141 INVITED

18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) staging of esophageal cancer

P.L. Jager. *Groningen University Hospital, Nuclear Medicine and Molecular Imaging, Groningen, The Netherlands*

Accurate preoperative staging of patients with cancer of the esophagus and the gastro-esophageal junction is essential to select patients who will benefit from surgery. Diagnostic imaging methods, usually employed for staging, include CT, sonography, and endoscopic ultrasonography (EUS). These methods are far from perfect, as metastatic spread may be encountered during surgery in up to 60% of patients.
Positron emission tomography (PET) using the tracer 18F-fluor-desoxyglucose (FDG) visualizes the increased glucose metabolism present in malignant tumors. FDG PET is increasingly used in clinical oncology, mostly to assist in staging, but also in lesion characterisation, tumor detection, response evaluation and determination of the prognosis. Also in esophageal cancer many studies are currently available, most of which have focussed on diagnostic accurary. In this presentation an overview will be presented on the current status of FDG PET in staging of esophageal cancer.
In T staging the added value of PET is nearly absent, as the spatial resolution of PET is insufficient for precise anatomical determination of tumor margins. Even CT has difficulty here, and currently EUS is considered the best modality for T staging. Also in N staging (locoreginal), the vicinity of the primary tumor and small size of metastases, lead to a relatively poor performance of FDG PET. Sensitivity to detect N1 disease is around 50% at a specificity of 85%. To assess locoregional metastases, EUS is the first-choice modality. The main value of FDG PET, however, is in the assessment of the M stage. Sensitivity both in detecting distant nodal (M1a) or hematogeneous (M1b) metastases is around 70%, and specificity around 95%, which is better than both CT and EUS. In contrast to N staging, M stage directly influences clinical decision making.
While many studies have focussed on diagnostic accuracy, (fewer) studies have currently reported the rate of upstaging (leading to e.g. cancellation of surgery) as a result of FDG PET to be between 3% and 20%. The large range depends partly on the quality of conventional modalities. Centralisation, expertise building, the use of multislice CT scanners are factors that increase the relative performance of conventional imaging methods. Also it has been demonstrated that the yield of FDG PET is lower in T1 and T2 tumors. Reports on the cost-effectiveness of PET are scarce and difficult to interprete. In a recent Dutch study diagnostic costs increased after inclusion of FDG PET, but the diagnostic costs are only a small fraction of total costs in these patients.
In conclusion, most centers agree that the application of FDG PET leads to improved patient care. With the new trend of combined PET-CT scanners it is expected that both the performance of PET and of CT will be further improved.

142 INVITED

The place of neoadjuvant treatment for oesophageal cancer

C. Mariette, J. Triboulet. *Centre Hospitalier Huriez, Department of Digestive and Oncological Surgery, Lille, France*

The question of which treatment approach is the most appropriate regarding oesophageal cancer is much debated. Resection is still the standard treatment for patients with localised oesophageal cancer and no medical contraindications to surgery, with resectability rates of 54 to 69%, operative mortality rates of 4 to 10% and 5-year survival rates from 15 to 24% in randomised trials. Because of the poor survival, preoperative combined modality treatment has been explored.
Comparing **preoperative radiotherapy** (RT) with immediate surgery, none of the randomised trials have shown a survival benefit for combined therapy. The results of trials exploring the addition of chemotherapy to resection are conflicting. Regarding the two large multi-institutional prospective randomised trials of **preoperative chemotherapy** (CT) vs a surgical control [1,2] only one [1] noted a significant median and 3-year survival benefit for patients who underwent CT. Consequently, we are still left with inexplicable disparate outcomes in these two trials and, therefore, the worth of preoperative CT remains questionable. If preoperative CT is beneficial for oesophageal cancer, such a benefit is small. Recognition of the need for improved local regional control, and also the fact that most patients succumb to distant disease, has prompted many investigators to explore **preoperative CRT** in an attempt to improve outcome. The only two large multi-institutional prospective randomised trials [3,4], enrolling sufficient number of patients to provide statistically meaningful results, failed to shown any survival advantage of preoperative CRT. Only one randomised study [5] showed a survival benefit with combined modality therapy, but this study has been mostly criticised. Consequently, despite the widespread use of preoperative CRT, the absence of benefit reported in phase III trials means that this approach should be considered investigational. A consistent finding in these trials is that 25% of treated patients with induction CRT have no residual tumour in samples of resected tissue after oesophagectomy.
To conclude, the management of oesophageal cancer will undoubtedly continue to evolve as improvements in technology, combined with a greater understanding of genomics and biology of tumours, better define effective therapeutic interventions and allow introduction of novel treatments into strategies for clinical management. Unfortunately, at present, we are unable to accurately point out those patients who require some kind of therapeutic intervention and those for whom particular treatments should be avoided.

References

[1] Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002; 359: 1727–33.
[2] Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998; 339: 1979–84.
[3] Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997; 337: 161–7.
[4] Burmeister B, Smithers B, Gebski V et al. A randomised phase III study comparing surgery alone with chemoradiation therapy followed by surgery for resectable carcinoma of the oesophagus: an intergroup study of the Trans-Tasman Radiation Oncology Group (TROG) and the Australian Gastro-intestinal Trials Group (AGITG). Lancet Oncol 2005 (in press).
[5] Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996; 335: 462–7.

143 Abstract not received

Thursday, 3 November 2005

Scientific Symposium

The hepatocellular carcinoma family of tumours in non-cirrhotic patients

144 INVITED

Where we are and where we go – lessons from the SIOPEL 1 and 2 international trials

P. Czauderna[1], B. Morland[2], R. Maibach[2], M. Casanova[2], M. Childs[2], D. Roebuck[2], J. Pritchard[2], J. Plaschkes[2], A. Zimmermann[2], G. Perilongo[2]. [1]*Medical University of Gdansk, Department of Padiatric surgery, Gdansk, Poland;* [2]*On behalf of SIOPEL Group*

Objectives: To collect information on: biology, patients' characteristics, outcome and prognosis of pediatric HCC family of tumors and compare it with pediatric HB and adult HCC experience.
Material: 40 HCC pts. were registered in the SIOPEL1 study (1990–1994). 31% of tumors were metastatic, 39% had extrahepatic extension/vascular invasion, 56% were multifocal. Only 31% of tumors were associated with pre-existing hepatic disease. All but 2, pts. received preop. chemotherapy (PLADO = cisplatin and doxorubicin). In SIOPEL 2 study (1994–1998) 17 pts. were analyzed. 18% tumors were metastatic, 35% had extrahepatic tumor extension/vascular invasion were found and 53% were multifocal. 13 of the 16 treated patients received intensified preop. CARBOPLATIN + PLADO chemotherapy (CHT).
Results: SIOPEL 1: Partial response to PLADO was observed in 18/37 cases (49%). Complete tumor resection was achieved in 14 patients (36%) (incl. 2 liver transplantations – LTX). Overall survival (OS) at 5 yrs was 28%, while event free survival (EFS) was 17%. FU time was 49–90 months (median 75). The following adverse prognostic factors were identified for EFS: metastases and vascular invasion. SIOPEL 2: Partial response to preop. CHT was observed in 6/13 cases (46%). Resection was achieved in 8 patients (47%) (incl.1 LTX). OS of HCC pts. in SIOPEL 2 study remained poor (22%) showing no improvement over the SIOPEL 1 despite CHT intensification.

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

146 INVITED

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

B.J. Morland. *Birmingham Children's Hospital, Department of Oncology, Birmingham, United Kingdom*

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

D. Carbone[1], P. Massion[1], T. Kikuchi[1], F. Taguchi[1], J. Amann[1], P. Chaurand[3], Y. Shyr[2]. *[1]Vanderbilt-Ingram Cancer Center, Medicine, Nashville, USA; [2]Vanderbilt-Ingram Cancer Center, Statistics, Nashville, USA; [3]Vanderbilt-Ingram Cancer Center, Biochemistry, Nashville, USA*

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

G. Giaccone. *Vrije Universiteit Amsterdam, Department of Medical Oncology, Amsterdam, The Netherlands*

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

J. Armstrong. *St. Lukes Hospital, Radiation Oncology, Dublin, Ireland*

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