the increase in WT might cause a bigger loss in tumor control and/or higher morbidity, with again a rise of health care costs.

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Intensity Modulated Radiation Therapy (IMRT) in lung cancer

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For patients with limited disease (LD) small cell lung cancer (SCLC), accelerated radiation therapy (40–54 Gy/3–3.5 weeks) applied simultaneously with the first or second cycle of full dose chemotherapy has lead to significant improvements in long-term survival in randomized trials[9, 5, 8]. However, a local relapse rate of 42–55% is an argument for radiation dose or dose-intensity escalation. In the randomized trials, an incidence of grade 3–4 acute esophageal toxicity of about 30% suggests that the maximum tolerated dose-intensity (MTDI) was reached for radiation. This was confirmed by Choi et al., who found that the MTDI was limited by acute esophageal toxicity at 45 Gy in 30 fractions over 19 days[2] in a phase I dose escalation trial of radiation simultaneously with chemotherapy in LD-SCLC. IMRT offers a window for dose(-intensity) escalation by its ability to generate intentionally inhomogeneous dose distributions from which i) the low-dose volume coincides with the location of the esophagus and ii) the dose intensity is consistent with the MTDI. The high-dose volume conforms to the tumour up to a dose-gradient zone at close distance from the esophagus. In locally advanced (LA) non-small cell lung cancer (NSCLC), dose escalation is limited at about 70 Gy by pulmonary toxicity when radiation only is used[7, 6, 11, 1]. Local control was less than 50% in these studies. With hyperfractionated accelerated radiotherapy or simultaneous radiochemotherapy, acute esophageal toxicity may become a second dose limiting factor[10, 12]. In planning studies, we have demonstrated that an assembly of parasagittal intensity modulated beams allowed 20–30% dose escalation (when compared to non-IMRT 3D-plans) at equitoxic levels for lung and spinal cord[3, 4]. With such promising news, why isn't IMRT investigated in dose escalation studies for LD-SCLC and LA-NSCLC? The answer lays in radiation-dose uncertainties in and around lung tissue, caused by inaccuracies of all conventional computation algorithms which are further aggravated by i) intensity variations in the beams and ii) narrow photon beam collimation. Inaccurate dose computation misguides the dose distribution optimization processes which are typical for IMRT. Monte carlo based dose computations are accurate and will allow safe introduction of IMRT for lung cancer as soon as more computer performance is widely available and the work-in-progress regarding the linear accelerator head modelling is finished

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Conformal radiotherapy of prostate cancer in clinical practice

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In three-dimensional conformal radiotherapy, the high-dose region is adapted in three dimensions to the shape of the tumor. The advantages are a reduction of acute and late side-effects. Furthermore, it is possible to raise the dose to the tumor, thereby potentially increasing tumor control rates. A prerequisite for conformal radiotherapy is a high geometrical accuracy. Geometrical uncertainties are mainly caused by deviations of the position of the tumor relative to the treatment portals. Three different sources of geometrical uncertainty can be distinguished: definition of the tumor volume, variations of the position of the tumor relative to the bony anatomy, and deviations of the set-up of the patient relative to the isocentre of the treatment.

Uncertainties in the definition of the prostate in MR and CT images were evaluated for 18 patients. The CT volumes were 40% larger than the MR volumes; the differences were mainly located at the apex and at the base of the seminal vesicles. This interscan variation was found to be larger than the interobserver variation.

The center of mass (CM) motion of prostate and seminal vesicles was studied, using repeat CT scans. The motion along the AP axis was larger than along the SI axis, while motion along the LR direction was small. The motion of the CM of the seminal vesicles was larger than the motion of the prostate. The systematic component (variation between patients) was larger than the random component (due to daily variations).

Patient setup deviations were studied using an electronic portal imaging device. Using the appropriate decision rules for setup corrections, the systematic component could be reduced substantially: the percentage of patients with a 3D systematic deviation larger than 5 mm was reduced from 30% to 1%.

The margin, necessary to account for these uncertainties amounts to 0.7 times the Standard Deviation (SD) of the total random component of the organ position variation. For the systematic component, the margin amounts to 2.0 - 2.5 times the SD of the total systematic component. Since tumor motion gives the largest contribution to the overall systematic deviation, reduction of margins can be obtained by reduction of the systematic component of tumor motion.

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Current status of Hadrontherapy with carbon ion beams

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Purpose: Heavy ions possess advantageous dose localization at depth and RBE increases with increasing LET in depth, which gives the improved ratio of the 'biologically equivalent dose' between the peak and plateau. In addition, heavy ions are specifically efficient against hypoxic cells or cells in a resistant phase, and exhibit little repair of cells irradiated in the peak. The NIRS has been evaluating the efficacy of carbon ions generated by Heavy Ion Medical Accelerator in Chiba(HIMAC) in Phase I/II trials ongoing since 1994.

Methods: As of April 2001, more than 1000 patients are enrolled in the study. Of them, 829 patients who have a minimum follow-up of 6 months are analyzed. In Phase I/II dose-escalation trials, doses were escalated by 5~10% increments to provide for patient safety and determine appropriate RBE values.

Results: In this study the patients with locally advanced tumors and those with medically inoperable tumors were mainly treated. As with the radiation related morbidity, there were 5 patients (0.6%) who developed Grade 3 late skin reactions. Two patients developed acute pneumonitis with severe dyspnea at rest. For them steroid treatment was required with significant improvement. Of the patients whose GI tract was partially or totally irradiated in the initial trials, 16 patients developed serious complications of the esophagus or bowels. Among them 2 patients died of recurrence but the remaining 14 patients are alive and free of tumor. Two year local control rates were 60~80% for head and neck tumor, 62~86% for Stage I NSCLC, 80% for liver cancer, 97% for prostate carcinoma, 50~75% for uterine cervix carcinoma, and 75% for bone/soft tissue sarcomas.

Conclusions: Carbon ion therapy has shown promise against a variety of tumors that are hard to cure with other modalities. Tumors that responded favorably to carbon ions include non-squamous cell tumors such as adenoca, adenoid cystic ca, malignant melanoma, hepatoma, and bone/soft tissue sarcoma. Locally advanced tumors, slow-growing tumors, or medically inoperable tumors are also suited for carbon ion therapy. In treatment of parallel organ tumors the overall treatment schedule was successfully shortened to 1~3 weeks or even shorter, which minimized the proliferation of tumor cells during treatment.

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Surgical treatment of metastatic disease: are the number of metastases a limit for surgical resection of lung metastases

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Surgery is a standard procedure for the treatment of lung metastases in selected patients with malignant tumors. The main selection criteria for candidates to such approach include the primary tumor type, duration of free interval between the initial tumor treatment and the lung relapse,

extra-pulmonary control of the disease, lung resection required and the number of metastases. It has been classically considered that a single metastasis with a lung resection<or = lobectomy represent the optimal candidates for surgery while other criteria for selection are often depending on modifications obtained with chemotherapy. In a retrospective analysis of 381 adult patients with surgically resected lung metastases, 230 with carcinoma and 151 with sarcoma, we observed a 5 and 10 year survival probability of 37% and 23%respectively in carcinoma, and 31% and 28% respectively in sarcoma. Death was disease related in 96% of cases in both groups. The number of metastases actually found was more frequently underestimated when there were >5 metastases. Three subgroups of patients were considered according to the number of metastases resected: 1, 2-4, and 5 or more. There were 1 metastasis in 181 cases, 2-4 in 118 cases and 5 or more in 82 cases. A wedge resection was performed in 75% of cases. The only statistically significant difference between the three subgroups was found between 1 and 2-4 metastases from carcinoma (log-rank test, p=0,02). No significant difference was observed in the other comparisons (2-4 or more metastases for carcinoma or any number of metastases for sarcoma).In a retrospective analysis of 36 patients surviving 10 years or more after resection of lung metastases in our Institute, the number of metastases was not found to have a prognostic influence These results suggest that the number of metastases is not a limit by itself to consider a surgical resection of lung metastases. Similar data have been reported in the large analysis of the International Registry of Lung Metastases where 5206 cases were included. Among 2169 patients with one metastasis, 5 and 10 year survival rates were 43% and 31% respectively with a median survival of 43 months. Results were 34% and 24% respectively with a median survival of 31 months for 1226 patients with 2 or 3 metastases. They were 27% and 19% respectively with a median survival at 27 months for 1123 patients with. 5 or more metastases. These results show that 5 or more metastases, are not a contra-indication to surgery in selected patients. Such proposal must take into account other prognostic parameters but a large tumor debulking in combination with systemic chemotherapy in order to obtain minimal residual disease might be useful before using cytotoxic agents and new targeted drugs

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Surgical treatment of colorectal liver metastases

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Refinement surgical techniques have made hepatic resection a safe and efficient procedure (morbidity <25% and mortality <5%). Mean 5-year survival is 30% and the 5-year disease-free survival rate 15%. However, only 10-15% of patients with colorectal liver metastases can undergo potentially curative liver resection.

Therefore, accurate staging is an important prerequisite in selecting patients who would benefit from surgery. Several clinicopathologic and biologic prognostic factors have been identified. The most generally accepted contraindication to liver resection is the presence of discontinuous extrahepatic spread and more than four metastases.

Recurrence of hepatic metastases after liver resection occurs in up to 60% of the cases after a median of only 9-12 months. Only 23 to 33% of these recurrent metastases appear to be reresectable resulting in an overall 3-year survival rate of 33%. Preoperative chemotherapy is a recent concept in the management of these patients. In several prospective studies adjuvant chemotherapy did not improve the prognosis of patients after liver resection and is investigated in a multicenter randomized EORTC trial (Pre-and Post-Operative Chemotherapy with Oxaliplatin 5FU/LV versus Surgery alone in Resectable Liver Metastases from Colorectal Origin- Phase III Study, 40983).

Interventional strategies (laser induced thermotherapy, cryosurgery, embolisation, ethanol injection, radiofrequency ablation) and combined modalities (surgical/interventional) are additive methods which may help to improve surgical treatment results in the future.

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In transit metastases

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Melanoma in-transit metastases, when multiple, are rarely eradicated by surgery. Isolated limb perfusion (ILP) with high dose melphalan yields around 50% CRs and 90% overal responses, whilst the best systemic treatments offer less than 5% and 35% respectively.

Cancer growth depends on angiogenesis which is promoted by angiogenic factors secreted by tumor cells. We designed an ILP protocol with double targeting: the combination of melphalan (M) to Tumour Necrosis Factor (T) and Interferon gamma (I). Melphalan induces apoptosis of melanoma cells and TNF apoptosis of angiogenic vessels. A multicentric randomized phase II showed 79% complete response with TIM-ILP and a 10% drop of CR rate with TM-ILP (NS). A comparison with matched cases from a databank confirmed that melphalan only results in 52% complete responses. Other european teams evaluated TM-ILP and found a complete response rate ranging from 60 to 70% and overall response of 80 to 90%. It was recently found that TIM or TIM-ILP is most efficient on bulky metastases which resist to melphalan alone. Therefore, ILP with TNF is indicated for bulkky disease or after recurrence post melphalan alone.

Despite the high response rates, ILPs are regional treatments and have no impact on survival with a median survival of 2.5 years. As a single high dose therapy, ILP should be considered as induction therapy. Current studies suggest that specific immunotherapy with peptides and antiangiogenic treatments could be good candidates as maintenance therapies.

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Surgical indications of metastatic bone disease

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Metastatic bone disease is nowadays a very frequent pathology. This is due both to prolonged survival of cancer patients and to elective localization to bone of metastases. Treatment of bone metastases should be more aggressive to enhance life quality of metastatic patients, but should not become an overtreatment. Therefore a new classification on bone metastases have been developed sharing patients into 4 classes. In class one patients present a single metastatic lesion and have a good general prognosis: surgical treatment should address oncological purposes as for a primary lesion, with a limb salvage surgery. In classes two (pathological fracture) and three (impending fracture) surgical treatment should lessen patient symptoms and give a good limb function. In class four, patients are referred first to radiation oncologist. Surgical treatment range from simple osteosynthesis to reinforced osteosynthesis to prosthesis reconstruction. Decision making is based on four features: the expected survival, the biomechanical importance of the involved side, the size of the lesion and the probable response to adjuvant therapy. Simple osteosynthesis is used for stabilization in diaphyseal lesions in patients with poor prognosis or in cases which have a good response to adjuvant therapy (ERT, CHT). Reinforced osteosynthesis employs acrylic cement to add strength to synthesis devices (plates, rods) and to reconstruct minor bone defects. It is indicated in small metaphyseal lesions and in diaphyseal lesion with metastatic lesions not well responding to adjuvant treatments or in patients with short life expectance (less than 1 year). When destructive lesions are located in the epiphyseal or metaphyseal segment of weight-bearing bone we prefer to resect the bone lesion and use a megaprosthesis. Patients with long life expectancy should also be treated with prosthetic reconstruction in weight-bearing bones.

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The challenge of cerebral metastasis

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The optimal management of patients with metastatic brain disease poses many difficult questions for patients, families, caregivers and society as a whole.

Issues related to quality of life as well as the cost of palliative treatment in terminal illness are valid concerns when treatment options for patients with brain metastasis are being considered. However statistical analysis and treatment costs mean little to the individual with metastatic brain tumour.

This review looks at the role of surgery in providing meaningful palliation in selected groups of patients. The ideal prognostic indicators are age less than 60 years, a Karnofsky score greater than 70%, a single metastasis in an accessible location and no systemic disease. Advances in surgery and imaging have led to minimal invasive surgery with reduced morbidity rates and decreased length of hospital stays with an effective reduction in overall costs. Surgical resection of brain metastases has routinely been followed by whole brain radiotherapy. However the increasing popularity of radiosurgery has challenged this combination. The current debate between the benefits of stereotactic radiosurgery versus surgical resection of brain metastases will be covered in this presentation.