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THE COMBINED CHEMORADIOTHERAPY APPROACH FOR SMALL CELL LUNG CANCER

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The role of radiotherapy in the management of small cell lung cancer must be considered at the level of the primary tumor (chest irradiation) or to prevent a brain relapse (prophylactic cranial irradiation, PCI) as an adjuvant treatment to chemotherapy. The latter remains mandatory and is an essential part in the management of this disease. The role and impact of irradiation at both levels have been better defined during the last years due to three metaaanalysis, which have helped to clarify the results of many randomized trials. The role of chest radiotherapy was addressed by several randomized. Until the publication in the middle nineties of two metaanalysis, there were a lot of controversies due to the wide difference between the trials and the low number of patients or the wrong endpoints (median survival instead of 2 or 3-year survival). Warde analysis based on the published data showed an improvement in local control (from 65 to 40%) and a gain of 6% in 2-year survival rate (from 16 to 22%)(1). The Pignon metaanalysis was based on individual data of 2140 patients: the 3-year survival rate rose from 8.9% after chemotherapy to 14.3% for the combined approach (2). Nowadays, chest irradiation is part of the management of limited small cell lung cancer. Those two metaanalysis did not help to resolve the following questions: what is the best way of combining drugs and radiation and what is the optimal radiation schedule? Timing, dose fractionation, drugs, and concurrent or sequential are some questions.

The timing was addressed by 4 trials with conflicting data: two trials suggested better progression-free survival and overall survival when chemotherapy was given during the first cycles of chemotherapy (3,4). In contrast, the two other trials did not observed any difference or the best arm was the late delivery of chest irradiation (with the 4th cycle of chemotherapy)(4,5). The metaanalysis conducted by Murray favored an early approach (6). The problem is that the timing per se is only one of the different parameters. What is the best schedule, a sequential concurrent or an alternating approach? Two randomized trials questioned the value of an alternating approach compared either to a sequential or a concurrent. The EORTC study used 4 courses of radiation intercalated within the last 4 cycles of CDE chemotherapy (cyclophosphamide, doxorubicin and etoposide)(the alternating arm) and a sequential approach (radiation was postponed after the end of the chemotherapy)(7). Regardless of the endpoint, there was no difference except in toxicity: the alternating schedule let to an increase in acute toxicity. Lebeau trial was close prematurely due to an increase in late toxicity (lung) in the concurrent arm (15% vs. 2%) probably due to the technique of radiation (8). The concurrent approach with a cisplatine–etoposide was tested against a sequential arm in a Japanese trial: overall survival was marginally superior for the early concurrent approach (9)

For the radiation oncologist, dose, fractionation and volume are important issue. In the past, it was often believed that small cell lung cancer is very “radiosensitive” tumor responding quickly during the radiation. Nowadays, the local cure rate is certainly not as high as expected: local failure ranged between 0% and 60%. In the review of Choi and Carey, the 2.5-year local control rates rose from 16% after 30 Gy to 63% after 50 Gy (10). The dose per fraction is another issue: in cell culture, small cell lines do not present a shoulder suggesting that this is a good candidate for an accelerated hyperfractionated schedule. In Turrisi trial, an hyperfractionated schedule of 45 Gy in 30 fractions and 3 weeks yields a better survival than the classical schedule of 45 Gy with daily fraction of 1.8 Gy: the 5-year survival rates were 20% for one fraction y and 28% for two fractions per day (11). The twice-daily irradiation let to a better loco-regional control but the failure rate remains quite high (36%). Is it possible to improve those figures? Increasing the dose with an hyperfractionated schedule in a concurrent approach seems to be limited by severe acute esophagitis. New drugs may be considered as well as a better selection of patients for a more aggressive schedule: the definition of limited disease is certainly too large and should be revised.

Brain relapse is a common feature of small cell lung cancer and PCI was proposed to prevent such relapse. Many trials were conducted demonstrating a reduction in brain metastases but there were also conflicting reports on the risk of brain damage. Furthermore, there was no clear benefit in term of survival. During the last years, two large-scale randomized trials and one metaanalysis were published (12-14). The following

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observations were made: the incidence of brain metastasis without PCI increased with time and might even reached 67%; PCI reduced dramatically the rate of brain metastasis from 67 % to 40 % at 2 years. Furthermore, for patients in complete remission, PCI let to a 5.4% survival benefit at 3 years (14). With an observation period, there was no difference in brain damage between patients receiving or not PCI. Nevertheless, there are still many questions : the timing, the optimal dose, and the very late of risk damage. Another issue is certainly the possible impact of brain magnetic resonance in the staging of the patients. Chest irradiation and PCI remains an important component in the treatment of small cell lung cancer but more trials are needed to better define the optimal schedule.

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