



## The challenge of local control for non-small cell lung cancer: is it a key issue?

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### Summary

Lung cancer remains a major challenge for radiation oncologists requiring a better treatment modality to overcome the high rate of local failures. Several trials have clearly demonstrated that a better local control is associated with a better survival. Those include combined approaches with chemotherapy, altered fractionation schedules and the new issue of dose escalation, which is now available due to the technical progress and will be discussed in detail.

**Key words:** lung cancer, radiotherapy.

## Efektywność miejscowa leczenia jako wyzwanie w raku niedrobnokomórkowym płuca: czy jest to kluczowy problem?

### Streszczenie

Rak płuc stanowi w dalszym ciągu wyzwanie dla radioterapeutów, wymagając lepszego dostosowania leczenia celem zmniejszenia wysokiego odsetka miejscowych niepowodzeń. Wiele prób jasno wykazało, że lepszy miejscowy rodzaj leczenia wiąże się z lepszymi wskaźnikami przeżycia. Ten rodzaj leczenia polega na łączeniu chemioterapii, zmienionych schematów frakcjonowania dawek oraz na nowej technice podwyższania dawki. Wszystkie te metody, które zostaną dalej szczegółowo omówione w niniejszej pracy zawdzięczać należy postępowi nauki.

**Słowa kluczowe:** rak płuca, radioterapia.

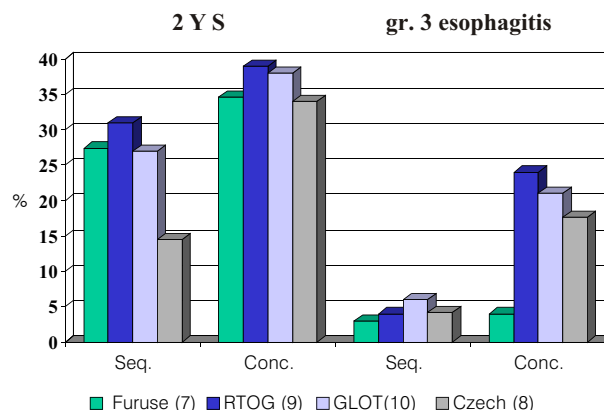
Lung cancer remains a major problem for medical community. Surgery remains the cornerstone of cure for early lung cancer. However only less than one third of patients qualify for surgical resection, usually with stage I to IIIa of the disease. Indeed, patients with a more extensive but still localized disease within the chest (some cases of stage IIIa and mainly stage IIIb) and those unfit for surgical resection due to medical contraindication were often in the past treated with radiation aimed either at a cure or more often at palliation. The results even in the best series were quite dismal with 5-year survival rates below 10%. Even in stage I disease, results were not very successful, and many local failures were recorded: in a series of 123 patients treated in several west European centres, the 5 year local failure rates were 42% for T1 and 82% for T2 tumours [1]. There are

several reasons for these poor results, such as a suboptimal radiation technique, an inadequate total dose, or poor staging procedure. Indeed, there is a well known relationship between the tumour size and the dose required to achieve local control. In head and neck cancers, doses in excess of 65 Gy are used to cure tumours of 3 cm in diameter, whereas in most series, lung cancer patients were usually treated with doses below 65 Gy. Furthermore, patients referred to the radiation oncologist were found to have quite large tumours e.g. in the series of Gouders et al., T2N0 their tumours varied from 3 to 10 cm, pointing out the weakness of the current TNM classification. Several approaches are under investigation to improve local control (a prerequisite for cure) and to reduce metastatic dissemination.

The first question is to see if a better loco regional treatment may lead to a better overall survival. Two old trials conducted by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) were able to demonstrate, within the frame work of a randomised trial, that some improvement in local control may translate into an overall survival benefit [2,3]. The former trial evaluated three different doses of 40, 50 and 60 Gy delivered with 2 Gy daily fractions. The local failure dropped from 58 % after 40 Gy to 35% after 60 Gy, whereas 3-year survival rates rose from 6% for 40 Gy to 15% after 60 Gy (2). The EORTC trial in a three-arm study comparing, a split course radiation schedule without or with weekly or daily cisplatin yielded similar results. The better survival observed with the two combined approaches was only due to a better loco regional control: the daily arm of cisplatin (6mg/m<sup>2</sup>) yielded a 2 year survival rate of 26% compared to 13% for radiation alone [3].

There are several ways to improve local control: combined treatments with chemotherapy and radiotherapy, altered radiation schedules and escalating the total dose. First, in the eighties, it was strongly believed that the best way of combining drugs and radiation was to start with drugs: among the theoretical advantages, induction chemotherapy may also improve the results of chest irradiation due to a better oxygenation of the tumour or to a possible protection of normal tissue in case of response. Indeed, the Dillman trial observed some improvement in long-term survival after two cycles of cisplatin and vinblastine followed by chest irradiation (60 Gy with daily 2 Gy fractions) [4]. Later, two large trials conducted in France, and that by the RTOG confirmed this result [5,6]. Nevertheless, the survival benefit was mainly due to a reduction in distant metastases and rather than to better loco regional control: in the well designed French trial, the local control rate at one year in the two arms was also below 20% [5].

A concurrent approach has become more popular over the last decade. The main concern is certainly the increase in acute haematological and non-haematological toxicity, especially esophagitis when combining radiation with cisplatin. Several trials have been published or presented during meetings. The Furuse, RTOG, GLOT and Czech trials yielded very similar results in favour of a concurrent approach in contrast to the induction approach. The 2 year survival rates rose to 35% for the concurrent arm and to less than 30% for the induction arm, but there is a price to pay with an increase in grade 3 esophagitis (Figure 1) [7-10]. In the only fully published trial, Furuse reported a lower incidence of local relapse for the concurrent approach: 50 out of 156 patients versus 65 out of 158 for the induction arm [7]. Nevertheless, we are still waiting for the publication of those different trials, as well as for a longer period of observation. There are also many unsolved questions: the best sequence (induction followed by a concurrent approach or,



**Figure 1.** Results of randomised trials comparing sequential radio-chemotherapy versus concurrent chemo radiotherapy: 2 Y survival rates and grade 3 or more esophagitis.

a concurrent approach followed by an adjuvant schedule), the place of maintenance chemotherapy, the drugs to be associated with cisplatin or carboplatin, the drug administration (single or multiple administration), and, of course, the radiation technique itself. Incidentally, all those trials used radiation doses below 70 Gy and, in the Furuse trial, patients were treated with a split course schedule delivering 56 Gy, which explained the low rate of severe esophagitis.

In an attempt to improve radiation efficacy, classical or accelerated hyperfractionated schedules have been developed to increase the biological dose and to overcome the problem of repopulation. The well-known CHART schedule (54 Gy delivered with 3 daily fractions of 1.5 Gy over 12 consecutive days including the weekend) was clearly superior to 60 Gy in 6 weeks with daily 2 Gy per fraction; the survival benefit was due to the improvement in local control especially for squamous cell carcinoma [11]. The 3-year survival rate rose from 11 to 21% in favour of the CHART, while the free local tumour progression survival rates at 3 years were 9% after 60 Gy and 17% after the CHART schedule respectively. What was interesting to note was the impact of this better local control on the rate of distant metastases: the CHART yields a 9% reduction in distant metastases at 3 years. Two other trials have compared a hyperfractionated schedule either conventional or accelerated to a conventional radiation schedule without showing a significant difference, however in both studies, the experimental arm yielded a better survival. In the RTOG trial, 69.6 Gy delivered with two daily fractions of 1.2 Gy yielded 2 and 3 year survival rates of 24 and 13% compared to 19 and 6% for the daily 2 Gy schedule [6]. The HART schedule of the ECOG delivered a dose of 57.6 Gy with 3 daily fractions over 2.5 weeks without a treatment during the weekends [12]. In this trial, patients had an induction chemotherapy with carboplatin and taxol and were randomised between the HART and 64 Gy in daily 2 Gy fractions. The 2 and 3-year survival rates were 44 and 23% for the HART and 30 and 14% for the conventional schedule

respectively. Most probably, both trials did not include a sufficient number of patients to demonstrate a small but an important benefit (the HART trial included only 112 patients and the RTOG 301 patients in the two radiation arms).

There is clear evidence of a direct relationship between dose and tumour control: increasing the total dose results in a better local control and survival. In the already old trial of the RTOG conducted in the seventies, the failure rate within the irradiated volume decreased from 58% after 40 Gy to 35% after 60 Gy when the total dose increased from 40 to 60 Gy [2]. There is another important basic principle of radiotherapy: the relation between the total dose and the volume effect. This applies both to the tumour and to normal tissue. The radiation dose necessary to control a tumour increases with its size, volume or the amount of cells present. In the Morita series including 149 patients treated for a stage I NSCLC with doses between 60 and 65 Gy, the local failure rate at 5 years was 38% for tumours smaller than 3 cm and 68% for tumours larger than 5 cm [13]. In the series of Bradley including 207 patients, the gross tumour volume was the most predictive variable for overall and cause specific survival in a multivariate analysis [14]. In a large series of patients included in phase III trials including stage I to IIIb, the in-field local control was below 20% after doses of 60 to 65 Gy delivered with daily 2 Gy fractions [5, 11]. Consequently, dose escalation is a very appealing approach to improve local control and survival for NSCLC. Nevertheless, in the past, dose escalation was mainly limited by the radiation-induced toxicity especially at the level of the lungs. This was well illustrated by large randomised phase II RTOG trial escalating the total dose with two daily fractions of 1.2 Gy. The optimal total dose was 69.6 Gy whereas a higher radiation dose (to 79.2 Gy) yielded lower survival rates [15]. This dose escalation is now possible due to technical advances in imaging (CT, PET), treatment planning (3D reconstruction) and delivery of irradiation by linear accelerators (multileaf collimator, portal imaging). This has led to the introduction in daily practice of 3D conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT). Studies have clearly demonstrated the feasibility of this approach and outlined some of the key problems.

There are several special issues to be discussed with the new approaches. The tolerance of a normal tissue, especially the lungs or the oesophagus in the case of a concurrent chemo radiotherapy schedule, is certainly one of the limiting factors. 3D-CRT have helped to clarify the tolerance of the lungs and the amount of normal lung volume which can be safely irradiated: in the experience of Graham et al., no case of grade 3 pneumonitis was seen when less than 25% of the lung received more than 20 Gy; this rate rose to 23% when this volume was greater than 40% [16]. Trials of dose escalation were based on the tolerance of normal tissues, and patients were stratified according to the volume of the normal lung receiving doses in excess

of 20 Gy. For small volumes, doses of 90 Gy or more were safely delivered but this was certainly not the case for larger volumes: in the RTOG trial, they reached 77 Gy when the V20 varied between 25 and 37% [17]. This is certainly the greatest paradigm of dose escalation: higher radiation doses are certainly more important for larger tumours but the tolerance of normal tissues which is partially volume related does not allow such escalation. Margins are usually added to take into account tumour movements due to the breathing. Different techniques are developed to limit those margins: breathing holding devices (the radiation is only performed when the patient keeps to a predefined measured deep inspiration), gating techniques (the irradiation is only performed during a predetermined part of the respiratory cycle while the patient is free breathing) and the tracking system (the radiation beam follows the tumour displacement during the breathing cycle).

In the past, elective nodal irradiation (ENI) was common practice to follow the classical philosophy of radiation oncology to cover the area at risk for nodal dissemination. This was also based on the observation of a very low rate of failure within a prophylactic irradiated nodal area. It was also a time when the imaging modalities were certainly not as effective as they are today. In a recent review of more than 1000 patients included in different RTOG protocols, only an inadequate coverage of the ipsilateral hilum had a significant negative impact; this was not observed for the mediastinum, the supraclavicular areas or the contralateral hilum [18]. This is in contrast with a prior analysis performed on a limited number of patients [19]. Furthermore, several authors have reported a very low rate of failure within a nodal area not irradiated regardless of the tumour stage: Senan reported 12 in-field failures and no nodal failure in a series of 50 patients with stage IIIa or b [20]. Rosenzweig et al. reported a 2-year elective nodal control of 91% in a series of 171 patients treated using a 3D-CRT approach [21]. In the series of Bradley et al., ENI had no impact on the pattern of failure for stage I disease: 5 failures out of 22 patients treated with ENI versus 2 out of 33 without ENI [25]. The current philosophy is to focus on the known disease and limit the treatment to the GTV in an attempt to be able to escalate the dose. Indeed, failure to control the GTV and distant metastases are overwhelming the role of prophylactic nodal irradiation but this may cause other problems with better treatments.

Furthermore, current imaging modalities allow us to better define our GTV especially with the introduction of PET not only for the tumour but also for the positive nodes. In a series of 73 patients, the treatment plan was based on a CT and on a PET and then compared to the surgical findings: CT was right in 55 cases and PET in 65 [22]. Interestingly, the PET errors were due to misinterpretation in 5 cases and to a minimal disease in three cases. The new generation PET machine including a CT may allow avoiding this problem of matching PET and CT data.

The IMRT is another interesting approach very successful for some indications such as head and neck or prostatic cancers, making it possible either to spare normal tissues (the salivary glands) or to escalate the dose. In the case of lung cancer, this seems to be more controversial partially due to the limited tolerance of the lungs. Grills et al have compared in a series of 18 patients 4 different treatment techniques: intensity modulated radiation therapy, optimised 3D-CRT using multiple beam angles, 3D-CRT with 2 to 3 beams, and a 2 fields radiation technique with elective nodal irradiation [23]. The use of 3D CRT with a limited num-

ber of beams offered possibility of reducing normal tissue toxicity but does not make it possible to escalate the dose beyond our current limits in node positive patients. For node negatives, IMRT is not beneficial but may be useful for node positives or for volumes close to the oesophagus.

Escalating the dose by using a conventional daily radiation schedule will protract the treatment leading to lesser potential benefit of higher radiation dose due to an active repopulation. The data from the randomised trials of accelerated hyperfractionated schedules and the negative impact of breaks during radiation suggest that the total treatment time remains an important factor. There are several ways to overcome the problem of repopulation in the case of dose escalation: using two fractions per day, a concomitant boost, increasing the fraction size during all the treatment or at the end. The radiotherapy group of the EORTC has just started a phase I/II trial where patients are stratified according to the V20: there is a dose escalation keeping the total time the same (6 weeks) for V20 smaller than 25% and for greater V20 by reducing progressively the treatment duration. In both cases, the daily doses will be greater than the classical and mythical 2 Gy fractions. There are already some data with larger fraction size and shorter treatment duration: Cheung et al. reported their experience in a series of 36 stage I patients treated with 48 Gy in 12 fractions over 2.5 weeks without ENI (24). Some unusual toxicity was observed: acute dermatitis and late subcutaneous fibrous, but some patients were treated with a Co60 unit.

**Table 1.** Results of selected series of stereotactic radiotherapy for lung cancer.

Authors	Patients	Lung Ca	Size cm	Dose Gy	Fractions	CR	Local Prog.	Nodal Failure
Lee (25)	28	9	1,2 - 4,5	30 - 40	3 - 4	8	1	
Uematsu (26)	50	50	0,8 - 5	50 - 60	5 - 10		3	2
Onimaru (27)	25	25	< 6	48 - 60	8		5	
Nagata (28)	40	31	< 4	40 - 48	4		1	

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Stereotactic radiotherapy is another way to combine the precision of 3D-CRT and to avoid the problem of repopulation. Most series reported a very high rate of local con-

Increasing the physical or biological dose will also open the door to new acute or late toxicity which were till now unknown or seldom reported such as bone toxicity, necrosis within the lung or cardiac problems. Thus, those patients should be treated in according to a well-designed protocol including a careful follow-up procedure to detect unusual late effects. Last but not least, the current TNM is a very weak tool for radiation oncologists to select the best treatment for their patients. It is rather a surgical vision as the tumour size is only used to differentiate between a T1 and a T2. Indeed, there is some correlation between stage and gross tumour volume but this is not always the case. In the past, it has often been considered that superior sulcus tumour with a Pancoast syndrome had a better prognosis but this was probably due to the size of the tumour [29]. Probably the GTV should be the key factor as reported by Bradley in his series of 207 patients treated with a 3D-CRT technique and doses ranging from 60 to 85 Gy [14]. The International Association for the Study of Lung Cancer (IASLC) is currently collecting worldwide data to search for some important prognostic factors to be proposed for the next TNM revision.

In conclusion, the data available clearly demonstrate the need for better treatments for NSCLC, including radiation and chemotherapy. 3D-CRT is becoming a part of the curative treatment of lung cancer as well as chemotherapy, either as an induction or a concurrent approach for well-selected patients. Dose escalation requires that the volume to the GTV is restricted and it will be more possible to apply to small tumours leading to the dilemma of dose escalation: larger tumours require a higher radiation

dose, have a greater probability of nodal involvement but larger volume of normal tissue, especially the lungs, will be irradiated thus limiting the possible dose escalation. Furthermore, dose escalation programmes should take into greater consideration the issue of repopulation if a classical 2 Gy per fraction is used, which opens the road for altered fractionation schedules. Thus, at the end, patient selection should not only be based on the TNM but should also take the GTV into account.

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