLR, normalized the ratio after two cycles of chemotherapy. The OS in patients with persistently abnormal NLR after chemotherapy was of 3.9 vs 8.8 months in patients with normalized NLR ($p = 0.042$). In the multivariate analysis histology (undifferentiated carcinoma) and elevated NLR were independent predictors of survival ($p < 0.01$).
Conclusion: In our analysis, elevated NLR is correlated with worse survival in advanced non-small cell lung cancer These results have highlighted NLR as a potentially useful prognostic marker due to easy accessibility and reproducibility.

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Evaluation of Hand–foot Syndrome (HFS) as a Potential Biomarker of Sunitinib (SU) Efficacy in Patients (pts) With Metastatic Renal Cell Carcinoma (mRCC) and Gastrointestinal Stromal Tumour (GIST)

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Background: Common side effects of tyrosine kinase inhibitors (TKIs) such as SU include HFS and related skin toxicities. SU is a multitargeted inhibitor of VEGFR, PDGFR and KIT, and is standard of care for the treatment of advanced RCC and imatinib-resistant/intolerant GIST. In this retrospective analysis, correlations between SU-associated HFS and efficacy endpoints were investigated in mRCC and GIST pts from 5 and 4 completed clinical trials, respectively (NCT00054886, NCT00077974, NCT00137423, NCT00083889, NCT00338884, NCT00075218, NCT00137449, NCT00372567; RTKC-0511–013).
Methods: Analyses included data from 1,186 pts with mRCC (n = 770) or GIST (n = 416) who received single-agent SU at 25, 50, or 75 mg/d on an intermittent schedule (4 weeks [wk] on/2 wk off, 2 wk on/2 wk off, or 2 wk on/1 wk off: n = 869; 73%) or at 37.5 mg continuous daily dosing (n = 317; 27%). Median progression-free survival (PFS) and overall survival (OS) were estimated by Kaplan–Meier methods and compared between pts with vs. without HFS by log-rank test. ORR was compared by Pearson's chi-square test. Tumour response was assessed by investigators and adverse events were recorded regularly. Multivariate, time-dependent covariate, and landmark analyses were performed.
Results: Of 1,186 pts, 260 (22%) developed any-grade HFS, compared with 926 (78%) who did not. Pts with mRCC who developed HFS had significantly better ORR (66.5% vs. 31.8%), PFS (14.3 vs. 8.3 mo), and OS (38.3 vs. 18.9 mo) than pts who did not ($P < 0.0001$). Pts with GIST who developed HFS also had significantly better ORR (22.2% vs. 10.7%), PFS (11.0 vs. 5.5 mo), and OS (35.7 vs. 16.6 mo) than pts who did not ($P < 0.01$). SU-associated HFS remained a significant predictor of both PFS and OS in a multivariate analysis (and of OS by time-dependent covariate analysis) in both mRCC and GIST pts. In 6- and 12-wk landmark analyses, pts with mRCC but not GIST who developed HFS had significantly longer OS, with a trend toward longer PFS, than pts who did not.
Conclusions: SU-associated HFS was associated with improved PFS and OS in both mRCC and GIST pts, although the landmark analysis suggests that HFS may not be a reliable biomarker of SU efficacy at early time points.

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HOXB9, a Gene Promoting Tumour Angiogenesis and Proliferation, is a Novel Prognostic Biomarker in Human Breast Cancer

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Background: Recently, it was reported that HOXB9, a member of homeobox genes, expression promoted tumour neovascularization and metastasis in vitro and in vivo assay. These findings imply that overexpression of HOXB9 contributes to tumour progression through activation of signaling pathways that alter both tumour-specific cell fates and tumour-stromal microenvironment, leading to increased invasion and metastasis. (Hayashida et al., PNAS 2010) In this study, we evaluated the correlation between HOXB9 expression, clinical outcomes, and the clinicopathological variables in breast cancer patients, and the contribution of HOXB9 expression to tumour cell proliferation and angiogenesis.
Materials and Methods: A consecutive series of 141 patients with invasive ductal carcinoma who underwent surgical treatment from January 2004 to January 2005 were examined. HOXB9 protein expression was analyzed immunohistochemically using the anti-human HOXB9 polyclonal antibody. Immunostaining of Ki-67, CD31, and CD34 were also performed to evaluate the association between tumour proliferation, and angiogenesis and HOXB9 expression.
Results: Of 141 tumour specimens immunostained for HOXB9, 69 specimens (48.9%) were positive staining. Statistical analysis revealed