lobectomy. As expected, the median survival increased to 34 months and the 5-year survival to 36%, but this is analogous as what has been achieved with concurrent chemotherapy and radiotherapy without surgery in patients with single nodal station N2 disease. Patients with small volume disease (<50 ml) may even have better survival rates with systemic treatment concurrently with radiotherapy.
Apart from emotion and "believes", there are no data to support surgery in patients with T4 and/ or N2/N3 disease over chemo-radiation.
As most patients still die of their cancer, due to both distant and local relapses, there is much room for improvement at all sites. This includes better treatment options for the old and/ or frail patient, characterisation of the tumour by fine needle biopsies, circulating tumour cells and imaging, tailoring systemic treatment and radiotherapy according to these characteristics, taking into account intra-tumour heterogeneity, including stem cells, for e.g. selective boosting of these areas, heterogeneity within organs at risk and the role of prophylactic cranial irradiation (PCI) to decrease the incidence of brain metastases.

66 INVITED

Evidence to Support Use of Planned Surgery

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There remains controversy on the role of surgical multimodality treatment for stage IIIA-N2 disease due to the lack of fully convincing randomized trials and the diversity of phase II studies. The main reason for this controversy can be explained by the fact that N2-disease is a very heterogeneous entity and compasses a broad spectrum of metastatic LN involvement. The two randomized trials failed to show a survival benefit for the surgical treated cohort. In the Intergroup trial, potentially resectable N2-disease was included. In the EORTC study, patients with irresectable N2-disease were included. In this study, induction chemotherapy did not convert unresectable disease into resectable disease as illustrated by the 50% incomplete resection rate in the surgery arm − and, not unexpectedly, did not result in better outcome compared with radiotherapy. However, in the Intergroup trial disease free survival was significantly higher in the surgical cohort and the 5-year survival was doubled (36%) compared to the radiotherapy arm when pneumonectomy could be avoided. Moreover, both trials observed substantial long- term survival in patients with mediastinal downstaging. Prediction of complete resection and downstaging seems to be essential in the setting of combined surgical multimodality. Therefore, careful baseline stage is very important. Patients with stage IIIA should be evaluated by a multidisciplinary team including an experienced thoracic surgeon in thoracic oncology. The thoracic surgeon has to assess baseline resectability. Bulky, extracapsular and/or multilevel disease are contraindicating surgical multimodality treatments. After induction treatment, restaging should be performed. Mainly patients with evidence of response in the primary tumour and LNs with benefit from surgical exploration. PET-CT and invasive mediastinal techniques are indicated. Patients should be carefully reassessed including new pulmonary function tests with diffusion capacity. (Mainly) right pneumonectomy should be avoided and the bronchial stump should be protected by viable tissue. In experienced centers, mortality after induction therapy can be as low as to 2 to 3% with very acceptable morbidity.
We believe that in experienced centers, selected patients with N2-disease may benefit from surgical multimodality treatment.
In this patient we would prove N2 disease by N2 disease. After induction chemotherapy, mediastinoscopy could be performed and histological response evaluated. IN case of downstaging to N0 or single level disease, resection by upper lobectomy would be the best option for her.

67 INVITED

Stage III-N2 Non-Small Cell Lung Cancer − Choice of Chemotherapy Schemes

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Surgical resection alone in stage IIIAN2 non-small cell lung cancer (NSCLC) is associated with poor outcome. In those patients with bulky ipsilateral mediastinal lymph nodes visible on a computed tomography imaging of the chest, only 18% complete resection has been achieved with a 9% 3-year survival despite complete surgical removal. The rationale of neoadjuvant chemotherapy lies in the eradication of micrometastatic disease, which is often present when ipsilateral mediastinal or subcarinal lymph nodes are involved. One of the earliest neoadjuvant combination chemotherapy programs was developed at MSKCC. Stage IIIA patients with clinical N2 disease were given mitomycin, vinca alkaloids and high-dose cisplatin (MVP). In a group of 136 patients, the objective major response rate to MVP chemotherapy was 77%. Overall, 65% of patients underwent complete resection; 14% had pathologic complete response at surgery. Overall, median survival was 19 months and the 3-year survival for completely resected patients was 41%. In a similar study using the same MVP chemotherapy program prior to surgery, the Toronto investigators reported a 69% response rate, a 49% complete resection rate, and a median survival of 19 months for all 35 patients included. These two studies demonstrated what appeared to be improved median survival time and prolonged 3-year survival when compared to historical controls.
Two subsequent randomized trials suggested that neoadjuvant therapy in stage IIIA disease improved survival. These trials established neoadjuvant chemotherapy followed by surgery as one reasonable means of treating stage IIIA NSCLC.
There has been some controversy about whether carboplatin can be used in neoadjuvant treatment. Based on two meta-analyses in stage IV disease, it was suggested that cisplatin should be used in fit patients with PS 0−1 who have adequate organ function. Another point for discussion was the optimal cisplatin dose to be used in the neoadjuvant setting. The Spanish Lung Cancer Group (SLCG) conducted a randomized trial to address whether higher neoadjuvant cisplatin doses result in improved survival and increased pathologic complete response. Patients with stage IIIA clinically enlarged and biopsy-proven N2 lesions were randomly assigned to receive either high-dose cisplatin (HDCP) (100 mg/m^2) or moderate-dose cisplatin (MDCP) (50 mg/m^2) in combination with ifosfamide and mitomycin. Eighty-three patients were randomized: 46 received HDCP, and 37 MDCP. Radiographic response rate was 59% for HDCP patients, and 30% for MDCP patients ($P = 0.01$). Thoracotomy was performed in 71 patients (86%), 58 of whom had resectable disease. Complete resection rate was 61% in the HDCP group, and 51% in the MDCP group ($P = 0.5$). Pathologic complete response was observed in one patient who received MDCP. Median survival in the HDCP and MDCP groups was 13, and 11 months, respectively ($P = 0.3$). Although, higher radiographic response rate was observed in patients who received HDCP, this study failed to show any significant improvement in either overall survival or pathologic complete response.
Third generation drugs have been analyzed in the neoadjuvant setting. The EORTC carried out a phase II trial in patients with stage IIIAN2 using cisplatin/gemcitabine followed by surgery or radiotherapy. Results showed that this was a well tolerated combination achieving a 70% response rate. A multicenter phase II trial evaluated neoadjuvant chemotherapy with cisplatin/docetaxel followed by surgery in 90 patients with stage IIIAN2 disease. The overall response rate was 66%. Pathologic complete response was observed in 19% of patients who underwent surgery. This phase II trial showed that cisplatin/docetaxel was effective and well tolerated in stage IIIAN2 NSCLC.
The SLCG conducted a phase II trial in patients with stage III disease analyzing a triplet combination as a neoadjuvant treatment (cisplatin/gemcitabine/docetaxel). The survival results obtained in this study were very similar to those reported with doublet combinations. Since this trial, a cisplatin doublet has remained the standard approach in the neoadjuvant setting.
In stage IV disease, randomized studies that have compared platinum-based doublets using third-generation drugs among themselves showed no differences in survival and gave no evidence for a single "standard" doublet for the treatment of metastatic NSCLC. A phase III randomized trial comparing cisplatin/pemetrexed *vs* cisplatin/gemcitabine showed no difference in outcome between the two combinations with a lower haematological toxicity profile for the pemetrexed-based regimen. A pre-planned subgroup analysis showed a survival advantage for cisplatin/pemetrexed as compared with cisplatin/gemcitabine in non-squamous histology (11.8 *vs* 10.4 months, respectively; $P = 0.005$) while a survival advantage for the gemcitabine-based combination was observed in squamous histology. These results may be translated to the neoadjuvant setting although no randomized trials focusing on these two combinations have been performed in stage III disease.
In summary, stage IIIA patients have systemic disease requiring a multimodality management approach. Different cisplatin-doublets using third generation agents have been included in the neodjuvant setting and are now the gold standard. Combined modality treatment in locally advanced NSCLC continues to evolve and is a subject of ongoing research. Improving the outcome for patients with stage IIIA NSCLC requires the close cooperation of surgeons, radiation oncologists and medical oncologists. One challenge for present research is to integrate new active agents into the neoadjuvant setting. A further aim is to use molecular biological markers to identify patients for more individualized treatment.

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Scientific Symposium (Sat, 24 Sep, 16:00−18:00)
New Insights in the Management of Renal Cancer

68 INVITED

Genetics of Clear Cell Renal Carcinoma

Abstract not received

69 INVITED

Drug Availability in England − the Health Economics and Politics of Drugs for Advanced Renal Cancer

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The National Health Service (NHS) in the UK offers free healthcare at the point of delivery. It is funded directly by taxation, has a fixed central budget and is subject to much political direction. Like all healthcare systems, the NHS cannot afford every intervention for every patient.
NICE was set up to assess value for money for the NHS so that clinically-effective and cost-effective treatments are instituted but cost-ineffective treatments do not displace more cost-effective therapies. NICE does this by estimating the incremental cost effectiveness ratio (ICER) which divides the cost of the new treatment minus that of current therapy by the health gain of the new treatment minus that of current therapy. Health gain is expressed as quality adjusted life years (QALY), this being a measure of a person's life weighted by a valuation of their health related quality of life. NICE recommends treatment to the NHS if the ICER is less than £20−30K. A positive NICE recommendation has a statutory funding directive to healthcare commissioners. NICE does not have the power to negotiate price directly with manufacturers but the cost of drugs to the NHS can be reduced by the manufacturer agreeing patient access schemes with government. NICE aims therefore to create a level playing field between drugs and diseases.
None of the renal cancer drugs appraised had ICERs below this funding threshold of £20−30K/QALY. The first renal cancer drug appraisal (sunitinib, temsirolimus, sorafenib and bevacizumab) led to a change in this cost effectiveness threshold for life-extending end of life treatments: for small patient populations in whom life expectancy is less than 2 years with robust data to indicate an extension of life of at least 3 months with a particular treatment, the cost effectiveness threshold can be raised to approximately £50K. NICE has since approved the use of sunitinib and pazopanib as first line treatments (with patient access schemes) but not the use of temsirolimus, bevacizumab, sorafenib or everolimus (despite patient access schemes). Examples of how the ICERs were calculated will be discussed.
The current UK government has announced its intention to introduce a system of value-based pricing from 2014 in which value will be assesed by NICE and a drug price set according to its cost-effectiveness. Following an election manifesto pledge in 2010 and in the interim period before 2014, the government has allocated £200m of additional funding per year for cancer drugs that have not been recommended by NICE or are for rare cancers and will therefore not be refered to NICE. Early projected information suggests that this fund will not be wholly spent in 2011−12.
In the UK there is currently a tension between rational rationing across all diseases/interventions and the politics of denying cancer drugs. The increasing rate of drug discovery and high cost of all new cancer drugs will stress this tension. The solution of value-based pricing is attractive but one that has many hurdles to overcome.

70 INVITED

New Approaches in Surgical Management of Renal Cancer

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Thanks to advances in cross-sectional imaging and liberal use for unrelated causes, most kidney cancers are diagnosed at an earlier stage when they are small and localized. We now know that preservation of renal function is crucial in long-term survival. Individuals with compromised renal function are at higher risk of cardiovascular disease, hospitalization and death. Despite the lack of prospective randomized trials, urologists have adopted nephron-sparing surgery for small kidney tumours. Today, when feasable, partial nephrectomy is the standard of care unrelated to the size of the tumour.
Minimally invasive techniques have been used for surgical treatment of kidney cancer for 2 decades, however, laparoscopic partial nephrectomy has only been popularized in the last decade. Superselective identification and ligation of the vascular supply to the tumour allows maximal parenchyma preservation with minimal morbidity. Today, even the most complicated kidney cancers can be dealt with by robotic partial nephrectomy. This technique allows precise excision of tumours in the kidney with minimal blood loss and morbidity.
Another advance in the management of small renal tumours is the emergence of ablative technologies. Radiofrequency ablation and cryoablation are now utilized either laparoscopically or percutaneously for well selected cases.
Finally, we now have a better understanding of the natural history of small kidney cancers. They grow at a small rate and usually do not metastasize untill they get larger. Since most renal cancers are observed in the elderly with multiple co-morbidities, active surveillance may be an option when the potential risks of surgical intervention is gretaer than the risk of metastatic spread.
Surgery can also be used in metastatic kidney cancer. Cytoreductive nephrectomy in metastatic kidney cancer is well established in the cytokine era and currently used with targeted agents. Metastasectomy in selected cases, and after stabilization with systemic therapy can also be curative.
Times are fast changing in management of kidney cancer. We rapidly moved from the old dogma of wide excision of localized cancer to a complete change in paradigm to preserve as much renal function as possible. Well-timed surgery with the aim of maximal renal parenchyma preservation can be curative with long term survival in majority of kidney cancer patients even in metastatic disease.