

ROLE OF ADJUVANT TREATMENT IN NON-SMALL CELL LUNG CANCER

P Van HOUTTE*

After a surgical resection for a non small cell lung cancer, there are three different problems: the locoregional control of the disease, distant metastasis including brain relapse and second primary. Pattern of failure analysis performed after a complete resection showed a low rate of local failure (less than 10%) for pathological stage I and II disease. This is no more the case for stage III disease: we must remember that this stage is a very heterogeneous group depending on the tumor extent T3 vs. T4, the type of N2 or even N3...but also the possibility to perform or not a complete resection. In contrast, distant metastasis is a common problem with figures ranging from 20 to 50% (1). A last issue is certainly the problem of second cancer induced by a long history of tobacco smoking requiring the study of a possible prevention (screening procedure, drugs...). A form of systemic treatment (chemotherapy, immunotherapy...) is the logical answer to prevent distant metastasis. The Cambridge metaanalysis suggested a slight non-significant benefit for a sequential cisplatin based chemotherapy (2). 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 (3). Sampling dissection included a removal of at least one lymph node at levels 4,7 and 10 during a right thoracotomy and at levels 5 and/or 6 and 7 during a left thoracotomy whereas a radical resection required a complete removal of all lymph nodes at those levels. Among the 222 patients with N2 disease, multiple levels of N2 were documented in 30% of patients with a complete mediastinal dissection and in 12% of patients with a systematic sampling. In this nonrandomized comparison, the mediastinal complete dissection let to a survival benefit for patients with right side lung tumors.

Several trials are on going worldwide: Anita mainly in France, ALPI in Italy, and IALT worldwide...What are the current lessons from those trials? They used usually a cisplatin or carboplatin based chemotherapy, they tried to recruit a large number of patients and there appears to be a low compliance to postoperative chemotherapy. The large number of patients implies necessary a small difference in long term survival. The main goal of adjuvant radiotherapy is to improve the local control and so perhaps to have an impact on survival. After the recent metaanalysis, is it still a place for postoperative radiotherapy? A quick overview of the randomized trials and of this metaanalysis let to a negative answer (1,4). Indeed, both observed either no effect or even a detrimental impact on survival. We should always remember the characteristics of those trials and the time frame: those trials were performed during the last three decades, a period of many improvements in imaging procedure (CT), in surgery and in radiotherapy (linear accelerators, three dimensional planning...). The data suggested an improvement in local control after postoperative radiotherapy especially for stage III disease (the Lung Cancer Study group trial, the MRC trial and the Feng trial) (5,6,7). Furthermore, in the PORT metaanalysis, there was a very interesting observation: the negative impact of postoperative radiation disappeared for stage III disease (a similar observation was made in Dautzenberg trial)(4,8). Two explanations are possible: either the patient had a too short life expectancy to develop the late effects induced by the radiation or the therapeutic effect of postoperative radiotherapy compensate for the negative impact due to a poor radiation technique (large volume, high daily doses, and cobalt equipment...). Nowadays, postoperative radiotherapy implies to use a modern and careful tailored radiation technique: the aim is certainly to minimize the risk of inducing severe life-threatening late effects particularly to the lung. The patient has already a loss of lung function due to the surgery but also to a long history of tobacco abuse. This is probably the place for a 3D conformal radiotherapeutic approach.

REFERENCES

1. Van Houtte P, Mornex F, Rocmans P. L'irradiation postopératoire des cancers bronchiques: la page est-elle tournée ? *Cancer Radioth.* 1999;3: 200-202.
2. Stewart L A, Pignon J P. (Non-small Cell Cancer Collaborative Group) Chemotherapy in non-small

* Department of Radiotherapy; Institut Jules Bordet Brussels, BELGIUM.

- cell lung cancer: a metaanalysis using updated data on individual patient from 52 randomized clinical trials. *Br Med J* 1995;311:899-909.
3. Keller S M , Adak S, Wagner H, Johnson DH. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group. *Ann Thorac Surg* 2000;70:358-365.
 4. PORT Meta-analysis Trialists Group Postoperative radiotherapy in non-small cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998; 352:257-263.
 5. Lung Cancer Study Group. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. *N Engl J Med*. 1986;315:1377-1381.
 6. Stephens R J , Girling D J, Bleeher N M, et al. The role of post-operative radiotherapy in non-small-cell-lung cancer: a multicentre randomised trial in patients with staged T1-2, N1-2, M0 disease. *Br J Cancer* 1996;74:632-639.
 7. Feng Q F, Wang M, Wang L J, et. al A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. *Int J Radiat Oncol Biol Phys* 2000;47:925-929.
 8. Dautzenberg B, Arriagada R, Chammard A R et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. *Cancer* 1999;86:265-273.