Solunum 3, Özel Sayı 2:207-209, 2001

HOW TO IMPROVE THE EFFICACY OF RADIOTHERAPY FOR INOPERABLE LUNG CANCER

P Van HOUTTE*

At the time of diagnosis, at least one third of all patients with a non small cell lung cancer are found to have inoperable disease due either to locoregional tumor extension or to medical contraindication. Radiation has been used for many years both to relieve the symptoms and to achieve a good palliation or in an attempt to cure the patients. Nevertheless, results in term of cure were often very disappointing with a very poor long term local and a dismal 5-year survival rate (less than 10%). The tumor extent (size, and nodal involvement), the host (performance status, weight loss) and the poor radiation treatment (dose, fractionation, and technique) can easily explain those results.

We should remember some basic principles of radiotherapy: the total radiation dose and the volume effect. They apply to the tumor and normal tissues. The radiation dose required for controlling a tumor increase with its size or the amount of cells present; this is a well known relation for many diseases including head and neck, cervix cancers and also lung cancers. This relation was well outlined by an already old RTOG trial conducted in the seventies. Three conventional schedules were compared: 40 Gy, 50 Gy and 60 Gy delivered in 4, 5 and 6 weeks. The 3-year survival rates were 6 % for 40 Gy and 15 % for 60 Gy (1). Nevertheless, in-field recurrence remains a very common problem: in Arriagada and Saunders trials using doses of 60 or 65 Gy, the rate of local control was less than 20%(2,3). Those figures can be easily explained through the relation between dose and tumor volume: doses of 70 Gy are required to control a tumor with a diameter of 3 cm. Most lung tumors referred to radiation oncologists are usually larger than 3cm. The impact of the tumor size was seen in many papers: in Morita series including 149 patients with stage I lung cancer, the local failure rate at 5 years rose from 38% for tumors less than 3 cm to 68% for tumors larger than 5 cm (4).

Several approaches are available to improve this poor local control but also to control the metastatic disease: increasing the physical dose (conformal 3D radiotherapy, endobronchial brachytherapy, peroperative radiotherapy…) increasing the biological dose (hyperfractionation, radiosensitizers) or combining drugs and radiation.

First, we will discuss briefly the role of fractionation. The new radiation schedules attempt to take advantage of two important observations: the differential repair process between tumor and normal tissues (several small fractions per day allows to increase the total radiation dose without increasing the risk of late effects) and the tumor repopulation. When tumor repopulation occurred, there is a loss of efficacy due to an increase in the number of clonogenic cells. To avoid this problem, the treatment should be complete before the onset of tumor repopulation; this may be achieved through an acceleration of the treatment delivering 2 to 3 fractions daily. This issue of treatment duration and repopulation is well illustrated by the randomized phase II RTOG trial evaluating different hyperfractionated schedules: the 2-year survival rate dropped from 33% to 14% if the treatment had been delayed for more than 5 days (5).

The CHART schedule (Continuous Hyperfractionated Accelerated Radiation Therapy) was a very successful way to increase the biological dose by reducing the treatment duration (3). Through this acceleration, the treatment is completed in 12 consecutive days (1.5 Gy three times a day with an interfraction interval of 6 hours, delivering a total of 54 Gy). A randomized trial including 563 patients compared this accelerated radiation to a classical radiation schedule of 60 Gy in 6 weeks. The 3-year survival rates rose from 13 % for the conventional schedule to 18% after CHART due to an improvement in local control but also by a 9% reduction of distant metastasis. For squamous cell carcinoma, the 3-year figures are even higher: 11 % vs. 21% in favor of the CHART schedule. The question is now how to integrate those approaches within a combined treatment with chemotherapy or even surgery.

There are several ways for increasing the physical dose: increasing the physical dose will allow to destroy more clonogenic cells; this is only possible if this increase in dose may be restricted to the tumor while protecting the normal tissues. Conformal radiotherapy (3D-CRT) is one approach and a very old concept: 3D-CRT is an approach aiming to match as closely as possible the tumor boundaries by taking a smaller safety margins. This is becoming possible due to the advances in imaging procedure, computed facilities and radiotherapeutic equipment. The new radiation treatment planning systems allows to obtain a three dimensional

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

(3D) representation of the volume to be treated, volumes of normal tissues (lung, heart, spinal cord) to be spared, and to know the radiation dose distribution to each of those volumes. The second problem is to deliver those tailored radiation fields: the new linear accelerators are equipped with a multileaf collimator (the field size and shape may be modified during irradiation). The last step is the irradiation itself: this implies to reproduce daily an accurate the patient repositioning under the linear accelerator: an on-line imaging system allows us to check the accuracy of the setup. It is now possible to increase safely the dose above 70 Gy or even higher. This dose escalation is often limited due to the volume of normal lung receiving low radiation doses. In Graham experience, no case of grade 3 radiation induced pneumonitis was reported when less than 20% of the lung received more than 20 Gy; the incidence rose to 36% when more than 40% of the lung received doses in excess of 20 Gy (6). Another concept has emerged over the last years: this increase in dose is only feasible by a reduction of the clinical target volume and there is no need to perform a prophylactic mediastinal irradiation. In the study of Rosenzweig et al including mainly stage III, the 2-year rates of elective nodal control was 92% but the local control was only 40% for doses around 70 Gy (7). Pet scan will play in the near future a great role in helping us to clarify and delineate our target volume both for the primary and for the possible nodal involvement. Repopulation at the level of the tumor is an important issue for squamous cell carcinoma. Increasing the duration of the treatment may lead to a loss of efficacy. One interesting approach is to combine a 3D-CRT with an hyperfractionated schedule aiming either to keep the total time constant or to even reduce it.

Endobronchial brachytherapy implies to insert a catheter through a fiberbronchoscopy and allows delivering a high radiation dose to a peribronchial tumor using an afterloading projector with a small source of high dose iridium. This treatment may be used to treat small endobronchial tumors especially in case of poor lung functions, to boost a course of external irradiation for larger tumor or to achieve a symptomatic response. In a series 64 patients with roentgenographically occult tumor, Saito observed a local control in 60 patients with a 5-year overall survival of 72% (8).

Combining drug and radiation is a very interesting approach both to try to take advantage of the drugs at the level of the primary tumor and to prevent distant metastases. Furthermore, many chemotherapeutic agents have radiosensitizing properties when they are given in close vicinity of radiation. There are several ways for combining drugs and radiation: a concurrent approach or a sequential (neoadjuvant or adjuvant)(9). Is a combined approach superior to a single modality for lung cancer? The response is yes according to the large Cambridge metaanalysis: the survival gain at 2 years was evaluated to be 4% and at 5 years 2% for a sequential schedule using a cisplatine based chemotherapy (2). This was also seen in several large randomized trials: in the French trial, the 2-year survival rose from 14 to 21% and in the CALGB trial from 13 to 26% in favor of the combined approach, this difference was even seen with longer follow-up (2,11) This benefit in survival was not due to an improvement in local control but only due to a reduction in distant metastases. The concurrent approach offers the possibility to use a possible radiosensitizing effect but there is also a risk of more acute and late toxicity. The classical study of the European Organization for Research and Treatment of Cancer compared a weekly administration of 30mg/m2 and a daily 6 mg/m2 of cisplatine delivered together with a split course radiation schedule to a radiation alone arm. There was a better 2–year survival rate for the daily administration (13 vs. 26%) due only to an improvement in local control (12). The main lesson gained from this trial is certainly that improving the local control may turn in a better long-term survival and that the metastatic disease is not the only challenge facing oncologists.

Two trials recently presented or published have compared a concurrent to a sequential approach using more aggressive chemotherapy (13,14). Both have showed better survival rates in favor of the concurrent approach. The Furuse trial used a MVP regimen (mitomycin, vindesine and cisplatin) given either before or concurrently to chest irradiation (56 Gy); the 2, 3 and 5 years survival rates were 27%, 14% and 9% for the sequential arm and 34%, 22% and 16% for the concurrent arm (14). An increase in acute toxicity, hematological and non-hematological including severe esophagitis was observed. New drugs (taxanes, gemcitabine and vinorelbine) are very potent radiosensitizing drugs and are currently under investigation

My last comments concern the quality of the radiation technique and the patient selection. Chemotherapy must not be used to compensate a suboptimal radiotherapeutic technique. Last but not least, if nowadays the data suggest a clear benefit in favor of a combined approach, this should not be used for all patients suffering from an inoperable lung cancer; patients included in those trials must have a very good performance status and underwent a complete work-

up. So, the choice of treatment for a patient must take into account the host (performance status, past history and needs): more treatment will not necessarily translate in better survival or quality of life.

REFERENCES

1. Perez CA, Stanley K, Grundy G, et al Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung. Report by the Radiation Therapy Oncology Group. Cancer 1982 ;50:1091-1099.
2. Arriagada R.,Le Chevalier T,Quoix E,et al. Effect of chemotherapy on locally advanced non-small lung carcinoma: a randomized study of 353 patients. Int J Radiat Oncol Biol Phys 1991;20:1183-1190.
3. Saunders M, Dische S, Barrett A, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer : mature data from the randomised multicentre trial. Radiother Oncol 1999; 52:137-148.
4. Morita K, Fuwa N, Suzuki Y, et al. Radical radiotherapy for medically inoperable non-small cell lung cancer in clinical stage I: a retrospective analysis of 149 patients. Radiother Oncol 1997;42: 31-36.
5. Cox J D, Pajak TF, Asbell S et al. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: Analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. Int J Radiat Oncol Biol Phys 1993;27:493-498.
6. Graham M V, Purdy J A, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment of non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1999;45:323-329.
7. Rozensweig K E, Sim S, Mychalczak B, et al. Elective nodal irradiation in the treatment of non-small cell lung cancer with three-dimensional conformal radiation therapy (3D-CRT). Int J Radiat Oncol Biol Phys 2001;50:681-685.
8. Saito M, Yokoyama A, Kurita Yet al .Treatment of roentgenographically occult endobronchial carcinoma with external beam radiotherapy and intraluminal low-dose-rate brachytherapy: a second report. Int J Radiat Oncol Biol Phys 2000;47: 673-680.
9. Mornex F, Van Houtte , Chapet O. Locally advanced non-small cell lung cancer: the role of neoadjuvant or definitive chemoradiation dans Concomitant chemoradiation : current status and future Eds Mornex F, Mazeron J J, Droz J P, Marty M.eds. Elsevier, Paris,1999;106-120.
10. Stewart L A, Pignon J P. (Non-small Cell Cancer Collaborative Group) Chemotherapy in non-small cell lung cancer: a metaanalysis using updated data on individual patient from 52 randomized clinical trials Br Med J 1995;311:899-909.
11. Dillman R O, Seagren S L, Propert K Jet. A randomized trial of induction chemotherapy plus high-dose versus radiation alone in stage III non-small cell lung cancer. N Engl J Med 1990;323: 940-945.
12. Schaake-Koning C, van den Bogaert W, Dalesio O et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer.N Engl J Med. 1992;326:524-530.
13. Komaki R, Seiferheld W, Curran W et al . Sequential vs. concurrent chemoherapy and radiation therapy for inoperable non-small cell lung cancer (NSCLC): analysis of failures in a phase III study (RTOG 9410). Int J Radiat Oncol Biol Phys 2000;48:113
14. Furuse N, Fukuoka M, Kawahara M et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non-small cell lung cancer. J Clin Oncol 1999;17: 2692-2699.