In chapter 1 an overview is given of the developments in staging and treatment of lung cancer. In chapter 2 we describe the results of staging NSCLC with FDG-PET in patients who are considered to be candidates for surgical resection of their tumour based on conventional staging. We found that FDG-PET is superior to conventional staging in detecting mediastinal and distant metastases, but FDG-PET has also several limitations. Detection of small pulmonary nodules less than 1 cm in diameter can be difficult and especially (bronchoalveolar) adenocarcinomas may show only low uptake of FDG. False negative results of FDG-PET in mediastinal lymph node staging are mostly due to micro-metastases or to the inability of FDG-PET to differentiate the primary tumour from adjacent lymph node metastases. However, due to its high negative predictive value, a FDG-PET scan without uptake outside the primary tumour region gives the surgeon the opportunity to proceed directly to a thoracotomy, because the chance of mediastinal metastases is less than 5%. FDG can also accumulate in benign inflammatory diseases and cause false positive results. Therefore, we recommend that patients with accumulation of the tracer in the mediastinum should be further explored in order to find pathologic confirmation of malignancy. An advantage of staging with FDG-PET is the immediate screening for distant metastases. As FDG-PET identified false positive sites of metastases subsequent procedures should still be taken to confirm these pathologically. Recently, a meta-analysis already suggested that metabolic staging of the mediastinal lymph nodes might be superior to anatomical staging. Although FDG-PET is expensive, it may be cost-effective when unnecessary thoracotomies can be avoided in case of mediastinal or distant metastases. Cost-effectiveness of PET has already been suggested, but this has not been proven in clinical studies. Studies are ongoing to investigate whether implementation of FDG-PET scan can improve the results of the diagnostic work-up in NSCLC. Till now, hardly any data have been published about the potential role of FDG-PET in staging of SCLC.

In patients with locally advanced NSCLC radiotherapy has always been administered, but with rather poor results. In chapter 3 we describe that gemcitabine weekly in a dose of 300 mg/m² can be safely combined with radiotherapy in these patients. This combination may induce a small increase in radiation-induced side effects, such as radiation pneumonitis and esophagitis. Whether this radiosensitising effect of gemcitabine will also improve tumour response rates and survival in these patients should be further investigated in a randomised phase III study. Other investigators are searching for more effective, systemic chemotherapy before irradiation and whether this approach will also improve survival.

We have also investigated the mechanism of radiosensitisation by gemcitabine. In chapter 4 we describe that in vitro non-homologous end-joining in DNA repair is not necessary for the radiosensitising effects of gemcitabine. As base and nucleotide excision repair of DNA are not involved in this process, homologous recombination may be necessary for radiosensitisation. We have shown that homologous recombination product of gemcitabine is important for its radiosensitising effect.

In chapter 5 we describe that in patients with metastatic NSCLC radiotherapy is not necessary and carboplatin and gemcitabine combination is the best treatment option. Trials reported tumour response rates of 39-49% and a median survival of 14-3 months. Whether addition of cisplatin and gemcitabine is superior will be further explored in trials. Other investigators are also searching for more effective, systemic chemotherapy before irradiation. Studies have not shown that cisplatin with gemcitabine is superior to carboplatin with gemcitabine in NSCLC.

In chapter 6 we focus on previously treated patients with metastatic NSCLC. Crino published a similar study in 1999. Critics to this study were that the design was not optimal. One which had be subject to bias. Although the last study considered to be chemotherapeutic agents that docetaxel might benefit these patients. In a randomised phase III study in survival and quality of life which patient will be treated with a combination of docetaxel and gemcitabine. It is important to define as early as possible the interval between first-line and second-line chemotherapy.

The problem of drug resistance is further explored in SCLC. Patients with metastatic SCLC, who previously had shown pronounced benefit from platinum-based chemotherapy, usually have a poor prognosis. In chapter 7 we describe that in vitro testing of drugs in cell lines may predict the response in patients. Clinical studies have demonstrated a significant benefit for these patients. In chapter 8 we describe the results of randomised phase III studies in SCLC. Although the introduction of intermittent combination chemotherapy has improved the survival of patients in the last years, the median survival has not changed significantly. The reason for this is that we are still exploring the optimal sequence of drugs and the duration of chemotherapy. Studies are ongoing to investigate whether implementation of FDG-PET scan can improve the results of the diagnostic work-up in SCLC.
SUMMARY AND DISCUSSION

treatment of lung cancer based on conglomeration in detecting metastases. Detection of sputum cytology and especially negative results of sputum cytology or to adjacent lymph node status. Detection of metastases or to adjacent lymph node status can improve the probability to proceed to a positive result. If the probability to proceed to a negative result is less than 5%, the patient will not be included. In conclusion, positive results can improve the mestastatic status of malignancy. An additional test for metastases should still be unnecessary thoracentesis in the mediastinum for the detection of metastases. As a result, this study suggested that bronchoscopy can improve the sputum cytology and is not necessary thoracentesis. This effectivity of bronchoscopy can improve the sputum cytology and is not necessary thoracentesis. This effectivity of bronchoscopy can improve the sputum cytology and is not necessary thoracentesis. This effectivity of bronchoscopy can improve the sputum cytology and is not necessary thoracentesis.

DNA are not involved in repair of DNA double-strand breaks we suggest that homologous recombination may be the primary pathway involved in the radiosensitising effect of gemcitabine. We have started additional experiments in cell lines without a functional homologous recombination pathway. Till now, these results suggest that the radiosensitising effect of gemcitabine is indeed mediated by homologous recombination.

In chapter 5 we describe the activity of the combination of epirubicin and gemcitabine in patients with metastatic NSCLC. The advantages of this schedule are that hospitalisation is not necessary and that toxicity of cisplatin can be avoided. The combination of cisplatin and gemcitabine has been evaluated in NSCLC, and several phase II and phase III trials reported tumour response rates between 21 and 54% and a median survival of 8.4 to 14.3 months. Whether epirubicin combined with gemcitabine is comparable to the combination of cisplatin and gemcitabine in terms of survival, quality of life and cost effectiveness will be further evaluated in an ongoing randomised phase III study. Other investigators are also searching for schedules without cisplatin, e.g. epirubicin with paclitaxel, gemcitabine with docetaxel, and vinorelbine with gemcitabine. Till now, randomised studies have not shown that cisplatin can be omitted in the chemotherapeutic treatment of stage IV NSCLC.

In chapter 6 we found that gemcitabine as second-line treatment in patients who had been previously treated for their advanced NSCLC shows only modest activity. Recently Crino published a similar study, which showed slightly better tumour response rates and survival. Criticism to our study might especially be that there are two different patient groups: one which has been pre-treated with chemotherapy and the other with radiotherapy. Although the last group of patients showed similar results, in general they may be considered to be chemotherapy-naive and not drug-resistant. However, recent studies suggest that docetaxel might be more valuable as second-line treatment after previous chemotherapy. In a randomised phase III study the response rate was low, but a significant improvement in survival and quality of life was shown compared to best-supportive care. To define which patient will benefit from a specific type of second-line therapy in NSCLC it seems important to define as exactly as possible the previous therapy, previous response and time interval between first-line and second-line therapy as possible predictors for tumour response to second-line treatment.

The problem of drug-resistance is already known, and second-line treatment has been further explored in SCLC. We investigated a three-drug combination in patients with resistant SCLC, who progressed or relapsed shortly after first-line treatment with CDE. We previously had shown promising activity of the combination of paclitaxel and carboplatin in...
this group of patients. We tried to improve the activity of this combination by the addition of ifosfamide. As described in chapter 7 this combination increased hematological toxicity to such an extent that only a low dose of ifosfamide could be added. It is therefore not obvious that patients will benefit from this three-drug combination compared to the combination of paclitaxel and carboplatin. We decided not to investigate this combination further. We also explored the activity of single-agent gemcitabine in these patients as is described in chapter 8. Although this group of patients had been heavily pretreated some activity of gemcitabine was still found. As a combination of cytotoxic agents is more active in SCLC we have recently started a phase II trial to study the activity of the combination of gemcitabine with cisplatin in patients with resistant SCLC.

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