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Guest Editor

Bruno Audhuy, Colmar (France)

Cancer Incidence in Alsace: Incidence – Comparisons – Trends

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In France, a general cancer registry exists only in a dozen departments. The first French registry was established in 1975 in the Bas-Rhin. Since 1988, the Haut-Rhin has possessed its own permanent registry. We present our findings bringing together data from these two registries.

The 8,120 new cases of cancer diagnosed in Alsace in 1997 (all sites and all ages taken together), represent a crude incidence, for 100,000 male inhabitants, of 556 in the Bas-Rhin and 522 in the Haut-Rhin, and a standardized incidence of 424 and 371, respectively. For 100,000 female inhabitants, the crude incidences are 396 and 421, respectively, and the standardized incidences 251 and 254. A comparison of standardized incidences reveals that in Alsace, the incidence of cancer is the highest in France for both sexes. The two departments have also a higher incidence than those of the surrounding regions: for men, the standardized incidence is 303 in the canton of Basel, and 266 in Baden-Württemberg. For women, the standardized incidence is 225 and 200, respectively.

The trends, from 1975 to 1999 in the Bas-Rhin and from 1988 to 1999 in the Haut-Rhin, are oriented towards a rise, similar in the two departments. The male incidence is consistently higher in the Bas-Rhin, while the female incidence is slightly higher in the Haut-Rhin.

We also present several significant sites with certain ones showing an important augmentation in number and in incidence (prostate, lymphomas and leukaemia in males, and breast, lung, lymphomas, and leukaemia in females), while others are characterized by a fall in number and incidence (mouth, oropharynx, larynx and rectum in men, and cervix in women).

EGFR-Targeted Drug Delivery via Immunoliposomes

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Purpose: We hypothesized that anti-EGFR immunoliposomes (ILs) can be constructed to provide intracellular drug delivery in EGFR-overexpressing tumor cells. **Methods:** We prepared anti-EGFR ILs containing either Fab' fragments (IMC-C225/Cetuximab, ImClone Systems, Inc.) or human scFv newly generated from our phage antibody libraries (e.g., scFv C10). MAb fragments were covalently conjugated to stabilized liposomes by incorporation of Mab-linker micelles into preformed liposomes with/without encapsulated drugs. ILs were evaluated for specific binding, internalization, cytotoxicity with encapsulated drugs in EGFR-overexpressing cell lines in vitro, and in a series of in vivo efficacy experiments. **Results:** Fluorescence-labeled anti-EGFR ILs efficiently bound to EGFR-overexpressing cells (A-431, MDA-MB-468, U-87) demonstrated extensive internalization in the cytoplasm of target cells consistent with receptor-mediated endocytosis. Non-targeted (no Mab) liposomes and irrelevant (anti-HER2) immunoliposomes did not bind to or accumulate in these EGFR-overexpressing cells. Quantitative studies of uptake and internalization showed binding to MDA-MB-468 cells within 5 minutes, followed by intracellular accumulation detectable at 15 min and increasing to a plateau after 240 min. Total uptake of ILs at 240 min was 1.70 fmol phospholipid/cell ($\approx$ 13,000 ILs/cell). Uptake of ILs was 43-fold greater than that of non-targeted liposomes ($<$ 300 liposomes/cell). In in vitro experiments anti-EGFR ILs prepared by conjugation of C225-Fab' to pegylated liposomal doxorubicin (Doxil[®]) showed significantly greater cytotoxicity than Doxil itself (29-fold). Anti-EGFR ILs containing encapsulated vinorelbine were 40-fold more cytotoxic than non-targeted liposomal vinorelbine, while anti-EGFR ILs containing encapsulated methotrexate were $>$ 20-fold more cytotoxic than non-targeted liposomal methotrexate. In each case, anti-EGFR ILs containing encapsulated drug were much less cytotoxic than free drug in non-EGFR overexpressing MCF-7 cells and equivalent to non-targeted liposomal drug.

Anti-EGFR ILs have also been generated with novel anticancer compounds. In vivo, ILs loaded with doxorubicin showed extended circulation time after i.v. administration, with an 18 h terminal half-life in rats and $>$ 90% drug retention at 48h. Therapy studies with anti-EGFR ILs-dox given i.v. showed potent anticancer activity in EGFR-overexpressing MDA-MB-468 breast cancer and U-87 glioma xenograft models. In each study, anti-EGFR ILs-dox produced significantly superior efficacy to all other treatments, including free and liposomal doxorubicin. **Conclusions:** Anti-EGFR ILs provide efficient and targeted delivery of anticancer compounds and may be applicable to a variety of EGFR-overexpressing tumors.

Prognostic Indicators for Survival in Head and Neck Squamous Cell Carcinomas: Analysis of a Series of 673 Cases and Implication in the Development of New Therapeutic Strategies

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Purpose: Whereas there is increasing interest in adjuvant radio-chemotherapy in head and neck squamous cell carcinomas (HNSCC), the prognostic indicators which allow the therapeutic indications to be established are not yet clearly defined. **Patients and Methods:** In this retrospective survival study, 673 patients who were operated on for HNSCC by the same surgical team between 1990 and 1997 and who underwent lymph node clearance were included. The site of the primary cancer was the buccal cavity (113), the oropharynx (302), the larynx (71), and the hypopharynx (187). 425 patients who had lymph node metastases, diseased resection margins or a tumor of large size, received adjuvant radiotherapy. **Results:** From a univariate analysis of overall survival, the statistically significant prognostic histological indicators were the pT stage ($p<0.0001$), the pN stage ($p<0.0001$), capsule rupture ($p<0.0001$), the number of lymph nodes invaded (0, 1–3, 4–9, ≥ 10) ($p<0.0001$) and the total tumor volume (≤ 5 , 5–20, 20–50, >50 cm³) ($p<0.0001$). Metastases free survival (MFS) at 2 years decreases depending on the pN stage (% MFS/pN): 93/pN0, 88/pN1, 78/pN2a-b, 66/pN2c and 48/pN3. Likewise, MFS at 2 years decreases depending on the number of invaded nodes (% MFS/nb of invaded nodes): 93/0, 80/1–3, 65/4–9, 45/ ≥ 10 . Cox survival models after adjusting for age, sex, and site of the primary cancer found the independent statistically significant prognostic indicators for overall survival to be pT stage ($p<0.0001$), pN stage ($p<0.0001$) and the total tumor volume ($p<0.02$). When, instead of the pN stage, the number of lymph nodes invaded was considered, it emerged as a statistically independent prognostic indicator. **Conclusion:** Our results therefore lead us to recommend to stratify future therapeutic trials, in particular with respect to the number of lymph nodes invaded or pN and the pT stages. Because of the high distant metastatic risk observed with bulky nodal involvement, additional neoadjuvant or adjuvant chemotherapy should be investigated.

Assessment of the Hypermethylation Status in Genomic DNA Samples Derived from Serum of Patients with Lung Cancer

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Hypermethylation represents an important mechanism to regulate gene expression without alteration of the genomic DNA sequence. Such epigenetic changes can lead to a complete suppression of transcription which in turn can considerably change the biological behavior of a cancer cell. We have investigated the promoter region of ten candidate genes for a potential hypermethylation. These genes include tumor suppressor genes (APC1A, APC1B, FHIT, p14^{ARF}, p16^{INK4a}, RAR β , RASSF1A) and genes involved in

apoptosis (DAPK), DNA-repair (MGMT) and cell adhesion (E-cadherin). Genomic DNA was purified from serum and was subsequently treated with sodium bisulfite to convert unmethylated cytosine bases to uracil. To increase the sensitivity we have developed a nested PCR approach. A first PCR amplifies a larger fragment using primers which do not discriminate between the methylated or wildtype genotype. The second PCR uses nested primers which specifically amplify either methylated or unmethylated sequences. We have investigated serum samples in a group of 83 patients with a confirmed diagnosis of lung cancer. The incidence of hypermethylation differed considerably between single genes. The lowest frequencies were detected in DAPK (6.0%) and MGMT (2.4%). In contrast, the promoter region of RAR β was found to be hypermethylated in 47% of the investigated samples. In 11 patients (13.3%) none of the tested genes showed an epigenetic alteration. The majority of samples exhibited one or two (41.0%) and three to four (33.7%) genes with a hypermethylated promoter region. In 10 DNA specimens (12.0%) at least half of the tested genes showed epigenetic modifications. The data are presently explored for a possible correlation with clinico-pathological parameters of these patients. Single parameters or a combination of several epigenetic alterations may provide useful clues for the prognosis and/or therapeutic efficiency.

Initial EBUS Guided TBNA Is the Most Cost-Effective Means of Lymph Node Staging – a German Experience

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Purpose: Lymph node staging is extremely important for the therapeutic decision in patients suffering from lung cancer. For mediastinal staging in non-small cell lung cancer different techniques are available. Most frequently, mediastinoscopy or TBNA are performed for diagnosis and staging. As we introduced EBUS for this purpose we tried to compare its costs vs. primary mediastinoscopy and CT guided TBNA followed by mediastinoscopy when necessary. **Methods:** For 3 methods, mediastinoscopy, conventional TBNA and EBUS guided TBNA we calculated the actual cost of the procedure for one hundred patients. In the cost analysis we calculated: equipment, write-off, personnel, disposables and costs for histological and cytological examinations. Because all patients underwent CT and flexible bronchoscopy in either group, we did not add these direct costs. The average diagnostic yield for CT guided TBNA was presumed to be 60% and for EBUS guided TBNA 75%. **Results:** The cost of conventional TBNA was 57 €, the cost for EBUS guided TBNA 180 € and for a mediastinoscopy 1,620 € per patient. In primary conventional TBNA 40 patients will have to undergo additional mediastinoscopy. The cost for lymph node staging in 100 patients amounts to 70,500 € (100 $\times$ 57 € plus 40 $\times$ 1,620 €). EBUS guided TBNA requires additional mediastinoscopy in 25 patients. The costs for 100 patients amounts to 58,500 € (100 $\times$ 180 € + 25 $\times$ 1,620 €). The costs for 100 mediastinoscopies amounts to 162,000 €. **Conclusion:** Comparing the three different methods for primary lymph node staging of lung cancer, EBUS guided TBNA reduces the costs significantly as compared to CT guided TBNA and primary mediastinoscopy. **Clinical Implication:** All patients with enlargement of mediastinal lymph nodes should undergo initial EBUS guided TBNA as the most cost-effective approach.

Conventional vs. Endobronchial Ultrasound (EBUS)-Guided Transbronchial Needle Aspiration (TBNA) – a Randomised Trial

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Purpose: TBNA is an established method for diagnosing mediastinal lymphadenopathy and staging of lung cancer. EBUS guidance seems to be beneficial in increasing the diagnostic yield, but has not yet been proven to be superior to conventional TBNA. We performed a randomised prospective trial comparing EBUS guided versus standard CT-guided TBNA. **Methods:** Consecutive patients referred for TBNA of enlarged mediastinal lymph nodes were enrolled into the trial. As by the endoscopic landmark subcarinal

lymph nodes are easily localized, these patients were analyzed separately (Group A) as compared to other locations (Group B). Patients in Groups A and B were randomized into an EBUS guided versus a conventional TBNA arm. Lymph node positions were classified according to the ATS scheme. **Results:** 200 patients (75 female, 125 male, mean age 51.9 years, SD $\pm$ 22.6) were examined. 100 patients underwent EBUS guided TBNA vs. 100 patients who underwent conventional TBNA. In group A (subcarinal lymph nodes) the yield of conventional TBNA was 76%, compared to 86% in the EBUS guided group. The difference was statistically not significant. In group B the overall yield of conventional TBNA was 58% compared to 84% in the EBUS guided group. The difference was statistically highly significant ($p < 0.001$). The overall yield for groups A and B was 66% for conventional TBNA versus 85% for EBUS guidance ($p < 0.05$). No complications were observed. **Conclusion:** Except for subcarinal lymph nodes EBUS guidance significantly increases the yield of TBNA in all other locations. With detection by EBUS the yield in those locations is equal to the yield in subcarinal lymph nodes. **Clinical Implication:** EBUS guidance should be considered as a routine adjunct to TBNA.

Gefitinib (Iressa® ZD1839): Single-Institution Experience with an Oral Dose of 250 mg/day from an Expanded Access Program (EAP) Involving Patients with Advanced Small-Cell Lung Cancer (NSCLC)

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In an EAP, NSCLC patients (pts) unfit to receive further chemotherapy were treated with Iressa® at an oral dose of 250 mg/day. A total of 87 pts, primarily in stage IV, were included of whom 68, recruited between June 2002 and July 2003, were analysed (n=68). Pt characteristics were as follows: (1) median age: 62.6 years (range: 35.2–80.5 years) (2) male/female ratio: 38/30 (55.9%/44.1%). Histology: (1) adeno: 28 (41.2%) (2) bronchioalveolar: 4 (5.9%) (3) squamous: 19 (27.9%) (4) large-cell: 3 (4.4%) (5) unspecified: 14 (20.6%). Pre-treatment with chemotherapy regimens: 0: 2 (2.9%), 1: 23 (33.8%), 2: 24 (35.3%), 3: 15 (22%), 4: 2 (2.9%), 5: 1 (1.5%), 6: 1 (1.5%). Thirty-three (48.5%) pts received loco-regional radiation to the primary tumor. Median duration of treatment: 49.5 days (range: 3–302 days). Response: (1) PR: 1 (1.5%) (2) NC: 15 (22.1%) (3) PD: 43 (63.2%). Median duration of response: (1) PR: 275 days (2) NC: 149 days. Median time to progression: 44 days (range: 9–264 days). Toxicity: (1) skin: G2: 3 (4.4%), G3: 1 (1.5%) (2) diarrhoea: G2: 2 (2.9%), G3: 1 (1.47%); no pt was found to have interstitial pneumonia. Median survival from start of treatment: 59 days (range: 4–306 days). At present 23 pts (33.9%) are still alive. Our observations confirm results previously obtained in randomised phase-2 studies: Iressa® single agent is well tolerated and effective in heavily pre-treated pts. We have seen no evidence of clinically relevant pulmonary toxicity following doses of 250 mg/day or of a correlation between response rates and skin toxicity.

Progress in Palliative Chemotherapy for NSCLC? Effects of Modern Chemotherapy Regimens

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Background: Randomized prospective trials (RPT) suggest that newer chemotherapeutic agents (i.e. gemcitabine, one of the taxanes or vinorelbine) improve survival in NSCLC. The goal of this retrospective study was to analyze outcome of 230 consecutive patients with inoperable NSCLC in a single institution and to a) determine whether there was an improvement in outcome over time and b) if so, to analyze factors associated with this improvement. **Methods:** 230 documented patients with NSCLC at the Basel University Hospital treated after 1990 were analyzed retrospectively. Breakpoints by year of treatment were determined using sequential Cox

proportional hazards regression models and the Kaplan-Meier estimator. Multivariate analysis was used to determine which factors were associated with improved survival over time. **Results:** One- and 2-year survival of patients diagnosed after 1997 was significantly better than of those diagnosed prior to 1997. ($40 \pm 8\%$ versus $19 \pm 9\%$ and $23 \pm 7\%$ vs $5 \pm 5\%$, respectively, $p < 0.0001$). The 2 cohorts, 80 patients diagnosed <1997 and 150 patients diagnosed >1997 did not differ significantly in sex (70% male), age (median 60 years), stage, performance status, histology, weight loss, proportion with elevated LDH. Of the factors analyzed, LDH, Albumin, Leukocytosis and performance status were significantly associated with survival. Further analysis showed that 1) patients treated with best supportive care only ($n=31$) had better survival after 1997 (median 5.7 vs 4.1 months, $p < 0.025$). 2) When comparing only patients who received palliative chemotherapy the cohort after 1997 had significantly improved survival ($n=199$, median 9.2 vs 6.9 months, $p < 0.0016$). 3) This improvement could also be shown for patients who received a platin agent plus a 'new' cytotoxic drug vs an older regimen (median 9.3 vs. 6.7 months, $p < 0.026$). Finally improved survival was also found for the group of patients who received second line chemotherapy after 1997 compared to before 1997 ($n=58$, median 9.9 vs 4.1 months, $p < 0.0046$). **Conclusions:** A significant improvement of survival in patients with NSCLC was observed since 1997. This is due to better supportive care, more efficient palliative chemotherapy and better second line chemotherapy, confirming results of RPT in unselected primary cancer center patients.

Total Resource Use and Chemotherapy Costs in Treating Advanced Non-Small Cell Lung Cancer by Various Chemotherapy Regimes in Germany

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Background: The cost of chemotherapy drugs for the treatment of non-small cell lung cancer (NSCLC) varies greatly. This study examines the extent to which various regimes produce differential costing profiles. **Methods:** A retrospective economic analysis was applied to two prospective randomised, controlled trials of gemcitabine/cisplatin (GC) and other regimens. Comella et al. (2000) compared GC with vinorelbine/cisplatin (VC); Schiller et al. (2002) compared GC with paclitaxel/cisplatin (PC), carboplatin/paclitaxel (CP) and docetaxel/cisplatin (DC). Costs were grouped under four main headings: chemotherapy, drug administration, hospitalisations and other medical resources. German health care costs were drawn from the literature and standardised questionnaires. **Results:** When costings were applied to the Comella et al. study the percentage of the total cost of the GC regime that was consumed by chemotherapy was 44.7%; the corresponding figure for the VC regime was only 30.2%. However, the total cost of the GC regime was only 86.7% of the VC regime (€ 7,061 vs. € 8,143). When costings were applied to the Schiller et al. study then chemotherapy costs for the GC combination, as a proportion of total costs of the regime, were found to be lower than the other three regimes (49.3% vs. 52.4% (PC), 74.1% (CP) and 53.8% (DC)). In addition, the total cost of the GC regime (€ 8,425) was only 76.2% of the total cost of the PC regime (€ 11,052) and 68.7% of the total cost of the CP regime (€ 12,265), the total cost for the DC regime (€ 8,329) was similar to the GC regime. **Conclusions:** Different chemotherapy regimes for the treatment of NSCLC produce different magnitudes and proportions of cost across the major resource headings. However, chemotherapy costs alone should not be the only cost element considered in the financial component of treatment decisions.

References:

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Hereditary Predisposition to Gastric Cancer

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Gastric cancer is part of the spectrum of tumours observed in Lynch syndrome (HNPCC) and in familial adenomatous polyposis, but it can also present as familial aggregations consistent with an autosomal dominant pattern of transmission. A family is presented in which four first-degree relatives developed gastric carcinoma at ages ranging from 31 to 55 years. The pathological reports available in two cases described diffuse type gastric carcinomas. The molecular analysis showed a deleterious germ-line mutation in CDH1, a gene coding for an epithelial-type calcium-dependant adhesion molecule and known to support the genetic predisposition to this type of cancer. This has been used for the purpose of predictive diagnosis in the family. Because of the rapid submucosal spread of diffuse type gastric carcinoma surveillance is not an efficient strategy. Prophylactic gastrectomy is preferred in persons bearing a CDH1 mutation. Sporadic cases of diffuse type gastric carcinoma have also been screened for germ-line mutations in CDH1 but was present only in a minority of cases.

The other familial gastric carcinomas are of the intestinal type and frequently associated with dysplasia or metaplasia or with *Helicobacter pylori* infection. The genetic basis for this is different from CDH1 and not yet identified. In these families surveillance gastroscopy, and eradication of *H. pylori* if necessary, are more adequate.

Treatment of Advanced Gastric Cancer with Infusional 5-Fluorouracil, Sodium Folinic Acid, Mitomycin C and Liposomal Pegylated Doxorubicin – Analysis of Toxicity of a Phase-II Study

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Background: Anthracyclins are commonly used in combination protocols for the treatment of advanced gastric cancer (e.g. ECF schedule). Pegylated liposomal doxorubicin (Caelyx®) is less cardiotoxic and has a prolonged plasma half-life. Caelyx has been combined with infusional 5-FU/folinic acid and mitomycin C in a phase-I study. This new combination therapy was well tolerated and showed promising preliminary activity in gastric and pancreatic cancer. We sought to evaluate this treatment schedule as first line therapy in advanced gastric cancer. **Treatment Schedule:** Treatment consisted of weekly 24-h infusions of 5-FU (2,000 mg/m²) mixed with sodium-FA (500 mg/m²) in one pump for six weeks. On days 1 and 29 caelyx (20 mg/m²) was added as 1-hour infusion and on days 8 and 36 bolus mitomycin C (7 mg/m²) was administered. Cycles were repeated on day 57. **Results:** Since April 2002 27 patients (18 m.; 9 f.; ECOG score 0-2; median 1) with advanced gastric cancer have been recruited. 68% had distant metastases (liver and/or lung) and 41% peritoneal carcinomatosis (bad prognosis group). Median age was 64 years (range 40-76). Patients received up to five treatment cycles. Toxicity data are available for 21 patients and for 51 treatment cycles. Main toxicities were (NCI-CTC): Nausea/vomiting (grade I/II: 52%, grade III: 12%), diarrhoea (grade I/II: 32%, grade III: 12%), mucositis/stomatitis (grade I/II: 32%, grade III: 4%) anorexia (grade I/II: 48%, grade III: 8%) thrombocytopenia (grade I/II: 16%; grade III: 8%) leukopenia (grade I/II: 32%, grade III: 8%) and anemia (grade I/II: 60%, grade III: 12%). The only grade IV toxicity was renal insufficiency caused by haemolytic uremic syndrome attributable to mitomycin C. No treatment related deaths and no cardiac toxicity occurred. Analysis of efficacy is pending. **Conclusion:** Liposomal pegylated doxorubicin in combination with mitomycin C infusional 5-FU/sodium-FA is a feasible and well tolerated treatment combination for advanced gastric cancer. Efficacy results will be available for the meeting.

Small Bowel Adenocarcinoma (SBA) with and without Crohn's Disease (CD)

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Background: Small bowel adenocarcinoma (SBA) has been recently recognized as a cause of increased late mortality in a population-based study of CD. The aim of this study was to describe the main characteristics of SBA associated with CD. We addressed the prognostic role of immunomodulators administration and duration of CD before SBA. **Methods:** In order to underline the characteristics of CD-associated SBA, a comparison was made with SBA without CD. Sixteen patients (7 men, 9 women) with CD, recruited from 8 tertiary referral centers, developed a SIA between 1986 and 2002. They were compared to 40 patients (21 men, crude rate: 0.26; 19 women, crude rate: 0.38) with SBA and no CD, indexed in a French population-based study of gastrointestinal cancers between 1986 and 1999. **Results:** SBA was found after a median of 15.5 years of CD (0–37). Three patients had received azathioprine. Two of them had stopped azathioprine 5 and 16 years before the diagnosis of SBA; 1 patient started azathioprine 40 months before and continued it until SBA was found. No other immunomodulator was prescribed. Five patients underwent bowel resection for CD before SBA (3 months–37 years). Characteristics of patients with and without CD appear in the following table. Diagnosis of SBA was suspected before surgery in 1/16 patient with CD and 22/40 without CD. **Conclusion:** SBA in CD patients mainly affects the ileum, after a median evolution of 15.5 years. Immunomodulators did not play an important role in this series. These results suggest that age at diagnosis is younger, diagnosis is more difficult, undifferentiated histology is more frequent and survival is shorter in patients with CD-associated SBA than in patients without CD.

	Median age at diagnosis (year)	Localization	Poorly differentiated histology	Median survival (months)
SBA and CD (n=16)	47 (33–72)	I: 15; J: 1	6	21 (1.5–75)
SBA without CD (n=40)	68 (41–95)	I: 20; J: 8; U: 12	0	32 (1–160)

I: ileum; J: jejunum; U: undetermined (mid small bowel).

Neoadjuvant Chemotherapy in Locally Advanced Colon Carcinoma

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Resection is still the only curative treatment for localized colon cancer and the long-term prognosis remains poor for those who cannot undergo surgery.

In contrast with other malignant entities, such as lung and rectal cancer, neoadjuvant chemotherapy for down-staging locally advanced and therefore inoperable tumors has not yet been established in colon carcinoma.

We treated two patients with stage-III (Dukes C) colon carcinoma with chemotherapy following the Roth protocol, including oxaliplatin, irinotecan, leucovorin and 5-fluorouracil.

One patient showed a partial response on CT-scan after three cycles of the regimen, but demonstrated persistent infiltration of the mesenteric fat and most likely of the psoas muscle, as well as the left ureter. Because the patient was intolerant of further chemotherapy, surgery was performed, resulting in a R0 resection of the sigmoid colon, the left kidney, ureter and adnexa (ypT2pN0 (0/16), G2).

The second patient has received three cycles of chemotherapy to date, with an excellent partial response after two cycles and good tolerability. A reevaluation is scheduled after four cycles and resection is anticipated.

Though limited data are available, this new strategy seems promising for patients with locally advanced neoplasms of the colon.

New therapeutic agents, such as thymidylate synthase inhibitors, antibodies and vaccines, should be included in future protocols for the neoadjuvant pre-operative treatment of otherwise unresectable colon cancers.

Phase-I Study of Irinotecan (CPT-11) and Capecitabine in Combination with Concurrent Radiotherapy for Locally Advanced Rectal Cancer

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Background: Several neoadjuvant radiochemotherapy protocols using simultaneous CPT-11 and infusional 5-fluorouracil (5-FU) have resulted in pathological complete response rates (pCR) of about 25% in the treatment of locally advanced rectal cancer. Capecitabine is known for its radiosensitizing properties. Moreover, it mimics the pharmacokinetics of infusional 5-FU. Therefore, it seemed rationale to combine capecitabine with CPT-11. **Methods:** We conducted a phase-I study applying weekly CPT-11 50 mg/m² (one hour before radiation on days 1, 8, 15, 22, 29) and increasing doses of capecitabine (days 1–35; dose level [DL] I: 1,000 mg/m², II: 1,250 mg/m², III: 1,500 mg/m²) to cohorts of at least three patients per DL. The radiation dose was 50.4 Gy (45 Gy + 5.4 Gy). The purpose of the study was to establish the recommended dose (RD) of capecitabine in combination with CPT-11 and radiotherapy. Surgery was performed within 4–6 weeks after the completion of chemoradiation. Patients (pts) with primary rectal cancer clinical stage uT3/N+ or uT4 Nx were eligible. DLT was defined as (NCI-CTC version 2.0) hematological toxicity grade 4, febrile neutropenia, diarrhea grade 3, organ toxicities grade 3 with the exception of renal toxicity grade 2. **Results:** 19 pts have been included: 16 male, 3 female; median age 62 years (range 34–78); median ECOG PS 1. uT3 n=18, uT4 n=1. N positive n=16. On DL I no DLT occurred. On DL II 3 out of 7 pts experienced DLT (diarrhea grade 3). Therefore, dose level II was determined as maximum tolerated dose. A total of 12 pts was treated on DL I: Median relative dose intensity was 100% for both drugs. No grade-3-4 toxicity was observed. Toxicities were (grade 1-2): Leucopenia 50% - 8%. Diarrhea 33% - 42%, nausea/vomiting 33% - 25%, radiodermatitis 33% - 33%. To date, 18 pts have undergone surgery. pCR was observed in 4 pts and another 4 pts had micro-foci (MF) of residual tumor. **Conclusion:** Preoperative chemoradiation with CPT-11 and capecitabine is a feasible and tolerable treatment. The pCR and MF rates and the toxicity profile observed in our series are comparable to those published for infusional 5-FU and CPT-11 schedules. We are currently evaluating this new combination therapy at the recommended dose of CPT-11 50 mg/m² and capecitabine 1,000 mg/m² in a phase-II study.

Phase-I Study of Oral Uracil/Fluorouracil (UFT®) plus Leucovorin (LV) Combined with Irinotecan (CPT11) in Patients with Metastatic Colorectal Cancer

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Background: UFT/LV and CPT-11 are active agents in the treatment of CRC, with different safety profiles. We determined the maximum tolerated dose (MTD) of the combination, evaluate the safety profile and dose limiting toxicity (DLT) and define the recommended doses and schedule for phase-II studies. DLT definitions (cycle 1): grade-4 hematological toxicity, febrile neutropenia, grade-3-4 non-hematological toxicity and inability to administer irinotecan on day 15, 29 or 43. MTD was defined when at least 2 out of 3 pts had experienced DLT at considered dose level. **Methods:** Inclusion criteria: histologically/cytologically confirmed non-resectable metastatic CRC, ECOG PS 0 or 1, adequate hematological, renal and hepatic functions, prior adjuvant chemotherapy allowed. Treatment: UFT and LV (90 mg/d) orally days 1–28, CPT-11 90 minutes i.v. infusion d 1, 15, 29, every 6 weeks. **Results:** 23 pts were included. Median age: 64 years (range 42–74); 16 males; ECOG PS 0/1: 14/9 pts; tumor site (pts): colon: 13; rectum: 10;

liver metastasis: 14; prior treatment (pts): surgery 22, chemotherapy 11, radiotherapy 11. A total of 71 cycles was evaluated for safety, median 3 (range: 1–9). MTD was reached at dose level of UFT 300 mg/m²/d, LV 90 mg/day, CPT-11 180 mg/m², diarrhea plus fever being the DLTs. The dose level immediately below dose (UFT 250 mg/m²/day, LV 90 mg/day, CPT-11 180 mg/m²) has been expanded to 4 patients and grade-3 diarrhea has been observed in 2 patients. Among 17 patients evaluable for response (3 patients too early), 1 CR, 3 confirmed PR and 3 not yet confirmed PR have been reported. **Conclusion:** To date recruitment is ongoing at the dose of UFT 250 mg/m² + LV 90 mg + CPT-11 150 mg/m² where 3 patients out of 4 have responded to treatment (1 CR, 2 PR) without significant toxicity.

UFT (mg/m ² /d) / LV (mg/d)	CPT-11 (mg/m ²)	DLT / N° pts	N° of cycles	DLT
200/90	150	1/6	16	G3 diarrhoea
250/90	150	1/4	17	G3 diarrhoea
250/90	180	First phase : 1/6 Second phase : 2/4	27	G3 anorexia G3 diarrhoea G3 diarrhoea
300/90	180	2/3	11	G3 diarrhoea G3 diarrhoea + Fever

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Curative Radiotherapy for Prostate Cancer: The Step from Conformal Radiotherapy to IMRT. Experience of the National Radiotherapy Center of Luxembourg (2000–2003)

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Introduction: In our institution we have reached the dose of 74 Gy with conformal radiotherapy in prostate cancer patients. From February 2000 to June 2002, 73 patients have been treated at this dose level. An adjuvant hormonal therapy with Gosereline and Bicalutamide was administered to patients with high risk prognostic factors (PSA ≥10 or Gleason ≥6 or prostatic volume >40 g). **Material and Methods:** The irradiated volumes have been defined by their margins, expanding from the prostate. For the first 44 Gy the periprostatic margin consisted of 12 mm, for the remaining 30 Gy the margin was decreased to 8 mm with a maximum of 5 mm in direction of the rectum. Our beams delivery technique has been developed over time from a four field box to a five field technique.

Toxicity:

– *Early acute toxicity* (during irradiation period): grade-2 toxicities have been observed in 53% of patients.

– *Late acute toxicity* (during the 6 months after completion of treatment): grade-2 toxicities have been seen in 5% of patients.

A transurethral resection (TUR) had been performed in 13 out of 73 patients with the same frequency and degree of early acute toxicity in these patients during radiotherapy (54% after TUR versus 53% without TUR).

On the other hand, the late acute toxicity was more frequent after TUR (15% versus 3% without TUR).

– *Late toxicity events* (occurring more than 6 months after treatment) of grade 1 or 2 was seen in 31% of the patients treated by TUR against 10% of the patients without TUR, with a follow-up of 6 months at 23 months (medium follow-up 13.5 months).

By June 2003, 27 patients have been followed for 24 months. No new, late occurring complication of grade 2 or 3 has been observed in this group of patients.

Conclusion and Evolution of the Irradiation Technique: A dose level of 74 Gy is achievable with conformal radiotherapy in prostate cancer with acceptable toxicities, if the irradiated volume is limited to the prostatic organ. With symptom-guided medication grade 2 and grade 3 early toxicity can be managed. With a follow-up of 24 months in a group of 27 patients, there were no late occurring complications and all former observed toxicities had resolved.

For the future we want to keep the same dose level of 74 Gy, but go ahead to an intensity modulated technique. The aim is to reduce early and late acute toxicity. A feasibility study is ongoing in our center.

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Grade of toxicity definition: Toxicity grading scale, NCI – CTC version 2.0.
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Bcl-2 Protein Expression Is the Strongest Independent Prognostic Factor for Survival in Primary Cutaneous Large B-Cell Lymphomas

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Background: Bcl-2 protein expression has been associated with poor prognosis in patients with non-cutaneous diffuse large B-cell lymphomas. In primary cutaneous large B-cell lymphomas, the location on the leg, the round-cell morphology defined as the predominance of centroblasts and immunoblasts over large centrocytes, and multiple skin lesions were identified as adverse prognostic factors. The prognostic value of bcl-2 protein expression has not been studied in large series of patients. **Methods:** We evaluated 80 primary cutaneous large B-cell lymphomas collected by the French Study Group on Cutaneous Lymphoma. The prognostic value of age, sex, number of lesions, cutaneous extent, location, LDH level, B symptoms, morphology and bcl-2 protein expression was studied. **Results:** The overall 5-year specific survival rate was 65%. In univariate analysis, advanced age, multiple skin lesions (n=48), location on the leg (n=25), round-cell morphology (n=32) and bcl-2 expression (n=39) were significantly related to death from lymphoma. In multivariate analysis, bcl-2 expression (p=.0003), multiple skin lesions (p=.001) and age remained independent prognostic factors. Five-year specific survival rates in bcl-2+ and bcl-2– patients were 41% and 89%, respectively (p<.0001). **Conclusion:** A new prognostic classification of primary cutaneous B-cell lymphoma should be based primarily on bcl-2 protein expression rather than the location of skin lesions.

Phase-I Trial of Repeated Intralesional Injection of TG1042 (Adenovirus-Interferon-γ) in Primary Cutaneous T- and B-Cell Lymphomas

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Background: Primary cutaneous lymphomas (CL) constitute a spectrum of diseases characterized by a clonal accumulation of lymphocytes in the skin. During the progression of the disease production of the Th1 cytokines decreases with a shift towards the immunosuppressive Th2 phenotype. This group of diseases has been therefore successfully treated with interferons (IFNs), counterbalancing the Th2-skewing state. **Methods:** We undertook a phase-I, open-label, dose-escalating trial of repeated intratumoral administration of TG1042 in patients with advanced primary cutaneous T-cell lymphomas (CTCL) and multilesional cutaneous B-cell lymphomas (CBCL). TG1042 product is made of a suspension of non-replicating (E1 and E3 regions deleted) recombinant adenoviral particles containing human IFN-γ cDNA insert. Nine patients (7 CTCL, 2 CBCL) were enrolled in 3 successive cohorts at the following TG1042 doses: 3 × 10E9 total particles (tp), 3 × 10E10 tp and 3 × 10E11 tp. Patients received intratumoral injections of TG1042 into the designated lesions on days 1, 8, and 15 with no injection in the fourth week (1 treatment cycle) and thereafter up to 4 cycles, if there was no evidence of progressive disease. The injected lesion was biopsied at baseline and

after 3 injections and assessed for changes in lesion's morphology, immunohistochemical changes of T- and B-cell (CD3, 4, 8, 20, 21, 79a), NK (CD56), cytotoxic (TIA-1), and dendritic cell markers (CD1a) as well as for the expression of coxsackie-adenovirus receptor (CAR) and HLA class-I molecules. In addition, the lesions were evaluated for the expression of transgene-derived IFN- γ as well as for total cytokine production (IFN- γ , IL-2, IL-13, IL-10) with respect to CD4 and CD8 T-cells population by quantitative PCR. **Results:** Clinical response has been observed in 4 out of 7 evaluable patients. Evaluations of the two last patients are still to be completed and will be presented. Following TG1042 injections, histology demonstrated pronounced changes in infiltrate pattern differing from initial lymphoma finding, with signs of vasculitis and increase in eosinophil and neutrophil numbers. Immunohistochemistry revealed increase in CD8 and TIA-1 immunoreactivity in various cell types. All lesions demonstrated clear up-regulation of CAR following injection of TG1042. Quantitative PCR showed decrease in CD4/CD8 ratio in 6/8 patients. Transgene-derived IFN- γ mRNA could be detected in injected lesions, implying successful IFN- γ gene transfer. **Conclusions:** Our results reveal for the first time the in situ immunological changes following the administration of adenoviral vector expressing IFN- γ in primary CTCL and CBCL, offering new information that might be of importance in the design of new gene delivery-based therapeutics in cancer.

Whole-Body MRI in Detection of Metastatic Disease of the Axial and Appendicular Skeleton in Patients with Solid Tumors: A Comparison with Skeletal Scintigraphy and Whole-Body FDG-PET

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Purpose: To compare the diagnostic value of whole-body MRI, skeletal scintigraphy and whole body FDG-PET in detection of skeletal metastases. **Methods:** Thirty-three cancer patients (19 male, 14 female, mean age: 66 ys) with different solid tumor were studied prospectively by whole-body MRI and skeletal scintigraphy with 99-Tc-DPD for staging and screening of metastatic bone disease. In 20/33 patients whole-body FDG-PET was performed. Between PET and MRI-examination no radiation therapy or chemotherapy was performed. No previous chemotherapy within the last two months prior to PET was performed. Only skeletal metastases were evaluated. The MR examinations were performed using a rolling table platform 'angiosurf' for unlimited field of view with a 1.5 Tesla system (Magnetom Sonata, Siemens, Erlangen, Germany). A coronal STIR-sequence (TR5500-4230/TE102-94 /T1160) was used for imaging of the different body regions including head, neck, thorax abdomen, pelvis and lower extremities. The skeletal scintigraphy was performed with 99m-Tc-DPD. For FDG-PET 300–500 MBq of FDG was injected intravenously. **Results:** In 28/33 (85%) patients the results of skeletal scintigraphy and whole body MRI were concordant. In 16/33 (49%) patients no skeletal metastatic disease was found with both imaging techniques. In 15 of these 16 patients with concordant negative imaging findings whole-body PET was available and negative too. 12/33 (36%) patients showed skeletal metastases detected with skeletal scintigraphy and whole body MRI and in 5/12 patients whole-body PET was positive. In 7/12 patients with concordant positive imaging findings of skeletal scintigraphy and whole-body MRI, MRI showed more extensive metastatic disease compared to skeletal scintigraphy and in one patient it was vice versa. 5/33 (15%) patients showed discordant imaging findings in skeletal scintigraphy and whole body-MRI. In 2 cases skeletal scintigraphy was false positive and in 3 cases false negative. Comparing whole-body MRI and whole-body FDG-PET in 20/33 patients, there was a concordance in 100%. In 15/20 (75%) patients the imaging findings were concordant positive and in 5/20 (25%) patients concordant negative. **Conclusion:** Whole-body MRI is an effective method for examining cancer patients by the use of a rolling table platform and it is more sensitive than skeletal scintigraphy in detection of skeletal metastases in pa-

tients with solid tumors. In comparison to whole body FDG-PET whole-body MRI is comparable and has the same sensitivity than whole-body FDG-PET.

Epidemiology of Skin Cancer in Haut-Rhin (France): A Population Based Study, with Trends from 1991 to 1999

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The 'département' of Haut-Rhin, an area of 3,522 km², is situated in the north-east of France, at the southern part of Alsace, close to the Swiss and the German borders. It has a total population of 706,790 inhabitants, according to the last census (1999). The Haut-Rhin Cancer Registry is a general population based registry. Created in 1989, it collects cases from 1988. Basal Cell Carcinoma (BCC) is recorded since 1991. WHO/IARC rules are applied. Three years periods are used to calculate Crude Incidence Rates (CR) and World Age Standardized Rates (WASR); these rates are calculated per 100,000 per annum.

Including BCC, skin is the main anatomical site of cancer for both sexes. BCC remains the main skin cancer throughout the life. SCC becomes the second skin cancer only beyond the age of 60. Melanoma is the second skin cancer before the age of 60. The BCCs age specific incidences remain stable throughout the studied period.

Trends between 1991 and 1993 and 1997–1999: BCC and Melanoma incidences have got among the larger increases, after Breast cancer by women. BCC increased more than Lymphoid Leukaemia by men.

Melanoma is the 2nd increasing incidence after women's breast, and non-melanoma skin cancer is the 2nd increasing incidence after prostate. Melanoma WASR increases by 79% among women, and by 44% among men. BCC WASR increases by 9% and 13%, respectively. SCC WASR remains stable, although cases number increases by +25%, cases occurring mostly among old people.

International comparisons: Skin cancer is still often the 'poor parent' in Cancer registries. Some of them, worldwide, don't register them but Melanoma. Many register SCC, and few include BCC. In France, only Doubs and Haut-Rhin cancer registries are registering BCC.

BCCs datas aren't published in Cancer Incidence in five Continents (Vol. VIII, 2002, IARC, No. 155). This book is however the source of the other incidences of Melanoma and SCC showed here. BCC and SCC seem to predominate in areas with fair skin people, mountain, and out-door human activities, whereas Melanoma predominates in areas of fair skin and sun addicted people.

The Introduction of a Psychological Screening Consultation in a Radiotherapy Center in Luxembourg

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Introduction: The National Center of Radiotherapy in Luxembourg provides the opportunity of psycho-oncological consultations (half time occupation of a psychologist) after its opening in 2000. The psychologist's task consisted at this time in accompanying the patients interested in having a psychological support. It appears that, with new tasks assigned to the psychologist such as for example the 'screening' consultation offered to every patient treated in the Center, and with the augmentation of the demands for a psychological support, a half time psychologist doesn't cover any more the needs of 800 patients treated every year in the National Radiotherapy Center of Luxembourg. **The Approach of the Patients and its Difficulties:** Psycho-oncology is a very recent discipline in Luxembourg and it isn't well known nor well accepted from the population of Luxembourg and from cancer patients. Even among the medical and paramedical population, the discipline isn't known very well. Psychology in itself still has difficulties in being accepted by the inhabitants of Luxembourg. That's why the develop-

ment of such an offer in the Radiotherapy Center was quite slow and difficult to realize at the beginning. From October 2000 till March 2002, the patients were informed by the doctors of the Center that there was a possibility of psychological support in the Radiotherapy Center. The patients themselves rarely asked for an appointment with the psychologist. Due to this reticence to consult a psychologist, a new way of approaching and informing them was developed. **The 'Screening' Consultation:** Since March 2002, the Radiotherapy Center offers a systematic 'screening' consultation to every patient. Half of the patients receiving an invitation accept the offer see the psychologist a first time. During this first appointment, the psychologist inquires about the physical and mental health of the patient, his/her social situation and his/her resources. The psychologist explains what she can offer to support them, to increase their quality of life, to manage the possible psychological side effects of the disease (depression, anxiety, ...) and she proposes a psychological support to those who need it. To document those first interviews, she uses the 'PO-BADO' (psycho-oncological basic documentation), which is still in its test phase. This 'screening' consultation facilitates the contact with the patients but it is also used to detect the patients who suffer from psychological problems, to inform and sensitize the doctors of the Center and to inform the patients about other services. **Conclusion:** During the period of the radiotherapy treatment, a psychological support seems to be necessary and indicated. The cancer patient is frightened by the end of all active treatments (operation, chemotherapy, ...) and it seems to be a good moment to begin a psychological support. 96,9% of the patients of the Center indicated in a satisfaction inquiry, that the offer of a psychological support is really appropriate in a radiotherapy Center.

Breast Cancer in Switzerland. Data for the Evaluation of the National Breast Cancer Control Program

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Background: Facing the burden of cancer disease worldwide in 1995 the WHO had a prominent role to start and establish national cancer control

programs with the aim to reduce the incidence and mortality of cancer and improve the quality of life of cancer patients for the next millennium. *Breast Cancer in Switzerland – data for the evaluation of the national breast cancer control program* is part of an analysis for the global evaluation of the national cancer control program in Switzerland. Breast cancer is the most common lethal neoplasm in women in the industrial world. Therefore the fight against breast cancer is an important matter of the control program in Switzerland. **Methods:** Retrospective study between 2001 and 2002 with data collection from the identified data inventory of the first part from the global evaluation 1999 (ordered by the Swiss Cancer League and the Federal Office of Health). **Results:** *Epidemiology:* Between 1993 and 1998 there was a significant increase of the breast cancer incidence in Switzerland with an incidence rate of 76.8/100,000 compared to the former period. The mortality rate was reduced between 1990 and 1994 from 25.1 to 23.7/100,000. This is a reduction of 5% compared to the former period. The 5-year survival rate is about 80% and compared to Europe in the upper level. *Lifestyle:* There is a significant increase in obesity in postmenopausal woman between 1993 und 1997 and an increase in lower level of exercise and physical activity. Only one third of the women interviewed in the Swiss Health Survey are informed about the possible impact of an healthy nutrition. 28% of these women are regular smokers with a significant increase in young women. Switzerland is the only country compared to countries in the EU with an increased nicotine consumption in women between 1992 und 1997. *Prevention and Therapy:* The coverage of screening for breast cancer throughout Switzerland in women between age 50 and 69 years is 60% (ever done), but only 28% had one during the last two years. In 2000 only 245 women were taking part in clinically controlled studies from the SIAK. Only few of the women in Switzerland with breast cancer, taking part in a European survey about female cancer, have been asked to take part in a controlled study. **Conclusion:** There are considerable missing data in the field of diagnostics, therapy and quality of life in breast cancer compared to the area of epidemiology, lifestyle and prevention in consideration of measurable indicators to evaluate a systematic cancer control program. The collected data of breast cancer in Switzerland regarding the aim of the national control program are useful instruments for further development, evaluation and implementation of the breast cancer control program in Switzerland.

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