

them remain in CCR with a median follow-up 19,5 months (range 1 to 96 months) and 66% probability of 8-year EFS.

#### **Conclusions:**

1. In children with ALL the FTBI-12Gy-containing regimen is well tolerated without the life-threatening toxic complications.
2. FTBI-12Gy-containing regimen demonstrates very good antileukemic efficacy for HR-ALL in I CR, but only limited for ALL in II CR.
3. In context of good tolerance of FTBI in a total dose of 12 Gy and its limited antileukemic efficacy in children with ALL in II CR the escalation of FTBI total dose from 12 Gy to 13,2 Gy appears to be justified in those children. *Supported by grant KBN 4 PO5E 108 18.*

### **48. COMBINED CHEMOTHERAPY AND RADIATION IN LOCALLY ADVANCED NSCLC**

**J. Jassem**

Dept. of Oncology and Radiotherapy, Medical University of Gdansk, Poland

In locally advanced inoperable NSCLC radiotherapy has traditionally been considered the mainstay of treatment. Unfortunately, in most instances this method does not allow for eradication of bulky tumor in the thorax and does not prevent uncontrolled systemic disease. In consequence the prognosis of these patients is dismal and has remained essentially unchanged within the last decades. The five-year survival rates after irradiation varies between 3 and 10%. During the last decades several approaches have been tested to improve this outcome. Of those, particular attention has focused on combining chemotherapy and radiation. Two most frequently used strategies have included induction chemotherapy followed by radiation, or concurrent chemoradiation. The results of a few phase III trials comparing radiation alone with radiation supplemented by chemotherapy have demonstrated modest yet significant survival benefit from the combined approach. Two recent studies suggested that concomitant chemoradiation might be more effective than

chemotherapy preceding radiation. The gain from the concurrent use of both modalities should however be weighted against increased toxicity. Further studies built upon recent positive results should focus on identifying means of optimal interactions between the two modalities. This research should define the most effective types and doses of anticancer agents as well as the optimal features of radiotherapy.

### **49. ADJUVANT TREATMENT TO SURGERY: IS IT STILL A PLACE FOR RADIO-OR CHEMOTHERAPY?**

**P. van Houtte**

Institut Jules Bordet, Brussels, Belgium

The two metaanalysis conducted by the Cambridge group has cent the scene for adjuvant treatment as well as the pattern of failure analysis after surgery. In the pattern of failure analysis performed after a complete resection, local failure is a rare event for pathological stage I and II disease (less than 10 %). In opposite, for stage III, local failure remains an issue due to the wide range of tumor extent, from resectable disease to unresectable tumor. In contrast, distant metastasis is a common problem with figures ranging from 20 to 50%. A last issue is certainly the problem of second cancer induced by a long history of tobacco smoking rising the question of chemoprevention.

To prevent distant metastasis, a systemic treatment is the logical answer. The metaanalysis suggested a slight nonsignificant benefit for a sequential Cisplatin based chemotherapy. The recent American trial of Keller et al comparing postoperative radiotherapy to a combined chemo-radiotherapy approach did not showed any difference for stage III disease: the only important prognostic factor was the type of mediastinal exploration: sampling vs. radical dissection. Several trials are on going worldwide: Anita, ALPI, and IALT... The main characteristics of those trials are to include a cisplatin based chemotherapy program and a large number of patients. This implies necessary a low efficacy; a small difference is expected. Furthermore, the already published trials showed a low compliance to chemotherapy.

Is the page turned for radiotherapy in a combined approach with surgery? In view of the available randomized trials and the recent metaanalysis, a quick answer is yes. Indeed, both observed either no effect or even a detrimental impact on survival. Nevertheless, those trials were performed during the last three decades, a period of many improvements in the knowledge of the disease, in imaging procedure, in surgery and in radiotherapy. Preoperative radiotherapy may increase the resectability rate in well-selected patient: some groups are still advocating this approach for superior sulcus tumor whereas many phase II and some phase III trials are combining radiation with chemotherapy in a preoperative settings. The data available suggested a higher rate of pathological complete response but also a slight increase in morbidity. In contrast, postoperative irradiation improves the local control especially for stage III disease: this was clearly demonstrated by the Lung Cancer Study group trial, the MRC trial and the Feng trial. Furthermore, we should remember that the PORT metaanalysis suggested a differential impact according to the tumor extent: the negative impact of postoperative radiation disappeared for stage III disease (a similar observation was made by Dautzenberg et al). One possible explanation is that the therapeutic effect of postoperative radiotherapy compensated the negative impact due to a poor radiation technique (large volume, high daily dose, and cobalt machines...). Both approaches imply to use a modern radiation technique minimizing the risk of inducing severe life-threatening late effects: this is especially the case for postoperative radiotherapy due to the already loss of lung function due to the surgery and a long history of tobacco abuse. This is probably the place for a conformal radiotherapeutic approach.

The last issue concerns the management of patients after induction chemotherapy followed by surgery: the current approach is to reserve postoperative radiotherapy for incomplete resection or for persistent nodal disease. Probably, another important factor may be the presence or not of nodal capsular rupture. We are certainly lacking good data on the postresection management and outcome of those patients.

In conclusion, radiation has still its place for stage III disease in a combined approach with surgery and chemotherapy providing the use of an adequate radiation technique.

## 50. THE IMPORTANCE OF MODIFYING HYPOXIA IN RADIOTHERAPY

J. Overgarad

Dept. of Experimental Clin. Oncology, Aarhus, Denmark.

## 51. BIOLOGICAL CONCEPTS OF BREAST CANCER: IMPLICATIONS FOR THERAPY

M. Tubiana, S. Koscielny

Institut Gustave Roussy, Villejuif, France

The data from over 3000 breast cancer patients treated without adjuvant chemotherapy and followed-up for over 15 years were studied with two aims:

- 1) to analyze the relationship between tumor diameter and incidence of distant metastases during the 25 years after initial treatment. The threshold volume at which dissemination occurs can be estimated in each subset of patients and varies widely; it is inversely correlated with the histologic grade and the number of involved axillary nodes.
- 2) to investigate the impact of a residual tumor on distant dissemination. In patients with local recurrence, the incidence of distant dissemination is elevated. The analysis of the delay between the initial treatment and clinical emergence of the metastases shows that the excess of metastases corresponds to disseminations which are initiated after initial treatment and therefore originated from the residual tumor.

This conclusion was supported by the update of a controlled clinical trial comparing two adjuvant treatments: A) a chemotherapy by CMF or B) post-operative radiotherapy (RT) followed by immunotherapy with poly A - poly U. At 15 years the cumulative incidence of local recurrence and of distant metastases is significantly lower in the B group (42% metastasis-free survival in the RT group and 29% in the CT group  $p=0.03$ ). This result seems to be due mostly to lower incidence of local recurrence.