Discussion: A large number of "de novo" HCC cases and fairly high response rate to preop.CHT constitute a significant difference in comparison with adult HCC series. Angiostatic treatment combined with standard CHT might find a role in HCC. It has potential advantages: broad spectrum of activity, decreased resistance, improved drug access to targets, more tolerable side effects. Thus in the next SIOPEL-5 trial PLADO will be combined with thalidomide. To prevent recurrence post resection prolonged metronomic chemotherapy with oral cyclophosphamide and thalidomide will be applied.
Conclusions: 1. Survival for pediatric/adolescent HCC patients remains unsatisfactory because of low rate of complete tumor excision due to advanced/multifocal disease and high rate of local recurrence. 2. Intensification of standard systemic chemotherapy has not improved prognosis. 3. New treatment approaches and novel concepts are needed. Efforts of pediatric and adult oncologists should be combined within the frames of the new SIOPEL-5 HCC Family of Tumors Trial.

145 Abstract not received

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SIOPEL 5, a new protocol for the management of the HCC family of tumours in children/adolescents and young adults

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The International Society of Paediatric Oncology Childhood Liver Tumours Strategy Group (SIOPEL) has conducted a number of successful multinational clinical trials since 1990. The group has focused on chemotherapy strategies for the commonest childhood liver tumour, hepatoblastoma. However in the three successive clinical trials conducted to date significant numbers of children with hepatocellular carcinoma (HCC) have been treated with combination chemotherapy based on cisplatin/doxorubicin +/− carboplatin. Results have been disappointing with 5yr OS figures in the order of 30% in common with the majority of reported series. This is despite the fact that chemotherapy "responses" can be observed in up to 50% of patients. Complete surgical excision remains the key to the successful management of HCC and the conversion of "unresectable" to "resectable" tumours confined to the liver will be the major goal to improvement in survival.
In an attempt to improve the proportion of resectable localised tumours, the SIOPEL group has devised a specific protocol (SIOPEL-5) for the management of children and young adults (up to 30yrs of age) with HCC not associated with underlying cirrhosis. A new chemotherapy strategy combining conventional cisplatin/doxorubicin with thalidomide in an attempt to target tumour vasculature is proposed. This in combination with guidance on the use of chemo-embolisation of localised tumours we hope will result in surgical options being explored in more patients. Alongside the chemotherapy strategy has been discussion concerning the applicability of patients for liver transplantation. A post operative anti-angiogenic "metronomic" maintenance chemotherapy schedule is also being piloted in those patients achieving disease clearance with surgery. The concept protocol will be discussed along with the scientific rationale proposed.

Scientific Symposium
The modern management of early stage NSCLC

147 INVITED

Proteomics of lung cancer

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Until recently, the only clinically useful classification of lung tumors was based on light microscopy and treatment was determined by this and the distribution of the tumor in the patient. It is clear that these features do not adequately describe the patient-to-patient variability observed in the clinic. Recent data are likely to change this situation in the near future. Mutations in the EGFr and gene amplification are associated with response to gefitinib/erlotinib. However, there are clearly those who respond to gefitinib or have stabilization of disease or symptom improvement in the absence of these features. Therefore, even for this targeted drug, the situation is more complex. It is as yet impossible to predict chemotherapy response, nodal involvement or patient survival. To better understand these more complex features of cancer cells, we have used a proteomics-based approach to classification and prediction of lung cancer biology.We have used matrix-assisted laser desorption/ionization mass spectrometry directly from 1 ng of a single frozen tissue section for profiling of protein expression from surgically resected tissues to classify human lung tumors. Class-prediction models based on differentially expressed peaks were found to classify lung cancer histologies, distinguish primary tumors from metastases to the lung from other sites as well as classify nodal involvement in both training and testing cohorts. We also obtained a proteomic pattern comprised of 15 distinct mass spectrometry peaks that distinguished resected non-small cell lung cancer patients with a poor prognosis. Many of the important discriminatory proteins have been identified and have already led to interesting potential mechanistic insights. We have also identified protein fingerprints associated with response to chemotherapy and targeted therapies.We have applied this technology to the analysis of serum samples to develop serum markers for early detection, and have a profile capable of detecting lung cancer with high specificity in a blinded test cohort.
New technologies are being developed that will allow the use of material from fine needle aspirates and greatly increase the amount of proteomic information obtained from biological samples, as well as generate protein and/or drug distribution images in tissue sections.

148 INVITED

Targeted therapies in non small cell lung cancer

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The last 20 years have witnessed an explosion of knowledge in the biology of cancer. This new knowledge has permitted the development of new medicines targeted at specific molecular alterations present in cancer cells. Several of these new agents are being developed for lung cancer where multiple cellular and molecular defects have been described. Among the most common genetic alterations are p53 mutations and mutations of K-ras. However, so far no medicine has been developed that successfully targets these common genetic alterations. The ErbB family of tyrosine kinase receptors has been successfully targeted by several monoclonal antibodies and small molecules, and some of them are now available for the treatment refractory NSCLC. Two tyrosine kinase inhibitors that target EGFR (erlotinib and gefitinib) have demonstrated a response rate in about 10% of these patients and erlotinib has also demonstrated greater survival in these patients compared to best supportive care. The activity of these two drugs has been reproducibly shown to be related to the presence of EGFR mutations in the ATP binding site; other genetic abnormalities, such as amplification might also help in identifying the patients who benefit from the treatment. Prospective studies testing these drugs in selected patients will be required in order to adequately validate these markers of sensitivity. Cetuximab, a monoclonal antibody to the extracellular domain of EGFR, also has similar activity, but the presence of EGFR mutations would not seem to be important and some degree of non-overlapping activity may be expected between monoclonals and small molecules.
Angiogenesis inhibitors have also been investigated in lung cancer. Bevacizumab in combination with chemotherapy has demonstrated increased survival compared to combination chemotherapy alone in patients with non-squamous histology, without brain metastases and serious hemoptisis. Development of other angiogenesis inhibitors or multiple targeted agents is underway.

149 INVITED

Image guided radiotherapy for early stage non small-cell lung cancer

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Some patients present with surgically resectable disease and have medical contraindications or refuse surgery [1]. For such patients, primary radiation therapy offers an alternative and potentially curative approach. The very good results reported with surgery for early stage disease may in part be due to the more favorable performance status of surgical patients and the fact that surgically treated patients are more rigorously staged and the results are reported by pathological stage rather than clinical stage. Most patients who receive primary radiation therapy are not surgically staged and may have occult N2 (mediastinal) disease, whereas such patients may be excluded or reported separately in surgical series.
Results of radiation alone for medically inoperable early stage lung cancer: There are many series which document reasonable survival following radical radiation alone for stage I and II cancers [2–6]. While 5-year survival from all causes may be low, the cause specific survival is often substantially higher due to high rates of intercurrent illnesses. Cause specific survival ranges from 20–50% at 5 years [7,8]. Locoregional failure (using traditional radiologic and clinical criteria) is the dominant cause of failure ranging from approximately 40–50% [8,9]. This may underestimate local failure as traditional clinical/radiologic assessment of local failure

following radiation underestimates the incidence in locally advanced cancer. In one series routine bronchoscopy was performed during follow-up, and local control was less than 20% at 1 year [10]. There is clearly a need to improve the locoregional disease eradication rates to impact on survival. This could be achieved by better patient selection and improved radiation technology.

Patient selection: Reports of PET scanning have demonstrated accuracy rates of 80–100% in the detection of nodal metastases compared to approximately 65% for CT and MRI [15]. PET also has the advantage of providing accurate whole body staging. PET can also be used in the process of radiation target volume delineation. The advent of accurate non-invasive staging with PET could have as substantial impact on the use of radiation for this category of patients by removing advanced stage patients from the series of the future. Radiation pulmonary toxicity could contribute to increased morbidity and even mortality. It would be useful to exclude patients in whom the treatment would be more likely to cause damage than improve survival. There are no strict guidelines for such selection, however it may be possible to identify patients likely to have very poor pulmonary function post–radiation in a manner analogous to the preoperative selection of patients. Investigators at the NKI calculate the FEV1 post-RT to be:
FEV1 post-RT = FEV1 pre-RT $\times$ [1-(0.01 $\times$ MLD)] (MLD = Mean lung dose) [11,12].

The influence of new radiation technology: 3-dimensional conformal radiation therapy (3-DCRT) has improved the therapeutic ratio of radiation for lung cancer and has facilitated trials of dose escalation [13]. Early studies identified lung dose safety limits and suggested that elective irradiation of uninvolved nodal areas was unnecessary and potentially toxic. Initially these trials increased dose by prolonging overall treatment time. Accelerated repopulation occurring during this extra time could detract form the benefit of the technology and increased dose. Consequently later studies have increased dose without prolonging time. It is hoped that future trials of escalated dose may demonstrate improved local control and survival.

Radiobiological assessment of a hypofractionated scheme:

	Experimental regimen	Standard regimen
Total Dose/Number of fr	72 Gy/24 fr	60 Gy/30 fr
BED (acute effect/anti-tumour effect)*	102	77
BED (long-term effect)**	137	78
Overall treatment Time (weeks)	5	6

NB: BED denotes Biological Effective Dose, Gy, Gray, fr, fraction.
*Used α/β ratio = 7, **used α/β ratio = 3.3.

At St Luke's Hospital we treated 30 pts with NSCLC with 70Gy in 24 fractions. The KPS was >70% and weight loss <10% in 3 months, with inoperable stage I/II (11 pts) or non-resectable stage IIIa/b, no effusion (19 pts). Initial chemotherapy was used in 13 pts. No more than 30% of the combined lung could receive $\geqslant$25 Gy and the max dose to the spinal cord was <61%. No oesophageal dose limits were used. We noted 8 CR and 11 PR in 27 evaluable pts. Median time to local progression, progression and survival: 18.6, 17.3 and 12.6 months. No grade-4 acute toxicity occurred. 2 pts had grade-3 acute oesophageal toxicity and 1 pt a grade-3 acute lung toxicity. 26 pts were evaluable for long-term toxicity (median follow-up: 9.5 months). Late grade-1 lung toxicity occurred in 5 pts. Late oesophageal toxicity was clinically dominant: Grade 1 in 2 pts, grade 2 in 1 pt and grade 3 in 1 pt. There was a significant association between late oesophageal toxicity and length of circumferential oesophagus receiving 97% of the prescribed dose. If the length was <1 cm late oesophageal toxicity occurred in 0/16 pts vs. 4/10 if it exceeded 1 cm ($p < 0.05$). We redesigned the treatment of patients with oesophageal toxicity and length of circumferential oesophagus receiving 97% of the prescribed dose >1 cm with IMRT to see if this length could be reduced. For 3 of 4 pts IMRT reduced the length without exceeding lung constraints. More data are needed to confirm the feasibility of this strategy, but early toxicity data and tumour response rates are encouraging. This radiobiologically intense high-dose accelerated strategy also has practical and economical advantages.

Control of respiration tumour motion and stereotactic radiosurgery (SRT): Peripheral lung tumours, particularly in the lower lobes move significantly with respiration. They may therefore be undersosed. Various strategies have been adopted to account for and reduce this effect with standard 3-DCRT. Accounting for tumour motion is a prerequisite for SRT. Uematsu from Saitama in Japan treated 50 patients with T1–2N0 NSCLC treated by CT-guided frameless SRT [15]. Of these, 21 patients were medically inoperable and the remainder refused surgery. SRT was 50–60 Gy in 5–10 fractions for 1–2 weeks. Eighteen patients also received conventional radiotherapy. With a median follow-up period of 36 months local progression free survival was 94%. Additional studies which demonstrate great potential for this technology will be presented.

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150 INVITED

Pre and postoperative chemotherapy

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Surgery remains the most important treatment modality for early-stage NSCLC. Yet, even with surgical resection, only 50% of stage I patients achieve long-term survival.

Postoperative adjuvant therapy may be defined as treatment administered to patients who have undergone surgical removal of all known disease, but who are considered at risk for recurrence.

A meta-analysis conducted in the early 1990s demonstrated a 5% improvement in overall survival at 5 years with adjuvant cisplatin-based chemotherapy but the difference did not reach statistical significance.

After 1995, 7 trials were completed in adjuvant setting. Recently, in 2003, Dr Thierry Le Chevalier presented the results of the largest adjuvant trial ever conducted in NSCLC.

Overall survival was statistically significant between the 2 groups with an absolute survival benefit of 4.1% in the chemotherapy group from isolated iv HR = 0.86 [0.76–0.98], $p < 0.03$. This survival benefit would translate into the prevention of approximately 7000 deaths per year if all eligible patients were treated with adjuvant chemotherapy and this is of similar magnitude to that seen in large adjuvant breast cancer studies.

The use of cisplatin-based chemotherapy is considered now as valid option in patients with a good performance status who have undergone complete resection.

Three trials, ECOG 3590, Adjuvant Lung Project Italy (ALPI) and the Big Lung Trial (BLT) failed to demonstrate an improvement in survival. In the Italian study there was a trend towards both improved progression-free and overall survival in resected stage II patients.

The Japan Lung Cancer Research Group (JLCRG) conducted a randomized phase III trial of complete surgical resection followed by 2 years of UFT compared to no treatment in 979 patients with stage I adenocarcinoma.

Overall survival was significantly better in the treatment arm (5-year survival was 87.3% versus 85.4%, $P = 0.035$). Patients with T_2 disease showed even better results.

Recently two very important studies were completed. In Canada, the NCIC JBR10 trial in co-operation with SWOG conducted an adjuvant trial using in the treatment arm the combination Cisplatin–Vinorelbine. The trial randomized 482 patients and the results were in favor of the treatment arm. Five-year survival was 69% versus 54% with an absolute benefit 15% at 5 years, $p = 0.0022$. There was a 30% reduction risk of death, $p = 0.012$.

The CALGB-9633 adjuvant trial used the combination Paclitaxel/Carboplatin in the treatment arm. Adjuvant Pac/Cb is safe (85% completed the 4 cycles treatment). Overall survival for 4 years was 71% and 59% in the chemotherapy and observation groups respectively. The absolute benefit was 12% at 4 years with a 38% reduction risk of death and a p value of 0.028.

Finally, in the Adjuvant Navelbine International Trialist Association (ANITA), 840 patients were randomized to vinorelbine/cisplatin adjuvant therapy or observation following completely resection of stage I (except T1NO), II, or IIIA NSCLC. The median survival was 65.8 months vs 36.5 months in stage 2 patients, and 38.6 months vs 24.1 months in stage IIIA patients. We are talking about an overall survival advantage of 5.1% at 2 years, and 8.6% at 5 years. The ANITA trial confirms the use of adjuvant therapy in patients with respectable NSCLC.

In conclusion, it seems that a significant number of patients with early stage NSCLC have benefit receiving chemotherapy, particularly with new drugs following surgery.

The administration of neoadjuvant chemotherapy for patients with respectable NSCLC has some potential advantages over postoperative chemotherapy.