best 5 fluorouracil, with expected median overall survival of 6−8 months. Outcomes could not be more different in 2009.
The definition of surgical resection with curative intent is now the ability to preserve 25−30% of disease-free functioning liver with good vascular inflow and outflow (which accounts for 20% of patients with liver only disease). Five and 10 year overall survival after hepatectomy is 50% and 26%. We now have good evidence to show the survival benefit of ablation therapies over chemotherapy alone in non-resectable disease. Modern chemotherapy regimens combined with state-of-the- art biological therapies can achieve median survival in incurable disease approaching 3 years, and perhaps more significantly can render over 40% of patients with non-resectable liver-only disease amenable to surgery with curative intent. Five year survival for all patients with CRCLM now approaches 30%.
Such progress has only been made possible by the adoption of multi-disciplinary team working (MDT). MDTs are now mandatory by law for the treatment of cancer patients in a number of European countries and being increasingly adopted in the others.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
The management of malignant pleural mesothelioma

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Biology of mesothelioma

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Malignant pleural mesothelioma is an aggressive tumor, with a poor prognosis. Its incidence is increasing worldwide as a result of widespread exposure to asbestos, and is predicted to peak in the next 10−20 years. The results of the available therapeutic resources are poor. Surgery and radiotherapy have a limited role in highly selected patients and systemic therapy is the only potential treatment option for the majority of patients. Despite some definite activity of the novel antifolates such as pemetrexed and raltitrexed, only small steps forward were recently made possible. Pemetrexed and raltitrexed are now a recognized standard treatment. However, the results even in combination with platinating agents, are still meager, with an extension of a median survivals by only 3 months and with a median survival of approximately one year.
An improvement of the knowledge of major molecular pathways involved in malignant mesothelioma is needed in order to define proper targets for the systemic treatment of this disease. Malignant mesothelioma cells show an increased or dysregulated growth. The cells produce and respond to many autocrine growth factors, such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), platelet-derived growth factors (PDGF) A and B, transforming growth factor b (TGFb), and angiogenic factors, such as vascular endothelial growth factor (VEGF). The corresponding receptors to these growth factors activate the PI3K−Akt pathway, which has a crucial role in malignant pleural mesothelioma cell survival and contributes to the anti-apoptotic phenotype. Unfortunately, the clinical results of available target therapeutics are still modest. Several compounds are in pre-clinical evaluation, and interesting results are emerging from cell lines studies. Moreover, novel biomarkers are under evaluation as a useful predictive or prognostic tool. The tailor-made treatment derived from the biologic and genetic characterization of tissue will offer better outcomes against malignant pleural mesothelioma in the future.
The principal goals of this presentation are to summarize the current knowledge in terms of major molecular pathways involved in malignant mesothelioma and outline the therapeutic approaches in development.

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Radiotherapy

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Patients with malignant pleural mesothelioma (MPM) often present with advanced symptomatic disease in which thoracic radiotherapy (RT) plays mainly a palliative role. The evidence to support the role of radiotherapy in this disease has mainly been derived from non-randomised data with the exception of the use of prophylactic irradiation to intervention tracts. The impact of radical or palliative thoracic RT on quality of life is not well known. In vitro studies have suggested that MPM is only partially radiosensitive.
Palliative RT: is routinely offered to control symptoms such as thoracic pain and dyspnoea on the basis of small retrospective studies. However there is no randomised data demonstrating the impact of palliative RT on symptom control, quality of life or survival.
Radical RT: there is no evidence to support the use of radical thoracic RT alone in MPM. This treatment modality is generally not offered as a routine treatment as the dose delivered to the disease is limited by the dose given to the adjacent organs at risk.
Post operative RT: the role of surgery for MPM is controversial. The best-documented multimodality approach to MPM is pleuropneumonectomy, followed by chemotherapy and radiotherapy in selected patients with earlier stages of disease. Post operative radical doses to the hemithorax have been reported to be tolerable and seem to decrease the rate of local failure after extrapleural pneumonectomy although no randomised data is available on the impact of postoperative RT compared to surgery alone. Post operative hemithoracic RT without extrapleural pneumonectomy is associated with significant toxicity on the normal lung tissue. Intensity-modulated radiotherapy allows for an increase in dose to the pleural cavity and a reduction in radiation doses to organs at risk. The ESMO 2008 clinical guidelines state that 'Modern radiotherapy techniques allow for delivering high-dose radiotherapy in an attempt to improve local control after EPP'
Prophylactic irradiation to intervention tracts (PIT): according to the current literature patients who undergo chest instrumentation, may develop seeding at the site of intervention, leading to subcutaneous tumour in 10 to 50% of cases. This is believed to be reduced by the common practice of prophylactic irradiation to intervention tracts (PIT). However two of the three published randomised controlled trials do not support the use of PIT but the evidence is contentious as these trials were not adequately powered. Furthermore they did not include patients receiving systemic chemotherapy and did not always collect data on the impact of PIT and track recurrence on quality of life and symptom control. The ESMO 2008 clinical guidelines state that 'Prophylactic radiotherapy to reduce the incidence of port metastases is controversial and not routinely applied'.
In conclusion, in MPM there are unmet needs to develop more effective radiation treatments that can improve quality of life and survival. Patients should be offered inclusion in a clinical trial whenever possible.

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The role of surgery in the management of malignant pleural mesothelioma

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Surgery has a primary role in the diagnosis and staging of malignant pleural mesothelioma (MPM). Therapeutic surgery has a role in symptom control and prolongation of disease-free interval. Radical surgery is intended to remove all macroscopic disease to offer long-term survival as part of multimodality therapy.
Whilst percutaneous biopsy is often used to diagnose MPM thoracoscopy is usually required in early disease. In most cases now medical thoracoscopy is employed but surgical thoracoscopy or open pleural biopsy may be needed in equivocal cases. Staging is as important in MPM as in other cancers particularly as major surgery carries high risk. Mediastinoscopy is the basis of surgical staging and video assisted mediastinoscopy may be combined with video assisted thoracoscopy via the cervical approach to offer diagnosis, staging and pleurodesis at one step.
Symptomatic control of pleural effusion can be achieved by video assisted thoracoscopic surgery (VATS) and talc insufflation. VATS can also be used to perform parietal pleurectomy which controls effusion and retards tumour progression. In cases of entrapped lung VATS may be used to perform visceral pleurectomy to allow lung re-expansion. Dyspnoea cannot be relieved in these cases unless the lung is decorticated.
Complete macroscopic tumour clearance can be attempted in selected patients in order to achieve long-term survival. This is conventionally achieved by extrapleural pneumonectomy (EPP) with en-bloc removal of pleura, lung, pericardium and diaphragm. This operation is associated with high morbidity and an operative mortality of around 5%. There is recently renewed interest in lung-sparing radical surgery or radical pleurectomy/decortication which is best termed total pleurectomy. There is evidence that this approach is equally effective as EPP in more advanced disease and carries lower operative risk and is suitable for a wider population.
Radical surgery alone is not considered optimum treatment and a multi-modality program is preferred. Additional chemotherapy can either be given preoperatively, intraoperatively as intravcavitary therapy or postoperatively. There is debate surrounding all these 3 routes. Additional radical hemithorax irradiation can only be given after EPP and while local disease control can be increased there are potentially toxic side-effects.
As the incidence of MPM increases in Western Europe evidence for these surgical strategies is urgently needed. The paucity of high grade therapeutic evidence is being addressed in anumber of on-going surgical trials. The CRUK sponsored MARS trial has completed its feasibility study of comparing EPP vs no EPP; an EORTC trial assessing the role of post EPP hemithorax irradiation is underway and the MesoVATS trial continues in UK to assess the benefits of VATS pleurectomy/decortication.