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## Prognostic significance of telomerase activity in oral squamous cell carcinoma

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**Background:** Squamous cell carcinoma of oral cavity is one of the ten most frequent cancers in the world. Recently, research had indicated that telomerase activity (TA) may play a role in carcinogenesis. We examined the expression and clinical association of TA with oral squamous cell carcinoma in an area where betel chewing is prevalent, to provide a theoretical foundation for further clinical applications of molecular prognosis.

**Methods:** A PCR-based EIA method was used to measure TA in 148 paired (normal and cancerous) tissues from the oral cavity cancer patients. Clinical information was available for all patients. Kaplan-Meier method and Cox logistic regression model were used for prognostic analysis.

**Results:** TA was detected of low, medium and high level in 36.4%, 51.6% and 12% in cancerous tissues, and 95.9%, 4.1%, 0% in normal mucosa samples, respectively.

Telomerase was marginal associated with T stage (P = 0.053), N stage (P = 0.085), and strongly associated with lymph node extra-capsular spread (P = 0.018), and poor survival (P = 0.001). On multi-variant analysis, only overall stage (P = 0.024) and telomerase (P = 0.046) were significantly associated with overall survival.

**Conclusion:** Telomerase activity and N stage are independent prognostic factors for survival of oral cancer. Telomerase may be a potential molecular target for clinical use in prognostication and therapy of oral cancer.

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## Cysteine proteinase inhibitor cystatin C (CC) in operable squamous cell carcinoma of the head and neck (SCCHN): expression pattern and relation to prognosis

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**Background:** To determine the role of cysteine proteinase inhibitor CC in the invasive behaviour of SCCHN and as a prognosticator in this particular type of cancer. Patients and methods: CC concentration was measured in cytosols of primary tumors and corresponding normal mucosa from 82 patients with operable SCCHN. Data available for each patient were age and sex, tumor site, stage (pT-, pN-, overall UICC TNM-stage), histopathological grade and extracapsular spread. CC concentration was determined using quantitative immunosorbent assay (ELISA, KRKA d.d., Novo mesto, Slovenia) and expressed in ng/mg tissue proteins.

**Results:** The median CC concentration was lower in tumors than in their normal counterparts (14.9 vs. 16.3; P=0.031). Considering normal mucosa measurements, the CC concentration was influenced by the site of sampling, being lower in non-laryngeal tissue samples (oral cavity, oro-, hypophyrynx) compared to those from the larynx (11.5 vs. 24.0; P=0.004). The tumor CC concentration correlated inversely with pN-stage (pN0 vs. pN+: 18.4 vs. 14.2; P=0.047), whereas a trend of lower CC concentrations was observed in the group with extracapsular tumor extension compared to that with no extracapsular spread (14.0 vs. 17.4; P=0.069). On univariate analysis, pN- and overall UICC TNM-stage, and extracapsular spread significantly influenced the disease-free survival (DFS) and disease-specific survival (DSS). When using a median CC concentration to divide the patient into low- and high-CC groups no difference in survival was observed. After optimization, using isotonic regression analysis, the CC cutoff concentration was the 68th percentile in the group. Five-year DFS and DSS rates were higher in a low-CC group giving in both cases the P-value of 0.013. On multivariate analysis, pN-stage was the most powerful predictor of DFS (HR 2.78, P=0,040) and DSS (HR 4.36, P=0.011), followed by CC concentration (DFS: HR 0.22, P=0.043; DSS: HR 0.25, P=0.061).

**Conclusions:** Our data indicate: 1. CC is implicated in the invasive behavior of SCCHN; 2. variations in regulation of cancer-related poteolytic pathways - the inherent characteristic of individual subsites inside the upper aerodigestive tract; 3. protective role of high CC concentrations as measured in tumor cytosols - the concept that has been proposed for other cysteine proteinase inhibitors by the survival results in breast and lung carcinoma as well as SCCHN.

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## Hemoglobin as a factor influencing the outcome in inoperable oropharyngeal carcinoma treated by concomitant radiochemotherapy

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**Background:** To analyze the prognostic significance of hemoglobin (Hb) concentration of patients with inoperable carcinoma of the oropharynx.

**Patients and Methods:** Seventy patients with inoperable carcinoma of the oropharynx were prospectively treated by concomitant regimen of conventional radiotherapy and chemotherapy with Mitomycin C and Bleomycin. The prognostic value of Hb concentration before and at the end of the therapy (Hb-S, Hb-E), the difference between both (Hb), and the average Hb concentration (Hb-Av) were analyzed.

**Results:** The median Hb concentration was falling from 139 to 122 g/L ($P<0.0001$) during the first three weeks of the therapy; after that, it reached a plateau. The median follow-up of the patients alive was 5.7 years (range 4-10.5 years). Longer disease-free survival (DFS) and disease-specific survival (DSS) correlated with higher values of Hb-S ($P=0.0005$, $P=0.008$) and Hb-E ($P=0.02$, $P=0.02$), while the Hb-Av was predictive for DFS only ($P=0.004$). The most significant difference between low- and high-Hb groups was calculated at cut-off concentrations of 122 (Hb-S), 116 (Hb-E), and 120 (Hb-Av) g/L. Only Hb-S was tested in multivariate model where its independent value for predicting both, DFS ($P=0.002$; RR 3.6) and DSS ($P=0.01$; RR 2.9), was confirmed.

**Conclusions:** In our patients, Hb-S was proved to be an independent prognostic factor in predicting DFS and DSS. We believe that the concentration of Hb=120 g/L should be maintained during radiotherapy course.

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## Prognostic value of 99Tc-methoxyisobutilisonitrile (MIBI), Ki-67 and p53 in head and neck carcinoma treated with chemo-radiotherapy (CT-RT). Preliminary results.

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**Background:** The prognostic value of MIBI was studied in various tumours with non-conclusive results. Ki-67 and p53 showed prognostic relevance in a number of tumours including head and neck. This study correlates the results of 99Tc-MIBI-SPECT with Ki-67 and p53 to assess the prognostic value after CT-RT for head and neck carcinoma.

**Material and Methods:** We enrolled 27 patients (pts), 19 M and 8 F, stage II-IV head and neck carcinoma, aged 17-79 (median 56), PS 80-100. Tumour sites were: 9 oropharynx, 2 oral cavity, 4 hypopharynx, and 12 nasopharynx. Treatment included 3 cycles of carboplatin 75 mg/m2 and 5-fluorouracil 1000 mg/m2, days 1-4 and concomitant RT to total dose of 70 Gy, 2 Gy/fx. SPECT with 99Tc-MIBI was performed prior and 45-60 days after CT-RT. SPECT images were obtained 10' after administration of 740 MBq of 99Tc-MIBI with double-head gamma camera with high resolution and parallel hole collimator. Positive MIBI was scored 0-3. Ki-67 and p53 were assessed by immunohistochemical staining on paraffin-embedded material, and percentage of positive cells was evaluated.

**Results:** Pre-treatment MIBI was highly positive in 12/27 pts (score 2-3) and slightly positive or negative (score 0-1) in 15. Ki-67 and p53 were studied in 16 pts: Ki-67 positive cells were =50% in 8, p53-positive nuclei were observed in =15% in 11. Correlation by Spearman regression test was found between pre-treatment positive MIBI and low p53 expression (p=0.018) and not between MIBI and Ki-67. To date, 18 pts have completed CT-RT and received the second MIBI assessment: 15/18 pts obtained complete remission (CR) and 3/18 partial or no response. After 9-36 months follow-up (median 22), 5/18 pts recurred locally. No correlation was found between pre-CT-RT MIBI, Ki-67 or p53 and CR. Seven of the 13 cases with MIBI positive at the first assessment turned negative or reduced the uptake after CT-RT. This change was correlated with CR after CT-RT

(p=0.033). A correlation was also found between the post-CT-RT positive MIBI and CR (p=0.030).

**Conclusion:** This preliminary report showed that pre-CT-RT MIBI, Ki-67, and p53 were not predictive for response to CT-RT, but the post-CT-RT MIBI and the decrease of uptake were correlated with the response. Pre-CT-RT MIBI was also correlated with low expression of mutated p53. These data suggest that changes of MIBI uptake after CT-RT can be related to the response to treatment.

# Gynaecological cancer

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## Overall survival advantage for pegylated liposomal doxorubicin compared to topotecan in recurrent epithelial ovarian cancer

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**Background:** A recent phase III study compared the efficacy and safety of pegylated liposomal doxorubicin (Doxil®/Caelyx®) with topotecan in patients with recurrent epithelial ovarian cancer that recurred after or did not respond to first-line, platinum-based chemotherapy (Gordon, et al. *J Clin Oncol.* 2001;19:3312-3322). Response rates were found to be similar for both treatment groups. Final survival data from this study are now reported.

**Material and Methods:** Patients (N = 474) were randomly assigned (1:1 ratio) to treatment with pegylated liposomal doxorubicin 50 mg/m$^2$ every 28 days or topotecan 1.5 mg/m$^2$/day for 5 consecutive days every 21 days. Patients were stratified prospectively based on whether they had platinum-sensitive/refractory disease and the presence/absence of bulky disease. Primary efficacy endpoints were progression-free and overall survival.

**Results:** Overall survival was longer in patients treated with pegylated liposomal doxorubicin compared to those treated with topotecan (median 63 and 60 weeks, respectively; $P$ = 0.05, HR = 0.82 [0.68, 1.00]). In the subset of patients with platinum-sensitive disease (46%), this survival advantage was even more striking for patients treated with pegylated liposomal doxorubicin compared to topotecan (median 112 and 77 weeks, respectively; $P$ = 0.002, HR = 0.63 [0.47, 0.85]). In the subset with platinum-refractory disease, survival was similar in the 2 treatment groups (median 36 and 41 weeks, respectively; HR = 1.01 [0.78, 1.31]). As of December 2002, 29 patients initially treated with pegylated liposomal doxorubicin and 10 topotecan-treated patients remain alive. A more favorable toxicity profile was reported with pegylated liposomal doxorubicin, as patients experienced fewer severe adverse events and required less hematologic support and significantly fewer dose modifications.

**Conclusions:** Patients treated with pegylated liposomal doxorubicin had longer overall survival compared to topotecan-treated patients. The overall survival advantage was more than 35 weeks in patients with platinum-sensitive disease treated with pegylated liposomal doxorubicin. To date, this is the only head-to-head study demonstrating a survival advantage in recurrent epithelial ovarian cancer.

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## Phase I dose finding study of capecitabine, cisplatin and radiotherapy in the treatment of locally advanced squamous cervical cancer

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**Background Materials and methods** 13 patients with Stage II (7) or Stage III (6) received pelvic radiotherapy (45Gy in 25f) plus a selectron intra-uterine insertion (median A point dose 26.00Gy at 1.53Gy/hr). All but one patient (4 cycles only) received 6 weekly cycles of cisplatin (40mg/m$^2$). It was planned to give daily capecitabine for 42 days to cohorts of 6 patients using escalating doses. The MTD was defined as 2 patients experiencing Grade(G) 3 toxicity in any one cohort. The starting dose level was 600mg/m$^2$ BD and the second 900mg/m$^2$/BD

**Results Capecitabine dosage** 6/6 patients in cohort 1 and 5/7 in cohort 2 received capecitabine at or very close to the protocol dose. Capecitabine was discontinued after 27 days in 1 patient in cohort 2 because of Grade 3 diarrhoea, febrile neutropenia and thrombocytopenia. 1 patient in cohort 2 had difficulty swallowing the tablets, discontinued treatment after 4 days and was replaced. Two patients in cohort 2 experienced G3 toxicity (diarrhoea and febrile neutropenia).

**Survival** 4 patients have died. The actuarial progression free survival at 12 months is 64% (se = 15%)with a 15 month survival of 55% (se = 17%).

**Acute toxicity** 1 patient in cohort 1 developed G 3 diarrhoea. 2 patients in cohort 2 developed febrile neutropenia and 1 of these also had G 3 diarrhoea.

**Late Toxicity** 2 patients (1 from each cohort) developed RTOG/EORTC G 3 late toxicity (bladder and vaginal mucosa respectively) at 9 and 15 months after treatment.

**Conclusion** The MTD of capecitabine given with pelvic irradiation and weekly cisplatin was found to be 900mg/m$^2$/BD. The recommended dose level of capecitabine in this combination is 600mg/m$^2$/BD.

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## Phase II study of OSI-774 given in combination with carboplatin in patients (pts) with recurrent epithelial ovarian cancer (EOC): NCIC ctg Ind.149.

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**Background:** Response rate to carboplatin in pts with recurrent EOC is proportional to the progression free period after completion of first-line platinum-chemotherapy. Pts relapsing within 6 months are considered platinum resistant (PR), and pts relapsing after 6 months, sensitive (PS). OSI-774 is an orally active, potent, selective inhibitor of EGFR tyrosine kinase inhibitor with single agent activity in ovarian cancer (Finkler et al P ASCO Abstract 831, 2001). EGFR inhibitors may potentiate the antitumour effects of cytotoxic agents, and may beneficially modulate drug resistance.

**Methods:** Pts with relapsed EOC, measurable disease, and $\leq$ 2 prior chemotherapy regimens (the first regimen must have contained platinum) were entered into one of 2 strata: PR or PS. Both strata have 2-stage designs, with sample sizes of 30 pts (15: 15) and 15 pts (8:7) respectively. Carboplatin was given at AUC 5 IV q 21days with OSI-774 150mg day.

**Results:** 34 pts have been accrued to date. Acneiform rash, fatigue, diarrhea, nausea and dry skin were the most common toxicities. 2 pts had carboplatin hypersensitivity allergic reactions. No grade 4 hematologic toxicity occurred. 18 PS pts were accrued in 2 stages; preliminary response data suggest 10 of 16 currently evaluable pts have achieved as yet unconfirmed objective responses. 16 PR pts have been accrued in stage 1. Response data are as yet immature.

**Conclusion:** OSI-774 can be administered in combination with carboplatin at a dose of AUC 5. The combination has activity in PS patients; mature response data on both PR and PS strata will be updated.

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## Patterns of relapse influenced by hematogenous tumor cell dissemination in patients with cervical carcinoma of the uterus

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The presence of isolated tumor cells (ITC) in the bone marrow at the time of primary diagnosis has been found to indicate an increased risk for subsequent development of distant metastases in various solid tumors. This study evaluates the prevalence and prognostic significance of ITC in patients with primary carcinoma of the cervix uteri.

We immunocytochemically analyzed bone marrow aspirates of 130 patients with newly diagnosed carcinoma of the cervix uteri for the presence of cytokeratin(CK)-positive cells from May 1994 until January 2001. We used a quantitative immunoassay with the monoclonal anti-CK antibody A45-B/B3 and evaluated 2 x10$^6$ bone marrow cells per patient. Patients were followed prospectively for a median of 43 (range, 1-85) months.

ITC were found in the bone marrow of 38 patients (29%). The presence of ITC did not correlate with the FIGO tumor stage (P = 0.61), pelvic and paraaortal lymph node involvement (P= 0.41), nor with histopathological grading (P= 0.67), the histological type of the carcinoma (P= 0.93), invasion of lymph (P=. 93) and blood vessel (P= 0.92), or menopausal status (P= 0.17). The bone marrow status at the time of primary diagnosis did not correlate with the overall survival as estimated by Kaplan-Meier-Analysis (P= 0.30). However, distant metastases occurred in 5% of the patients (n=5) with negative and in 15% of the patients (n=6) with positive bone