The role of radiotherapy and the value of combined treatment in lung cancer

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Preoperative and postoperative adjuvant treatments

The two meta-analyses conducted by the Cambridge group and pattern of failure analysis have set the scene for adjuvant treatments after surgery [1,2]. In the pattern of failure analysis performed after a complete resection, local failure is a rare event (less than 10%), for pathological stage I and II disease. For stage III disease, local failure remains an issue due to the wide range of tumour extent, from resectable disease to unresectable tumour. Distant metastasis is a common problem with figures ranging from 20 to 50% [3]. Finally, there is the problem of second cancers induced by a long history of tobacco smoking raising the question of chemoprevention strategies for high-risk patients.

To prevent distant metastasis, a systemic treatment is the logical answer. The meta-analysis 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 show any difference for stage III disease: the only important prognostic factor was the type of mediastinal exploration: sampling vs. radical dissection [4]. Several trials are ongoing worldwide: Anita, ALPI, and IALT, etc., all of these trials include a cisplatin-based chemotherapy programme and a large number of patients. This implies that they are looking for a small difference. Furthermore, the published trials have shown a low compliance to postoperative chemotherapy.

Is the page turned for radiotherapy in a combined approach with surgery? In view of the available randomised trials and the recent meta-analysis, a quick answer is yes. Indeed, both observed either no effect or even a detrimental impact on survival. Nevertheless, those trials were performed over the last 30 years, a period where many improvements in the knowledge of the disease, in the imaging procedures, in surgery and in radiotherapy have been made. Preoperative radiotherapy may increase the resectability rate in selected patients: some groups are still advocating this approach for superior sulcus tumour, whereas many phase II and some phase III trials are combining radiation with chemotherapy in a preoperative setting. The data available suggested a higher rate of pathological complete responses, but also a slight increase in morbidity [5]. Large phase III trials are ongoing to test the impact of a preoperative chemoradiotherapy schedule for selected patients with stage III disease.

In contrast, postoperative irradiation improves local control especially for stage III disease: this was clearly demonstrated by the Lung Cancer Study group trial, the Medical Research Council (MRC) trial and the Feng trial [6–8]. Furthermore, we should remember that the postoperative radiotherapy (PORT) meta-analysis suggested a differential impact according to the tumour extent: the negative impact of postoperative radiation disappeared for stage III disease (a similar observation was made by Dautzenberg et al.) [1,9]. There is one possible explanation: the therapeutic effect of postoperative radiotherapy may compensate for the negative impact due to a poor radiation technique (large volume, high daily doses, and cobalt equipment ...). Both approaches imply that a modern radiation technique minimising the risk of inducing severe life-threatening late effects should be used: this is especially the case for postoperative radiotherapy due to the loss of lung function following surgery and a long history of tobacco abuse. This is probably the place for a conformal radiotherapeutic approach.

The last problem concerns the management of patients after induction chemotherapy followed by surgery: the current approach is to reserve postoperative radiotherapy in case of an incomplete resection or persistent nodal disease. Probably, another important factor may be the presence or not of a nodal capsular rupture.

Radiotherapy for 'inoperable' non-small cell lung cancer

For non-small-cell lung cancer (NSCLC), surgery remains the cornerstone for a curative treatment whenever a complete surgical resection may be performed. Nevertheless, only 20 to 30% of the patients may be considered operable after a careful staging procedure. So, at the time of diagnosis, at least one third of all patients with lung cancer are found to have inoperable disease due either to locoregional tumour extension or to medical contraindication. In this context, radiotherapy, as a locoregional treatment able to achieve local control, has a major role to play in the management of lung cancer either alone or in a combined approach.

Recently, several prognostic factors have been clearly identified that are related to the tumour (tumour extent, size and nodal involvement), the host (performance status, weight loss) and the radiation treatment (dose, fractionation and the radiation technique). Radiotherapy is based on two key principles: the total radiation dose and the volume effect. They apply both to tumour and normal tissues. The radiation dose required controlling a tumour increase with its size or the amount of cells present this relationship was well known from the 1950s for head and neck or cervical cancers. In the 1970's, the Radiation Therapy Oncology Group demonstrated the same relationship in a randomised trial comparing 40 Gy, 50 Gy and 60 Gy delivered in 4, 5 and 6 weeks with 3-year survival rates of 6% for 40 Gy and 15% for 60 Gy [10]. Nevertheless, in-field recurrences were still very common, especially if the repeated work-up included a fibrebronchoscopy: local control at one year was below 20% [11,12]. These poor results may easily be explained by the relationship between the dose delivered and the tumour volume: doses of 70 Gy are required to control a tumour with a diameter of 3 cm, but most lung tumours referred to the radiation oncologist usually have a diameter greater than 3 cm. The role of tumour size for NSCLC was well illustrated by several observations: in the series of Morita including 149 patients with stage I lung cancer, the risk of local failure at 5 years was 38% for tumours less than 3 cm and rose to 68% for tumours larger than 5 cm [13].

The use of higher radiation doses represents a challenge due to the limited tolerance of several vital normal tissues: the remaining lung, the heart, and the spinal cord. Several approaches are available to improve this poor local control, and also to control the metastatic disease: increasing the physical dose (conformal 3-dimensional (3D) radiotherapy, endobronchial brachytherapy, peroperative radiotherapy ...) increasing the biological dose (hyperfractionation, radiosensitisers) or combining drugs and radiation.

Conformal radiotherapy (3D-CRT)

This is very old concept: according to the basic principles of radiotherapy, increasing the physical dose will allow the destruction of more clonogenic cells. However, this is only possible if this increase in dose is restricted to the tumour, while protecting the normal tissues. 3D-CRT is an approach fulfilling these criteria and interest has been renewed in this technique following the advances made in the imaging procedure, computed facilities and radiotherapeutic equipment. The development of powerful radiation treatment planning systems allows a three dimensional (3D) representation to be obtained of the volume to be treated, and volumes of normal tissues to be spared, and enables the radiation dose distribution to each of these volumes to be calculated.

Furthermore, it is necessary to use a linear accelerator equipped with multileaf collimator making it possible to modify the field size and shape during the rotation and/or irradiation, in order to be able to achieve an accurate patient repositioning using immobilisation devices and to check the accuracy of the treatment set-up using an on-line imaging system. The phase I/II studies showed the great potential of this technology where normal tissues were increasingly spared radiation damage, especially the lungs and heart: the radiation dose delivered to the target volume could be increased to 70, 90 and even 100 Gy, while keeping the dose to the normal tissues within the accepted tolerance dose levels. The main limiting factor of thoracic irradiation is often the volume of normal lung irradiated even for low radiation doses: in the 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 [14]. Thus, this requires reducing the margins, to avoid an elective nodal irradiation and taking into account displacements due to the patient breathing. The latter may be avoided by selectively performing the irradiation during a specific phase of the respiratory cycle; this is the so-called gating technique (it obviously requires patient collaboration).

Pattern of failure analyses have clearly outlined the low risk of nodal failure: in the study of Rosenzweig et al. including mainly stage III patients, the 2-year rate of elective nodal control was 92%, but the

local control was only 40% for doses around 70 Gy. Only 8 patients out of 132 had a failure in an area of the mediastinum that was not irradiated [15].

Positron emission tomography (PET) scan is becoming a very useful technique to help us to clarify and delineate our target volume both for the primary tumour especially in case of atelectasia and for cases with nodal involvement. An increase in the total dose using a conventional radiation schedule will also prolong the duration of treatment. If re-population is an important issue, then this increase in total time will reduce the efficacy of the extra dose delivered. One very interesting approach is to combine a 3D-CRT with hyperfractionated schedule aimed at either keeping the total time constant or even reducing it. In a phase II trial, Sibley et al. showed the feasibility of delivering two fractions per day of 1.6 Gy to a total of 80 Gy. The total treatment time was 5 weeks [16]. Nowadays, several teams are exploring the possibility to use even higher total radiation doses and/or to integrate this 3D-CRT with chemotherapy.

Endobronchial brachytherapy

This technique allows the insertion of a catheter through a fibrebronchoscopy to deliver a high radiation dose to a peribronchial tumour using an afterloading projector with a small high dose iridium source. This treatment is performed on an outpatient basis. It may be used to treat small endobronchial tumours, especially patients with poor lung function, to boost a course of external irradiation for larger tumours or to achieve a symptomatic response. For a treatment with curative intent, we should mainly consider those patients with small endobronchial lesions: Saito et al. combined an external irradiation course of 40 Gy with an endobronchial brachytherapy insertion delivering 25 Gy. In a series 64 patients with roentgenographically occult tumours, local control was achieved in 60 patients with a 5-year overall survival rate of 72% [17]. As an exclusive treatment modality for small inoperable lung tumours, Marsiglia achieved local control at 2 years in 29 out of 34 patients and Hennequin in 44 out of 73 patients [18,19].

Fractionation

The new radiation schedules attempt to take advantage of two important observations. The differential repair process between tumour and normal tissues (the late effects are directly related to the fraction size and the use of several small fractions per day allows an increase in the total radiation dose without increasing the risk of late effects), and the problem of tumour re-population (the onset of tumour repopulation will lead to a loss of efficacy due to an increase in clonogenic cells and implies that the treatment duration should be reduced). This mechanism of re-population was well illustrated by the negative impact on survival due to a prolongation of the radiation treatment by a few days, in the Radiation Therapy Oncology Group (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 [20].

The best illustration of a success story is certainly the CHART schedule: Continuous Hyperfractionated Accelerated Radiation Therapy [11]. Through this acceleration, the treatment is completed in 12 consecutive days (1.5 Gy three times a day with a minimal interfraction interval of 6 hours, delivering a total of 54 Gy). A randomised trial including 563 patients compared this accelerated radiation to a classical radiation schedule of 60 Gy in 6 weeks. The 2-, 3-, 4- and 5-year survival rates were respectively 21, 13, 8 and 7% after a conventional radiation schedule and 30, 18, 14 and 12% after CHART [11]. This difference was even more marked for squamous cell carcinoma with 3- and 5-year figures of 21% and 15% for CHART and 11% and 7% for the control arm. These differences were highly significant and were due to an improvement in local control, but also to a 9% reduction of distant metastasis. The acute morbidity, mainly dysphagia, was slightly more pronounced in the CHART-treated cases: moderate or severe dysphagia were seen in 49% of the CHART patients compared with 19% after 60 Gy in 6 weeks. At two years, 7% and 5% were considered to have dysphagia related to radiotherapy in the CHART and conventional arms, respectively. No difference was seen between the two arms in late morbidity. This CHART trial has confirmed the relevance of the radiobiological observations, but also the impact of an improved local control on survival. The question now is how to integrate these approaches within a combined treatment with chemotherapy or even surgery.

Drugs and radiation

When combining drugs and radiation, we may pursue several aims depending on the type of drug and sequence used. Drugs may be used as a radiosensitising agent often at very low doses, which are non cytotoxic, or at higher doses, which may then be cytotoxic. The respective dose of the therapeutic agents should be limited to overcome their combined

toxicities. This is particularly true for a concurrent approach when both modalities are delivered during the same time interval. In contrast, a sequential approach allows the avoidance of additive simultaneous toxicities and is the most common way used to combine drugs and radiation until recent years.

Do we know that a combined approach is superior to a single modality for lung cancer? Chemoradiation administered in a sequential way was found to be superior to radiotherapy alone in the large Cambridge meta-analysis: the survival gain at 2 years was evaluated to be 4% and 2% at 5 years [2]. Furthermore, patients achieving an objective response after induction chemotherapy with cisplatin, ifosfamide and mitomycin C were randomised between 3 additional cycles of chemotherapy or chest irradiation. The 2-year survival rates were 18% for the chemotherapy alone and 22% for the combined approach, whereas the 2-year local control rates were 24% and 57%, respectively [21]. Thus, patients with good performance status may be treated with a combined approach. The next question is to define the best schedule: induction or concurrent approach, the search for a radiosensitisation or a cytotoxic effect.

The induction approach

Several trials have clearly demonstrated the benefit of using a cisplatin-based chemotherapy before a radiation course. This has clearly led to better long-term survival. In the French trial, the 2-year survival rose from 14 to 21% and in the Cancer and Leukaemia Group B (CALGB) trial from 13 to 26% in favour of the combined approach, this difference was even seen with a longer follow-up [12,22]. In the 1980's, it was believed that induction chemotherapy might improve the efficacy of chest irradiation due to the tumour response to the drugs leading to a better oxygenation and/or less clonogenic cells. Nevertheless, the careful pattern analysis conducted in the French trial have clearly showed that the survival benefit from this sequential approach was due to a reduction in distant metastases without any difference in the local control of the tumour [12].

The concurrent approach

The radiosensitising effect was mainly evaluated for cisplatin and carboplatin with varying results. The classical study of the European Organization for Research and Treatment of Cancer (EORTC) compared a weekly administration of 30 mg/m^2 and a daily 6 mg/m^2 of cisplatin delivered together with a split-course radiation schedule with a radiation alone arm. There was a better 2-year survival rate for the daily administration (13 vs. 26%) due only to a better local control [23]. The main lesson gained from this trial is certainly that improving the local control may result in a better long-term survival and that metastatic disease is not the only challenge facing the oncologist. Other trials with cisplatin or carboplatin using different schedules have yielded different results.

More aggressive chemotherapy aimed at achieving a cytotoxic effect was used in phase II and III trials: most regimens used a cisplatin-based chemotherapy. Unfortunately, where the 2-year survival rates appeared to yield promising results, acute severe oesophagitis was becoming a limiting factor, besides the classical haematological problems [5]. Two trials recently presented or published have compared a concurrent to a sequential approach [24,25]. Both have showed better survival rates in favour of the concurrent approach. The Furuse trial used a MVP regimen (mitomycin C, vindesine and cisplatin) given either before or concurrently to chest irradiation (56 Gy); the 2, 3 and 5 year survival rates were 27%, 14% and 9% for the sequential arm and 34%, 22% and 16% for the concurrent arm [25]. There was also an increase in acute toxicity, haematological and non-haematological including severe oesophagitis. The latter will become an even more limiting factor for accelerated hyperfractionated schedules. We should notice that the trial of Furuse used a suboptimal radiation schedule with a break in the middle.

New drugs (taxanes, gemcitabine and vinorelbine) are very potent radiosensitising drugs. These drugs have been evaluated in phase II trials with cisplatin or carboplatin: tolerance, response and survival were equivalent for the three drugs with an encouraging median survival of 17 months. The haematological and oesophageal toxicities were manageable if adequate dose reductions were used with the concurrent radiation: in the phase II CALGB trial, the dosage of the drugs was reduced by 2-fold during the chest irradiation [26]. Those schedules are still under investigation.

A last important point is that chemotherapy must not be used to compensate a suboptimal radiotherapeutic technique: to take full advantage of the chemotherapy, it is mandatory to integrate a modern radiation technique including 3D conformal radiotherapy. This will enhance the therapeutic index and so the probability of curing the patient. Last, but not least, if there is a clear benefit in favour of a combined approach, this should not be extended to all inoperable lung cancer patients: the patients included in these trials often have a very good performance status and underwent a complete work-up. The treat-

ment design should take into account the patient status and needs: more treatment will not necessarily translate in a better survival or quality of life.

The combined approach for small cell lung cancer (SCLC)

A rapid proliferation rate and an early metastatic spread explain the poor results achieved in the past for this pathological entity by local treatments such as radiation or surgery and highlight the necessity for a form of systemic treatment. Nowadays, radiation may be added to chemotherapy either to control the chest disease or to prevent brain metastases.

Chest irradiation

The goal of chest irradiation is to prevent a local relapse, to improve the disease-free interval and, ultimately, to improve survival. This issue for limited disease was already addressed by Salazar and Create in 1980 through a large review of published data: the locoregional relapse rates were 82% after multiagent chemotherapy, 33% after radiation alone and 28% after the combined approach [27]. Many randomised trials have addressed the role of chest irradiation, but this question was only solved after the publication of two meta-analyses: in Warde's meta-analysis based on published data, the local relapse rate dropped from 65 to 40% after a chest irradiation leading to a 6% benefit in the 2-year survival rate (from 16 to 22%) [28]. In the Pignon meta-analysis 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, but there was increased toxicity [29]. Chest irradiation is a partner in the management of limited SCLC, but several issues must still be clarified including drugs, timing, schedule, radiation dose and fractionation.

Cisplatin and etoposide have become a widely accepted standard chemotherapy for limited SCLC because they can be easily administered with concurrent thoracic irradiation. Furthermore, these drugs are known experimentally to enhance the radiation effect on several tumour models, but not on normal lungs. However, cisplatin is well known to increase the oesophageal toxicity of thoracic irradiation: grade 3 oesophagitis is often a limiting factor especially when cisplatin is combined with an accelerated radiation schedule. In Turrisi's trial, combining cisplatin and etoposide with 45 Gy delivered in 3 weeks with two fractions per day, one patient out of 3 experienced a grade 3 oesophagitis [30]. The optimal way of delivering the drugs (one injection, continuous administration, type of drugs ...) is still not known.

The question of the timing was addressed by 4 trials with conflicting data. In the National Cancer Institute (NCI)-Canada trial, patients received 3 cycles of chemotherapy (alternating cyclophosphamide, doxorubicin, vincristine (CAV) and cisplatin (CDDP)-VP16) combined with 40 Gy given concurrently either with the first cycle (early radiation, week 3), or with the last cycle of chemotherapy (late radiation, week 15) [31]. There was a significantly higher progression-free survival and overall survival with an early radiation. In contrast, in the CALGB trial, chest irradiation (50 Gy in 6 weeks) was delivered either with the 1st or 4th cycle of a CAP chemotherapy (cyclophosphamide, doxorubicin, cisplatin). With a 5-year follow-up, the best arm was when chemotherapy was delayed to the fourth cycle of chemotherapy. The drug dosage was reduced in the early radiotherapy arm [32]. In the Murray meta-analysis, chest radiotherapy was more efficient when it was delivered during the first cycles of chemotherapy [33].

Another problem is to define the optimal schedule for administering the drugs and the radiation: sequential, concurrent or alternating. The later was tested in two randomised trials: in the EORTC study, the alternating schedule used 4 courses of radiation intercalated within the last 4 cycles of CDE chemotherapy (cyclophosphamide, doxorubicin and etoposide) and was compared with a sequential approach (radiation was delivered at the end of the chemotherapy): there was no difference in response or survival, but the alternating schedule had more acute toxicity [34]. Lebeau et al. compared a concurrent schedule to an alternating programme: the study was closed due to a high number of late lung toxicities seen in the concurrent approach (15% vs. 2%) [35]. In this study, survival figures were quite low in contrast to many published series (the 2-year survival rates were around 12%): this raised the issue of which radiation technique should be used. A Japanese trial compared chest radiation delivered together with the first cycle of chemotherapy (cisplatin-etoposide) or after the fourth cycle (sequential approach): overall survival was marginally superior for the early concurrent approach [36].

Local failure remains a major issue in many trials: figures as high as 60% have been reported even in modern series. Is there a known dose response relationship for SCLC? 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 [37]. Only one trial has addressed the question of the total radiation

dose: in the NCI Canada trial, responding patients to chemotherapy were randomised to receive 25 Gy in 10 fractions or 37.5 Gy in 15 fractions. The incidence of local progression at 2 years decreased from 80% after 25 Gy to 69% for the higher radiation dose of 37.5 Gy, both very poor figures [38].

The radiobiological characteristics of SCLC suggest that an accelerated hyperfractionated schedule (more than one fraction is delivered each day) may be quite useful to overcome the issue of re-population and the different repair capacity. The intergroup trial compared a daily schedule with 1.8 Gy to a total of 45 Gy to a twice daily schedule, (2 fractions of 1.5 Gy were delivered each day for 3 weeks for a total of 45 Gy) [30]. Cisplatin and etoposide were delivered concurrently. The acute toxicity was higher with the two fractions per day especially acute oesophagitis, however, there was a clear survival benefit: the 2, 3 and 5 year survival rates were 40.8%, 26.7% and 20%, respectively for one fraction per day and 46.6%, 31% and 28% for two fractions per day. The twice daily irradiation led to a better loco-regional control, but the local failure rate remained quite high (36%).

There are several roads to be explored in an attempt to achieve either better local control and survival, better radiation programme (higher physical or biological dose using the modern facilities of 3D conformal radiotherapy), new drugs (taxanes and topoisomerase inhibitors are under investigation) or better patient selection. Limited disease is a very poor definition introduced in the early 1970's and referred in fact to the volume of tumour, which could be included in one field of irradiation: at that time, the equipment enabled us to treat only limited fields. This definition has evolved over the years to include all tumours limited to the ipsilateral lung, mediastinum and supraclavicular fossa. This volume of irradiation is certainly too large to allow more aggressive treatment and many authors are in fact selecting a subgroup of patients for a concurrent approach with an accelerated radiation schedule.

Prophylactic brain irradiation (PCI)

In the early 1970's, it was considered that cytotoxic drugs did not pass the blood brain barrier; the brain was considered as a sanctuary site and following the experience with acute leukaemia, PCI was proposed to prevent brain metastases. Many randomised trials were conducted leading to a lot of controversies: PCI did decrease the rate of brain metastases, but the major concerns were the absence of a clear survival benefit and the observation of severe neurological toxicities (leucoencephalopathy and abnormalities in the computed tomography (CT) scan). During recent years, the role and risk of PCI have been partially clarified by two large scale randomised trials and one meta-analysis [39–41]. They allowed the following comments:

(1) The incidence of brain metastases without PCI increased with time and may even reach 67%
(2) PCI reduced dramatically the rate of brain metastases from 67% to 40% at 2 years
(3) The absence of significant neurological damage evaluated with CT or neuropsychological tests with a 2-year observation period;
(4) Many patients with SCLC presented neurological impairment before treatment
(5) For patients in complete remission, PCI led to a 5.4% survival benefit at 3 years.

Improving survival implies that brain metastasis is the only site of progression. So, this figure of a 5% survival benefit is in close agreement with the Ball data: brain was the only site of progression in 46 patients out of 675 patients (7%) [42]. Several questions are still unresolved: the optimal timing, the total doses and the possible very late damage (at 5 years). The data from the meta-analysis and the Gregor trial suggested that an early administration and higher radiation dose yielded better results [40, 41]. This question of the total dose is addressed by an ongoing European trial.

Radiotherapy and palliation

The aim of palliative radiotherapy is the relief of symptoms with minimal discomfort to the patient. Quality of life is the only goal. Some symptoms may be due to the primary tumour (major airways obstruction, haemoptysis, superior vena cava obstruction), to major locoregional tumour extension (chest pain, bone involvement, spinal cord compression) and to metastatic disease (brain, bone, liver, abdomen ...). Radiation treatment provides effective palliation in two thirds of all patients: this may be achieved with radiation schedules using a few fractions [43]. As an example, effective palliation of bone metastases may be achieved with one single fraction of 8 Gy [44].

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