Radiotherapy for locally advanced non-small cell lung cancer

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Introduction

Radiotherapy is one of the major therapeutic options in thoracic oncology. Besides surgery for early-stage tumours, and chemotherapy for metastatic tumours, radiotherapy is the standard treatment for unresectable locally advanced non-small cell lung cancer (NSCLC) [1]. The development of radiotherapy is relatively recent and has been correlated with improvements in computational data-processing and medical imaging. Current modalities of radiotherapy include three-dimensional conformal techniques, allowing dose escalation and combination with most recent chemotherapy agents to occur. New techniques of radiation may also increase the efficacy and feasibility of radiation in lung cancer. Phase III trials are currently evaluating the benefits of induction and consolidation chemotherapy in this setting. Radiotherapy may also be combined with targeted therapies. These constant progresses make radiotherapy one of the most promising treatments in thoracic oncology.

Locally advanced NSCLC

Locally advanced NSCLC usually refers to NSCLC tumours that are located within the thorax, i.e. with no systemic metastases, but that are not eligible for surgical resection, either because of the invasion of intrathoracic structures, such as chest wall, mediastinum, diaphragm, mediastinal pleura, heart, or great vessels (stages T3 and T4), or because of ipsi- or contra-lateral mediastinal invasion (stages N2 and N3) [2]. Overall, locally advanced NSCLC not only corresponds to stage IIIB tumours, but also to stage IIIA tumours with macroscopic N2 disease [3]. All these tumours share a high risk of local and systemic recurrence (80% and 60% of cases, respectively) [4], thereby justifying the need for a therapeutic strategy combining focal and systemic treatment.

The role of radiotherapy in locally advanced NSCLC

Historical perspective

Thirty years ago, exclusive thoracic radiotherapy was regarded as the standard treatment of locally advanced NSCLC, following the results of studies reporting a survival benefit when compared to best supportive care and exclusive chemotherapy [5,6]. As most patients experienced early systemic recurrence, radiotherapy was progressively associated with chemotherapy, along with the development of platinum-based chemotherapy in metastatic NSCLC. Numerous randomised trials then compared chemoradiation to radiotherapy [7–12]. In these studies, chemotherapy was delivered either before (sequential chemoradiation) [7–9], or during radiotherapy (concurrent chemoradiation) [10–12]. Eleven of these trials were included in the 1995 Non-Small Cell Lung Cancer Cooperative Group meta-analysis, which evaluated the survival benefit following chemoradiation to be 4% at 2 years, and 2% at 5 years [13]. This meta-analysis was recently updated [14]: 22 randomised trials (3839 patients) were analysed for the comparison of sequential chemoradiation to exclusive radiotherapy, and the absolute survival benefit favouring sequential chemoradiation was 2.6% at 3 years; 16 randomised trials (2910 patients) were included for concomitant chemoradiation versus radiotherapy, showing an absolute survival benefit of 3.2% favouring chemoradiation at 3 years [14]. These updated data further support the fact that chemoradiation is the standard treatment of locally advanced NSCLC.

Sequential and concurrent chemoradiation

Compared to sequential chemoradiation, the concurrent combination of chemotherapy to radiotherapy has several theoretical advantages: sensitisation of the tumour cells to radiation-induced apoptosis, spatial cooperation, and reduction of the emergence of resistant cell clones. From a clinical point of view, concurrent chemoradiation allows a higher number

of patients to receive radiotherapy, along with an increased dose-intensity through a reduction of the total duration of the treatment in patients with a limited survival. Nine randomised trials compared sequential and concurrent chemoradiation, five of which did not identify significant survival differences in the two arms (Table 1) [15–23]. Five of these studies (1114 patients) were included in a recent meta-analysis [24]. Concurrent chemoradiation led to a significant survival benefit of 6.6% at 3 years (24.8% versus 18.2% for sequential chemo-radiotherapy), but also to higher oesophagial toxicity rates (18% versus 3%). In these studies, the survival benefit of concurrent associations was mostly due to a better local control (hazard ratio [HR] = 0.76, $P = 0.011$). Systemic recurrence rate was similar in the two schemes (HR = 1.04, $P = 0.669$). As of 2009, concurrent chemoradiation is the standard treatment of locally advanced NSCLC.

Current guidelines for radiotherapy in locally advanced NSCLC

Current modalities of radiotherapy

The selection of patients with locally advanced NSCLC that are eligible for radiotherapy is crucial to reproduce the results reported in phase III trials. In addition to the careful evaluation of co-morbidities which are frequent in patients with NSCLC, pulmonary function tests are mandatory: a forced expiratory volume in 1 s that is lower than 40% and/or a monoxide diffusing capacity lower than 60% of the theoretical values usually contra-indicate standard radiotherapy, even using conformal techniques, and require the use of respiratory gating (see below) [25].

Preliminary steps for conformal radiotherapy include the three-dimentional acquisition of anatomical data as well as treatment planning. A "dosimetric" computed tomography (CT)-scan is performed in the position of the radiotherapy treatment in blocked inspiration, with serial 5 mm-cuts and without contrast-injection. To ensure a perfect reproducibility along the planning and treatment procedure, a personalised frame is cast for each patient. The tumour (Gross Tumour Volume (GTV)) and all intrathoracic organs (non-tumoural lung, heart, spinal cord, oesophagus) are then delineated on each CT-scan image. Delineation may be difficult in case of lobar atelectasia secondary to bronchial obstruction by the tumour mass. Integration or fusion with data from a F18-fluorodeoxyglucose positon-emission tomography (PET)-scan or from magnetic resonance imaging (MRI) may then be useful. This delineation creates a three-dimensional virtual model of all intrathoracic structures.

As pre-treatment anatomical data can significantly evolve during radiotherapy courses, this model takes into account some uncertainties, defined in reports 50 and 62 of the International Commission on Units Radiation [26]. In addition to GTV, which includes the visible extent and location of the tumour, the radiotherapist defines (1) a Clinical Target Volume (CTV), that encompasses surrounding subclinical microscopic malignant disease by adding a 5–7 mm margin around the GTV, and (2) the final Planning Target Volume (PTV), with an additional margin for body movements (Internal Target Volume (ITV)) and technical deviations during the treatment course. For intra-thoracic tumours, cranio-caudal breath-induced movements range from 7 mm in the upper lobes to 65–70 mm in the lower lobes [27]. ITV margins, in the absence of respiratory control, are then usually 10 mm for the tumour and 5 mm for lymph nodes. Similarly, the repositioning variation along treatment courses is estimated to be 6 mm on average, with errors higher than 10 mm in 32% of the patients, for an estimated loss of tumour control of 5% [28]. Overall, margins around the GTV usually range from 15 to 25 mm in the absence of respiratory gating, and 10 to 15 mm with respiratory gating.

The actual treatment planning step consists of working on the virtual three-dimensional model to determine the number, the incidence, and the energy of each radiation beam, as well as the shape of the fields, modelled by personalised masks or a multiblade collimator. In Europe, the dose is prescribed at the PTV margin. The quantification of radiation-dose distribution within the virtual model makes possible the comparison of several treatment plannings using dose-volume histograms (DVH), which represent for each structure, the volume receiving at least a certain dose [29], and normal tissue complication probabilities (NTCP), which are available for each critical organ [29,30].

Radiotherapy doses for locally advanced NSCLC

The major objectives of treatment planning are to deliver a total dose ranging from 66 to 70 Gy, using a standard fractionation scheme (one 2 Gy-fraction per day), without acute toxicities on non-tumoural tissues: the lung V_{20} (percentage of pulmonary volume receiving at least 20 Gy) has to be lower than 30%, the lung V_{30} (percentage of pulmonary volume receiving at least 30 Gy) lower than 20% (and even less in case of chronic obstructive pulmonary disease); similarly,

Table 1
Randomised trials comparing sequential and concurrent chemoradiation in locally advanced non-small cell lung cancer

Author	*n*	Chemotherapy		Radiotherapy (Gy)		Median survival (mo)		Overall survival (%)			*P*
		Sequential	Concurrent	Sequential	Concurrent	Sequential	Concurrent	Sequential	Concurrent		
CALGB 8831, 1994 [15]	91	vinblastine cisplatin	carboplatin	40S	40S	11.9	12.4	26%	33%	(2-year)	NS
Furuse et al., 1999 [16]	320	mitomycin vindesine cisplatin	mitomycin vindesine cisplatin	56 S	56 SC	13.3	16.5	9	16	(5-year)	0.04
GATA Ankara, 2000 [17]	30	etoposide ifosfamide cisplatin	cisplatin	56.9 SC	56.9 SC	10	11	?	?	?	NS
Zatloukal et al., 2000 [18]	102	cisplatin vinorelbine	cisplatin vinorelbine	60 S	60 S	12.9	16.6	9	19	(3-year)	0.02
GLOT, 2001–2005 [19]	205	cisplatin vinorelbine	cisplatin etoposide	66 S	66 S	14.5	16.3	14	21	(4-year)	0.24
LAMP, 2002 [20]	276	carboplatin paclitaxel	carboplatin paclitaxel	63 S	63 S	13.8	17.4	31	33	(2-year)	0.30
RTOG 94-10, 2003 [21]	610	cisplatin vinblastine	cisplatin vinblastine	60 S	60 S	14.6	17.1	12	21	(4-year)	0.04
BROCAT, 2004 [22]	219	carboplatin paclitaxel	paclitaxel	60 S	60 S	14.0	19.0	?	?	?	<0.01
EORTC 08972, 2007 [23]	158	cisplatin gemcitabine	cisplatin	66 H	66 H	16.2	16.5	22	29	(3-year)	NS

Gy: Gray; S: standard fractionation; SC: split-course; H: hypofractionated; NS: not significant.

the maximum dose delivered to the cardiac tissue is 40 Gy, with a cardiac V_{20} lower than 60%; the maximum dose to the spine is 40 Gy per segment. Finally, the volume of oesophagial tissue has to be limited as much as possible, especially in concurrent chemoradiation regimens [31,32].

Quality assurance

Individual quality control

On the treatment day, the patient is installed in the same position as for the dosimetric CT-scan, with the help of skin tattoos that are aligned with room lasers. The accurate positioning of the patient is also checked by superimposing images from beam-eyed tomography to Digitally Reconstructed Radiographs created from the three-dimensional virtual model, with the help of the diaphragm, the carina, or bony structures for image matching. The actual amount of radiation delivered along the treatment may be monitored using thermoluminescent dosemeters specifically placed on the patient skin surface (*in vivo* dosimetry). Positioning variations have been reported up to 22 mm, but the use of such "online" correction strategies reduces these errors to less than 2 mm [33]. Recently developed cone-beam CT-scan allows tridimensional verification of the position of the tumour volume and other organs, with an even higher accuracy [34].

Insitutional quality control

The high precision of conformal radiotherapy paradoxically generates (1) important risks of uncertainty, since the reduction of margins increases the risks associated with potential variations due to the positioning and the movements of the patient, and (2) technological risks related to the use of data processing, with the constant evolution and complexity of the linear accelerators and associated software. Delivering radiotherapy to lung tumours is a multi-step process that requires safe and reliable installations, precise human procedures, and optimal quality control allowing maximum precision and reproducibility [35].

In 1997, quality assurance guidelines for institutions have been elaborated within the framework of the DYNARAD (development and standardisation of new DYNAmic RADiotherapy techniques) programme [35]. The development of these quality standards has established a culture of self-evaluation and risk management. In this way, publication 76 of ICRU analysed each accident of radiotherapy reported to date, and proposed adapted quality control procedures to avoid similar technical and clinical failures [36]. The immediate and complete description of even minimal deviations to DYNARAD standards is then encouraged to serve the community, similarly to what is done in civil aviation.

Application to clinical trials

Despite these recent recommendations, only limited data are available regarding the compliance of clinical trials with quality assurance procedures. In France, a retrospective quality control analysis was performed during the multicentre GLOT/GFPC/IFCT 02-01 trial [37]. This randomised trial compared induction to consolidation chemotherapy with cisplatin and paclitaxel, before or after concurrent chemoradiation (66 Gy with cisplatin and navelbine) in locally-advanced NSCLC [38]. The protocol of the study required (1) the use of conformal radiotherapy with six radiation fields or more, (2) a standard fractionation scheme, (3) a PTV with 15 mm margins around the GTV, (4) no prophylactic mediastinal radiotherapy, and (5) the analysis of DVH for the tumour, the non-tumoural lung, and the spinal cord. Beam-eyed portal imaging had to be done on a weekly basis.

In this study, quality control data were available for 111 patients treated in academic centres, cancer centres, and private centres. The planned total dose of 66 Gy was delivered in 77% of cases; interestingly, 4% of the patients received higher doses, ranging from 67 to 70 Gy, and 19% of patients lower doses. Similarly, 34% of treatment planning protocols included less than six fields. Nearly 20% of patients were not immobilised using a personalised treatment frame. Beam-eyed portal imaging was done for each radiation field before and during treatment in only 70% and 43% of patients, respectively [34].

Such extended results on radiotherapy quality control are barely reported for randomised trials, and these data suggest that deviations to planned procedures may actually be frequent. In locally advanced NSCLC, the application of good practice and protocol recommendations may also be difficult for large tumoural volumes. However, in the above trial, oesophageal and pulmonary acute toxicity rates (10–17%, and 0–1.7%, respectively) did not correlate with total doses, number of radiation fields, or use of DVH, and were actually in the same range as those reported in similar trials (for which quality control data are not available). Ongoing multicentre trials include the initial use of a "dummy-run", consisting of CT-scan data from a virtual patient, which is used to define common radiation planning criteria. Thermoluminescent dosimeters may also be regularly sent for each patient to investigators in addition to on-

Table 2
High-dose radiotherapy studies in locally advanced non-small cell lung cancer

Author	Phase	*n*	Chemotherapy		Radiotherapy dose (Gy)	Nonhaematologic grade 3–4 acute toxicity			2-year overall survival (%)
			Induction (%)	Concurrent (%)		Lung (%)	Oesophagus (%)	Heart (%)	
Hayman et al., 2001 [39]	I	104	25	0	65–103 S	1	7	NR	40
Rosenman et al., 2002 [40]	I	62	100	0	60–74 S	0	8	NR	50
Wu et al., 2003 [41]	I	50	100	0	75–78 S	2	4	0	44
Socinski et al., 2004 [42]	I	25	100	100	78–90 S	0	16	NR	46
Marks et al., 2004 [43]	I/II	44	89	0	74–86 BF	5	0	NR	47
Bradley et al., 2005 [44]	I/II	177	14	0	71–90 S	17	0	NR	42–50
Kong et al., 2006 [45]	I	109	19	0	63–103 S	15	0	NR	37
Belderos et al., 2006 [46]	I/II	88	18	0	61–95 S	6	0	NR	NR
Urbanic et al., 2006 [47]	R	35	0	0	76–90 S	9	0	0	50
Sura et al., 2007 [48]	R	82	27	0	⩾80 S	4	0	0	58
Socinski et al., 2008 [49]	II	43	95	93	74 S	16	16	0	48
Stinchcombe et al., 2008 [50]	II	21	100	100	74 S	NR	20	10	18
Bellière et al., 2009 [51]	R	50	80	28	68–74 S	16	4	6	37

R: Retrospective; NR: not reported; Gy: Gray; S: standard fractionation; BF: bifractionated.

site visits, in order to check portal imagings, possibly improving quality control for clinical trials.

Optimising radiotherapy for locally advanced NSCLC

Doses

Several radiobiological studies conducted in the 1980s showed the proportional relationship between total doses of radiation and local control and overall survival of locally advanced NSCLC. Over the past 10 years, the development of conformal radiotherapy has allowed a better focalisation of the ballistics, leading to a more precise targeting of the tumour volume while sparing non-tumoural structures. More than reducing toxicity rates, conformal radiotherapy also allows dose escalation to occur. Several studies reported the feasibility of radiation-dose escalation in non-resectable NSCLC, both sequentially and concurrently with cytotoxic chemotherapy (Table 2) [39–50]. In these studies, total doses were increased from 65 to 102 Gy with acceptable grade 3–4 lung and oesophageal toxicity rates (4–12%). Compared to historical results, dose escalation protocols produced higher local control rates (50–60%) than standard radiotherapy, with prolonged median and 2-year survival between 17 and 25 months, and 35–50%, respectively (Table 2). Even if higher, oesophageal toxicity is actually not dose-limiting, as symptomatic treatments usually allow the continuation of radiation administration. We also recently reported the need to further analyse heart toxicities, which occurred in 8% of a cohort of 50 patients treated with total doses up to 74 Gy [51]. Cardiac toxicities occurred in all cases in patients with a previous history of coronary disease. Overall, results of radiotherapy to doses higher than 70 Gy need to be validated in randomised trials.

Fractionation

Hyper-fractionation consists of scheduling the administration of radiation more than once a day. Such protocol allows on the one hand to reduce the dose per fraction (and thus late radiation-induced toxicities), and on the other hand to increase the total daily amount of radiation delivered to the target volume. The purpose of *accelerated* hyper-fractionation regimens is to administer several daily fractions, while decreasing the total duration of the treatment. In locally advanced NSCLC, only Continuous Hyper-fractionated Accelerated RadioTherapy (CHART), delivering three daily fractions of 1.5 Gy during 12 consecutive days, showed a survival benefit over standard radiotherapy, mostly due to improvements in local control rates [52]. Hyper-fractionation regimens have actually not been further developed, mostly because of the technical and organisational constraints such protocols require.

Techniques

Intensity-modulated radiotherapy

Recent technical improvements in the delivery of radiation doses may also help to optimise chemoradiation protocols in locally advanced NSCLC. Intensity modulated radiotherapy (IMRT) consists of a real-time modelling of the contours and the amount of photons delivered within the radiation beam, using a programmed movement of the blades of the collimator. This allows the administration of beams of variable shapes during a single sequence, possibly proving to be helpful to target tumours that are close to critical tissues. In a retrospective study, lung toxicity rates were lower using IMRT than using conformational radiotherapy (8% and 32%, respectively) thanks to a reduction of the pulmonary volume receiving a high amount of radiation [53]. Our group also reported the interest of IMRT and non coplanar fields to reduce lung and heart V_{20} [54].

Respiratory gating

Standard practice of radiotherapy is to deliver radiation under shallow breathing, and it is then necessary to add sufficient ITV, so that the prescription dose is reached everywhere within the moving tumour. With so called "4D-techniques", the motion-encompassing volume is much smaller. Respiratory control involves assisted or voluntary blocking of respiration in a selected phase of the respiratory cycle, during which radiation is delivered. Respiratory gating enables the photon-beam only when the motion amplitude coincides with a pre-selected sector of the respiratory cycle. Respiratory tracking involves intentionally moving the irradiating beam so that it follows the movement of the tumour.

The typical device for 4D-techniques is a pneumotach apparatus with real-time visual monitoring [55]. A preliminary dosimetric study showed that, for a total dose of 81 Gy, NTCPs were 27% for free-breathing conformal radiotherapy, and 2% for respiratory gating [56]. The clinical evaluation of 4D-techniques is ongoing.

Stereotactic radiotherapy

Stereotactic radiotherapy corresponds to the administration of high daily doses of radiation (theoretically higher than 3 Gy, but usually ranging from 12 to 26 Gy) in a low number of fractions (one to four on average), for a total dose equivalent to 66–74 Gy using standard fractionation schemes [57]. This technique may be less toxic as it uses highly focalised radiation beams, sparing normal tissues. Initially developed for brain tumours, the stereotactic procedure requires at the thoracic level, (1) a whole-body immobilisation device usually using a vacuum pillow within a rigid individualised mattress, (2) the use of respiratory gating or other 4D-techniques, and (3) a strict quality control with beam-eyed portal films controlled before each fraction.

Currently, stereotactic radiotherapy is mostly developed for stage I tumours, as an alternative to surgery for non-operable patients with NSCLC [58]. In locally advanced NSCLC, this technique might even allow higher dose-escalation to occur: a recent study reported the use of stereotactic radiotherapy in 30 patients, with a total dose of 40 Gy in four fractions (equivalent to 120 Gy). Response rate was 63%. No grade 3–4 toxicities were reported. Further investigations are needed in a prospective setting.

Proton-beam radiotherapy

More recently, proton beam radiotherapy, which delivers protons intead of photons, has been developed. Protons do not scatter much in the tissue, and allow the maximum dose to be delivered at a precise depth within the lung; tissues situated beyond the maximum intensity peak receive no radiation. Proton-beam therapy also requires respiratory gating, and a strict quality control. In an analysis conducted at the MD Anderson Center and reported at the 2008 Chicago Multidisciplinary Symposium in Thoracic Oncology, 142 patients with locally advanced NSCLC were treated either with chemotherapy and proton-beam therapy ($n = 67$) or chemotherapy and IMRT ($n = 75$). The median radiation dose in the proton-beam therapy group was 74 Gy, compared with 63 Gy in other group. Interestingly, patients treated with proton-beam therapy experienced significantly less haematological toxicities compared to the other treatment group. These differences remained significant even when the gross tumour volume, which was higher in the proton-beam arm, was considered. In 2009, the availability of proton-beam radiotherapy is limited worldwide, and only a few prospective studies are ongoing.

Optimising chemotherapy in locally advanced NSCLC

Third generation cytotoxic agents have been combined with radiation, both using standard doses to achieve an antitumour effect, and using low daily doses to radiosensitise tumour cells. The ultimate aim is to increase systemic control rates following chemoradiation.

New cytotoxic agents

Concurrently with the integration of third-generation cytotoxic agents in the treatment of metastatic NSLC, chemoradiation protocols have progressively evaluated the opportunity to combine platinum with etoposide, vinca-alkaloids, and more recently taxanes. The Cancer and Leukaemia Group B (CALGB) study 9431 was a three-arm phase II trial evaluating induction chemotherapy followed by concurrent chemoradiation [59]. Three chemotherapy regimens were compared: gemcitabine and cisplatin (arm 1), paclitaxel and cisplatin (arm 2), and vinorelbine and cisplatin (arm 3). These drugs were administered at full doses as induction treatment, and then reduced during the concurrent phase. Median survival for arms 1, 2, and 3 was 18.3, 14.8, and 17.7 months, respectively, and response rates were 74%, 67%, and 73%, respectively. The gemcitabine arm had the highest 3-year survival rate (28% versus 19% for arm 2 and 23% for arm 3), but was associated with more frequent haematological and gastrointestinal toxicities. The combination of cisplatin and vinorelbine is currently considered as the standard regimen in association with radiotherapy for locally advanced NSCLC.

Chemoradiation with gemcitabine is currently under investigation. On the basis of preclinical and clinical studies, it was expected that gemcitabine given concurrently with radiation may produce radiation enhancement; however, the initial study of gemcitabine with concurrent radiation ended with undesirable results [60]: eight patients with locally advanced NSCLC received full-dose gemcitabine (1000 mg/m^2) with 60 Gy of radiation in large treatment volumes. The results were intriguing: seven of the eight patients (87%) responded at the primary tumour, and four of five patients (80%) responded at nodal sites. The toxicity, however, was unacceptable: three patients had treatment-related deaths (two from pulmonary toxicity, one from haemorrhage), three patients had complications due to acute radiation toxicity (pneumonitis or severe oesophagitis), and another two had other serious side effects. Based on the experience of this trial, gemcitabine was contra-indicated in association with radiotherapy. Several guidelines were formulated for subsequent trials: dose reduction to 150–300 mg/m^2/week, concurrent total doses of radiation limited to 63 Gy, PTV inferior to 2000 cm^3 [61].

Radiosensitisation

In most studies of concurrent chemoradiation published in the 1980s, cisplatin was actually delivered as a radiosensitiser rather than as a cytotoxic chemotherapy. In these studies, chemoradiation led to higher local control rates, but failed to increase overall survival, mostly because of early systemic recurrences [7,9,10]. Using modern techniques of radiation, a recent phase III trial compared, after induction treatment, radiotherapy to concurrent chemoradiation using daily low doses of carboplatin (15 mg/m^2). The two arms resulted in similar local control rates, with an increased number of toxic deaths in the radiosensitisation arm [62]. This approach is currently abandoned.

New sequences

In order to deliver higher doses of chemotherapy and to increase systemic control rates, several investigators developed mixed therapeutic sequences, associating induction and/or consolidation chemotherapy, before and/or after concurrent chemoradiation (Table 3) [20,38,63–69]. Overall, results of recently published studies suggest that both induction and consolidation may increase results from concurrent chemoradiation. Taken together, these studies do not suggest consistent or significant differences between induction and consolidation chemotherapy, which has also been reported in recent meta-analyses [24]. Some data suggest that consolidation protocols may increase progression-free survival [67], but further studies are needed. Moreover, routine practice favours induction chemotherapy, allowing (1) the initiation of the treatment sequence while preparing the patient for radiotherapy with shorter delays, (2) a tumour response to be potentially obtained and the GTV to be decreased, and (3) selection of the most appropriate patients that do not present with early progression.

Targeted therapies and radiotherapy

Over the past 15 years, major insights have been discovered to further our understanding of the molecular bases of lung carcinogenesis. Major molecular and genetic alterations that are specific to lung cancer cells have been identified, and a newer class of "targeted therapies", involving selective kinase inhibitors, has been developed [70]. The promising effect of these agents in metastastic NSCLC, together with their selectivity for tumour cells, prompted further investigations in combination with radiotherapy.

Radiotherapy and epidermal growth factor receptor (EGFR) inhibitors

Two recent trials evaluated the feasibility of combining radiotherapy with EGFR inhibitors. The CALGB-

Table 3
Phase II/III trial evaluating induction and consolidation chemotherapy before or after concurrent chemoradiation for locally advanced non-small cell lung cancer

Authors	n	Treatment				Median survival (months)			*P*
		Induction CT	Chemoradiation		Consolidation CT	Induction	Chemoradiation	Consolidation	
			Radiotherapy (Gy)	Chemotherapy					
Induction CT-chemoradiation versus chemoradiation alone									
Komaki et al., 2002 [63]	163	cisplatin vinblastine	63 S	cisplatin	NA	16	16	NA	NS
CALGB 39801, 2004 [65]	366	carboplatin paclitaxel	66 S	carboplatin paclitaxel	NA	14	12	NA	NS
Kim et al., 2007 [69]	131	cisplatin gemcitabine	66 S	paclitaxel cisplatin	NA	13	18	NA	0.18
Chemoradiation alone versus chemoradiation-consolidation CT									
SWOG 9504/9019, 2003 [64]	133	NA	61 S	cisplatin etoposide	docetaxel	NA	15	26	?
HOG LUN 01-24, 2007 [66]	73	NA	59.4 S	cisplatin etoposide	docetaxel	NA	24	22	NS
Induction CT-chemoradiation versus chemoradiation-consolidation CT									
Belani et al., 2005 [20]	276	carboplatin paclitaxel	63 S	carboplatin paclitaxel	carboplatin paclitaxel	13	NA	16	NS
GFPC-GLOT-IFCT 02-01, 2006 [38]	133	cisplatin paclitaxel vinorelbine	66 S	cisplatin	cisplatin paclitaxel	19	NA	16	NS
PulmonART, 2007 [67]	70	cisplatin docetaxel	66 S	cisplatin docetaxel	cisplatin docetaxel	13	NA	15	0.8
SLCG 0008, 2007 [68]	151	docetaxel gemcitabine	60 S	carboplatin	docetaxel gemcitabine	15	NA	14	0.38
ECLWP 01063, 2009*	49	cisplatin docetaxel	66S	cisplatin docetaxel etoposide	cisplatin docetaxel	24	NA	17	?

Legend: CT: chemotherapy Gy: Gray: S: standard fractionation; NA: not applicable; NS: not significant
*Presented at the Swiss Academy of Multidisciplinary Oncology, 2008.

30106 study is a phase II trial which tested the association of standard radiotherapy to a total dose of 66 Gy, with chemotherapy (carboplatin and paclitaxel) and gefitinib [71]; 64 patients were included and stratified on loss of weight and performance status (PS). Interestingly, median survival was significantly longer for high-risk patients (loss of weight higher than 5% and PS 2) than for low-risk patients (loss of weight of less than 5% and PS 0–1) (respectively 19 and 12 months) [71]. More recently, a randomised phase II trial evaluated the interest of erlotinib delivered concurrently with a standard irradiation (66 Gy), in 30 patients with unresectable NSCLC who were not eligible for chemotherapy [72]. Erlotinib was continued as maintenance treatment for 6 months. Oesophageal, cutaneous and lung acute toxicities were actually less frequent in the combined treatment arm (respectively 23% versus 40%, 8% versus 50%, and 8% versus 20% in the exclusive radiotherapy arm). Response rate was significantly higher in patients treated with erlotinib (83% versus 56%), which may not be surprising as exclusive radiation is known to be a sub-optimal treatment [50]. EGFR inhibitors may have a role in specific subgroups of patients, especially those that are not eligible for chemotherapy. However, none of the above studies included a selection or even a retrospective analysis of the "EGFR status" of the included patients.

Associations of cetuximab, an anti-EGFR monoclonal antibody, with radiotherapy were developed following the favourable results obtained in head and neck carcinomas [73]. Following a feasibility study with cetuximab alone including 12 patients [74], the RTOG-0324 study evaluated the association of cetuximab with carboplatin and paclitaxel, delivered concurrently with radiotherapy to a total dose of 60 Gy [75]. This phase II trial enrolled 93 patients. Haematologic oesophageal and pulmonary toxicity rates were 20%, 8% and 7%, respectively, which is similar to those observed without the cetuximab. Response rate was 62%, and median survival was 23 months. Interestingly, the response rate was higher in case of EGFR amplification in the tumour (measured by FISH) [76]. Several phase II trials evaluating chemoradiation with cetuximab are ongoing [77]; in France, the French Group of Pneumo-Cancerology has launched a randomised trial comparing two chemotherapy regimens (cisplatin-vinorelbine versus cisplatin and etoposide), in combination with cetuximab and concurrent radiotherapy to a total dose of 66 Gy.

Radiotherapy and angiogenesis inhibitors

The interest in angiogenesis inhibitors for NSCLC developed after bevacizumab, a humanised antibody directed against vascular endothelial growth factor receptor (VEGFR), demonstrated that it significantly increased survival when associated to standard chemotherapy in metastatic tumours [78]. In the landmark ECOG-4599 phase III trial including 878 patients, the addition of bevacizumab led to a 2-month survival benefit [79]. Only limited clinical data have been reported so far regarding the feasibility of the association of bevacizumab with radiotherapy. A phase I trial tested, in 20 patients, the addition of bevacizumab to chemoradiation to a total dose of 74 Gy with carboplatin and paclitaxel [80]. The results show the good tolerance of this regimen, even in the case of squamous cell carcinoma, with only one case of grade 5 haemorrhage. A phase II trial is currently ongoing in non-squamous tumours.

Chemoradiation and surgery in locally advanced NSCLC

The EORTC 08941 trial included patients with unresectable stage IIIAN2 NSCLC [81]. Responders to three cycles of platinum-based chemotherapy were randomised between surgical resection and standard radiotherapy to a total dose of 60 Gy. There were no significant differences in progression-free and overall survival (9.0 months (surgery arm) versus 11.3 months (chemoradiation arm), and 16.4 months (surgery arm) versus 17.4 months (chemoradiation arm), respectively). Interestingly, 50% of patients included in the surgery arm had an incomplete resection, and were finally assigned to receive postoperative radiotherapy. Two major prognostic factors were identified in the surgery arm: the mediastinal lymph node downstaging after induction chemotherapy (5-year survival was 29% in pN0 tumours versus 7% in pN+ tumours), and the extent of surgery (5-year survival was 27% after lobectomy versus 12% after pneumonectomy) [81]. This trial, even if comparing surgery to a suboptimal sequential chemoradiation protocol, suggests the absence of benefit and the increased toxicity of surgery in unresectable stage IIIA NSCLC.

Conclusions

Overall, concurrent chemoradiation is the standard treatment of locally advanced NSCLC. The recent and

future optimisation of radiation delivery and chemotherapy regimens allows significant improvements in tumour response rates and overall survival to occur in the majority of patients. These developments make radiotherapy one of most effective and promising therapeutic options in thoracic oncology [82].

Conflict of interest statement

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