State of the art in the treatment of lung cancer

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Lung cancer continues to be the major cancer killer in both sexes. Despite many biological and technological achievements, it is still mostly an incurable disease, and survival figures are only modestly improved in the past few decades. Optimisation of treatment is usually sought through clinical studies, but unfortunately only a few per cent of lung cancer patients enter these world-wide. So it is in spite of the fact that we have witnessed the introduction of robotic surgery, computerised radiation therapy and targeted agents in daily clinical practice. More emphasis on clinical research is therefore needed to improve our capability to successfully treat lung cancer.


NSCLC

Early stage

In patients with early-stage (I-II) NSCLC, surgical resection remains the cornerstone of treatment. Unfortunately, less than 30% of patients have their disease resectable at the time of presentation, and 50% of these have significant comorbidities. While being technically operable, they are considered medically inoperable. Furthermore, approximately 70% of the patients with early-stage resected disease develop recurrence at distant sites. Therefore, additional systemic therapy is needed to eradicate micrometastatic disease. In this setting, platinum-based CHT has emerged as an effective adjuvant systemic therapy after resection. The International Adjuvant Lung Trial (IALT), with more than 1 700 patients with stages I-III NSCLC, demonstrated a significant but modest improvement in 5-year survival rate of 4% when adding cisplatin-based doublets after surgery (versus observation).[6] Similarly, cisplatin-vinorelbine v. observation was compared in patients with stages IB and II NSCLC in the National Cancer Institute of Canada (NCIC) trial.[6] An overall 15% improvement in 5-year survival in the adjuvant CHT group was observed. Finally, a meta-analysis of trials with adjuvant cisplatin-based CHT demonstrated a 5% improvement in overall survival (OS)[6] ultimately leading to a shift of treatment paradigm. However, it must be clearly stated that the role of adjuvant CHT has been limited to stage II and III resected NSCLC due to a preferential benefit observed in these subgroups. However, controversy remains including the data to support its use in those with tumours ≥4 cm in size.[6] For patients with stage I A disease, adjuvant CHT is not usually recommended.[7]

Cisplatin-based CHT is the ‘standard of care’ in the adjuvant setting. However, a controversy exists on whether carboplatin can be substituted for cisplatin in the adjuvant setting. A trial of carboplatin/paclitaxel combination in patients with stage IB disease failed to show a survival benefit, despite improvement in disease-free survival.[7] The optimal number of cycles of adjuvant CHT has also not been addressed in randomised studies. Currently, 3 - 4 cycles of cisplatin-based CHT are administered in routine practice settings.

Approximately two-thirds of all resected patients are able to receive adjuvant CHT as others have comorbidities of varying degree and/or postoperative complications. Neo-adjuvant (induction) CHT has also been investigated to improve the delivery and compliance of CHT. A phase III study demonstrated an improvement in overall survival with neo-adjuvant CHT followed by surgery versus surgery alone.[8] However, the difference was not significant and the trial was closed early because adjuvant CHT became the new ‘standard of care’. Similar data have also been reported from another trial that evaluated pre-operative therapy.[9] Neo-adjuvant CHT prior to surgery versus surgery alone versus surgery followed by adjuvant CHT was compared in the Spanish Study. The delivery of CHT was found to be superior in the pre-operative setting (90% v. 66%).[10] Neo-adjuvant CHT in this trial was associated with a non-significant trend towards longer disease-free survival compared with surgery alone. The power of this study was limited and there was a high proportion of stage I patients who supposedly do not benefit from systemic therapy. Neo-adjuvant CHT is an efficacious and safe approach for patients with early-stage NSCLC.
but the ‘standard of care’ for patients with R$_3$ resection is adjuvant CHT. In the adjuvant setting, epidermal growth factor receptor (EGFR) inhibitors have also been investigated for patients with resected early-stage NSCLC. Though gefitinib as adjuvant therapy failed to demonstrate a benefit in this group, this was not conclusive as the study was stopped early.\textsuperscript{[19]} Erlotinib has been evaluated in a randomised trial (RADIANT) in the adjuvant setting. The trial has completed accrual and the results are eagerly awaited. While surgery remains the gold standard in operable early NSCLC, there are patients who either cannot tolerate lobectomy or are considered borderline cases. Beside more limited surgery (e.g. segmentectomy or wedge resection) occasionally used in such cases,\textsuperscript{[12-15]} standard fraction, hyper- or hypo-fractionated thoracic radiation therapy (TRT) and even TRT-CHT was used with modest success in this largely unfavourable patient population.\textsuperscript{[18,17]} Importantly, stereotactic body radiotherapy (SBRT) has been used with excellent local control and overall survival largely surpassing results achievable with conventional RT.\textsuperscript{[18,19]} Recent comparisons, though not done in a prospective randomised fashion, indicated similar outcomes with surgery versus SBRT.\textsuperscript{[20,21]} Although both limited surgery and SBRT produce excellent results given exclusively, requests for more formal comparison of two treatment approaches led to two prospective randomised trials that are currently underway.

**Locally advanced disease**

Approximately one-third of all patients with NSCLC present with a locally advanced, mostly stage III disease. It has been the major battleground for investigating various treatment options. Surgery (e.g. in very selected T4N0), TRT (altered fractionation regimens with curative intention in stage III or palliative hypofractionated regimens in mostly stage IIIB patients) and various CHT agents (again, mostly in stage IIIB) can all be used alone in this disease. However, this is not so frequent practice nowadays in the majority of patients who can tolerate a more intensive (combined) treatment approach owing to the propensity to develop symptoms in the near future. In this setting, any intervention should have the goal of effective palliation avoiding unacceptable toxicity. Various TRT fractionation schemes are in use for palliative treatment, ranging from as low as single fraction of 8 - 10 Gy to as high as fractionated 50 - 60 Gy. Until the first study from the Medical Research Council (MRC) UK was published in 1991,\textsuperscript{[30]} a typical course was 30 Gy in 10 fractions. Since then, several randomised phase III trials\textsuperscript{[37-41]} comparing a strict hypofractionated schedule versus a normo-fractionated regimen have been published, with >2 500 patients being treated. All trials have either a single (8 or 10 Gy) or two large fractions (17 Gy/2 or 16 Gy/2) as the short-course experimental arm. The comparative fractionated schedules ranged from 20 to 50 Gy. The trials included patients up to World Health Organization performance status (WHO PS) 3 with a huge shift towards stage III patients. One trial (MRC II)\textsuperscript{[37]} included only patients with WHO PS 2 - 4 comparing a single fraction versus 17 Gy/2 fractions. In two trials,\textsuperscript{[42,43]} the effect on symptoms was in favour of the higher dose, otherwise the effect on disease-related symptoms was equal. In three trials,\textsuperscript{[38,44,45]} the survival was in favour of the high-dose arm: 39 Gy/13 fractions, 30 Gy/10 fractions and 30 Gy/10 fractions.
respectively. One trial[44] reported a survival benefit for the low-dose arm: 16 Gy/2 fractions v. 20 Gy/5 fractions. In another trial,[41] 17 Gy/2 fractions (n=143) was compared with two high-dose arms: 42 Gy/15 fractions (n=140) and 50 Gy/25 fractions (n=124), with no difference in median survival found.

Five randomised phase III studies[45-49] have compared different normo- to high-dose regimens, including more than 1 000 patients. Nearly all had stage III localised disease with a reasonably good performance status (WHO PS 0 - 2). One study reported better palliation in the high-dose arm.[46] Four studies provided data on survival, being equal in three and better for the high-dose arms in one.[48] The latter study[40] is particularly interesting since one arm in this three-armed trial was a ‘wait and see’ arm; 40 Gy/10 (split) v. 50 Gy/25 v. ‘wait and see’. The survival in this ‘wait and see’ arm was inferior compared with the two actively treated arms.

While the effect on symptoms and palliative effect may be similar regardless of dose and fractionation, the trend of more rapid relief of symptoms in favour of hypofractionation is observed with no major difference in median survival. To investigate the issue of whether some patients with localised stage III disease may benefit from a protracted high-dose TRT, an MRC study[49] was undertaken focusing only on stage III disease with good performance status. It compared 17 Gy/2 fractions (arm 1) with 39 Gy/13 fractions (arm 2). The median survival increased from 7 to 9 months in arm 2 (p<0.05), with a 1- and 2-year survival of 31% and 9% v. 36% and 12% in the arm 1 and arm 2, respectively. Another study[41] compared a strict low-dose with high-dose schedules and found a trend in better survival in the high-dose arms. Further analysis of the same study (restricted to stage III patients)[50] disclosed a 3- and 5-year survival in the three arms (17 Gy/2, 42 Gy/15, 50 Gy/25) of 1%, 8% and 6%, v. 0%, 4% and 3%, respectively. General observations from all of these studies can be extrapolated to patients with stage IV, which can also safely be treated with a hypofractionated schedule. Acute toxicity with dysphagia is mild, temporary and manageable. Late toxicity is rare, sporadic and usually not severe.

Although there was no strong evidence that higher dose gives a better outcome concerning symptom relief and survival, and that a hypofractionated regimen is an option for most patients, patients with stage III disease with a reasonable performance status and less weight loss could be treated with a protracted fractionated regimen 30 - 45 Gy. Stage IV patients can be treated safely with a hypofractionated regimen 30 - 45 Gy/25 v. ‘wait and see’. The survival in this ‘wait and see’ arm was inferior compared with the two actively treated arms.

Palliative TRT aims to treat symptoms from intrathoracic tumours. In otherwise symptom-free patients, however, immediate treatment is likely to give unnecessary side-effects like dysphagia and may not prevent development of later symptoms.[53,54] A ‘wait and see’ procedure is therefore advocated until the patient becomes symptomatic.

**Advanced/metastatic disease**

Systemic therapy remains the mainstay for treatment of advanced-stage NSCLC. Combination CHT with a platinum-based regimen (cisplatin or carboplatin) has emerged as standard therapy for patients with advanced-stage disease.[55] Improvements in overall survival and quality of life have been demonstrated with platinum-based regimens over best supportive care alone in randomised clinical trials.[56] In general, carboplatin-based regimens have a favourable tolerability over cisplatin-based regimens.[57,58] Despite the marginally higher response rate with cisplatin-based regimens, and considering the palliative intent of therapy, carboplatin-based regimens have found wide applicability in routine care. Recent improvements in anti-emetic therapy have made cisplatin-based regimens more tolerable.

A number of randomised clinical trials have established the superiority of platinum-doublets over single-agent therapy.[59-61] The ‘third-generation’ cytotoxic agents (paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan and pemetrexed) have all demonstrated efficacy when given in combination with a platinum compound in patients with advanced NSCLC.[59-61] The use of triplets has generally resulted in higher toxicity without clear evidence of improvement in efficacy and has therefore largely been abandoned.[50] With the currently available platinum-based two-drug regimens, the median survival and 1-year survival rate are 8 - 11 months and 30 - 40% in patients with a good PS.[60]

**Histology-based treatment of advanced NSCLC**

Choice of systemic therapy based on the histological subdivision of NSCLC is a new paradigm. It was shown that the cisplatin-pemetrexed combination was associated with increased efficacy in non-squamous NSCLC.[60] In patients with adenocarcinoma, the median survival with the cisplatin-pemetrexed regimen was 12.6 compared with 10.9 months with cisplatin-gemcitabine (p<0.05).

Improved efficacy of pemetrexed in adenocarcinoma may in fact be due to low levels of expression of thymidylate synthase (TS), a known target for pemetrexed (68, 69) in adenocarcinoma compared with squamous or small-cell carcinoma.[51] In addition, this regimen was also associated with a favourable tolerability profile. These results led to the approval of the cisplatin-pemetrexed regimen for patients with only non-squamous NSCLC.

**Maintenance therapy**

Until recently, 4 - 6 cycles of combination CHT formed the ‘standard of care’ for patients with advanced NSCLC.[71-72] Extension of the same treatment failed to demonstrate any evidence of benefit. Recent trials of maintenance therapy in stable/responding patients to front-line regimen have shifted the treatment paradigm in favour of this approach. Pemetrexed and erlotinib, administered as single agents, are widely used for maintenance therapy based on the results of randomised trials.[73,74] Maintenance therapy in stable/responding patients to front-line regimen have shifted the treatment paradigm in favour of this approach. Pemetrexed and erlotinib, administered as single agents, are widely used for maintenance therapy based on the results of randomised trials.[73,74] including tolerability and the lack of a significant cumulative toxicity. The benefit is more provocative with erlotinib in those with activating mutations in the EGFR TK domain although it is modest at best in the overall populations. The meta-analysis of maintenance therapy studies demonstrates a significant
improvement in progression-free survival and a modest improvement in overall survival.\cite{79}

Continued controversy among lung cancer care providers exists regarding the optimal patient type for the maintenance therapy and the choice of agent (continuation of the same agent v. switch to a new agent). For now ‘switch maintenance’ has been established until new data become available. Patients with poor or declining PS should not be offered maintenance therapy.\cite{80}

EGFR tyrosine kinase inhibitors (TKIs)

EGFR pathway inhibitors gefitinib and erlotinib were evaluated in patients with refractory NSCLC, with a single agent activity observed in approximately 10 - 20% of the patients.\cite{77-79} The NCIC-BR21 study documented significant improvement in overall survival and progression-free survival with erlotinib in patients with recurrent (second-line) advanced NSCLC.\cite{81} However, gefitinib failed to show a difference in overall survival when compared with a placebo\cite{82} but the subsets of never-smokers/Asian ethnicity patients demonstrated a benefit. Clinical characteristics for response for EGFR TKIs in the early trials included female sex adenocarcinoma histology, never-smokers and those with Asian ethnicity;\cite{83} likely due to an incidence of EGFR activity mutations in the tyrosine kinase domain of the receptor responsible for the selective activity with EGFR TKIs being much higher (~40%) in those with Asian ethnicity. Recent landmark Asian phase III study confirmed the role of EGFR mutation as the main predictor of outcome with EGFR tyrosine kinase inhibitors.\cite{84} It was also shown that administration of gefitinib in patients with wild-type EGFR was not warranted and CHT remains the preferred treatment. Another Asian study\cite{85} confirmed these observations. Adding CHT and EGFR TKIs in the front-line setting in patients with tumours harbouring the EGFR mutation has no benefit.\cite{86,87} Furthermore, a recent trial in never- or light-smokers investigated erlotinib alone or in combination with carboplatin and paclitaxel\cite{88} and found no difference between the two groups even in patients with EGFR mutation, thus excluding a role for combination of EGFR TKIs with CHT.

Cetuximab, a chimeric monoclonal antibody against the EGFR, has minimal activity when given as monotherapy for patients with advanced-stage NSCLC.\cite{89} However, when given in combination with platinum-based CHT, a modest improvement in overall survival was noted (11.3 months v. 10.1 months) over CHT alone.\cite{90} However, with other combination regimens, cetuximab has failed to demonstrate significant improvement in survival.\cite{91}

Anti-angiogenic agents

Bevacizumab was the first targeted agent to demonstrate survival advantage in patients with advanced-stage NSCLC and is now routinely used in the first-line setting for patients with metastatic non-squamous NSCLC. The ECOG4599\cite{92} trial tested 6 cycles of carboplatin-paclitaxel with or without bevacizumab given as monotherapy for non-progressive patients. The overall survival was superior for patients treated with bevacizumab (10.3 months v. 12.3 months, \(p=0.003\)). The progression-free survival duration was also improved with bevacizumab (6.2 v. 4.5 months, \(p<0.001\)). Treatment was tolerated well overall, with <5% incidence of major bleeding events. Another trial (cisplatin and gemcitabine with either bevacizumab or placebo) noted similar efficacy, though a survival benefit was not evident.\cite{93} The AVAiL study also noted no increase in incidence of bleeding when bevacizumab-based regimens were given to patients on full dose anti-coagulation therapy. The safety and efficacy of bevacizumab have also been documented when used in combination with other commonly used platinum-based doublets for the treatment of advanced NSCLC.\cite{94,95} Despite promising phase II data, the combination of bevacizumab with erlotinib failed to improve survival in a randomised study conducted for second-line therapy of advanced-stage NSCLC.\cite{96,97} The same combination used as maintenance therapy also failed to improve survival compared with bevacizumab alone.\cite{98}

Other vascular endothelial growth factor receptor inhibitors

A number of novel multi-kinase inhibitors, which also target the vascular endothelial growth factor (VEGF) receptor, have all been tested for the treatment of advanced NSCLC. When given in combination with CHT, sorafenib failed to show an improvement in survival\cite{99} and in patients with squamous cell histology, the placebo group fared better. When combined with erlotinib in the second-line recurrent NSCLC, sorafenib demonstrated a modest improvement in efficacy in unselected patients when compared with erlotinib alone (PFS, 1.9 v. 3.1 months and OS 6.0 v. 8.1 months).\cite{100} Vandetanib has also been studied in the front-line treatment of advanced NSCLC, where the combination of carboplatin and paclitaxel with vandetanib was associated with a modest improvement in median PFS over that of the same CHT given without vandetanib.\cite{101} In the second-line setting, docetaxel was given alone or in combination with vandetanib,\cite{102} with a modest and significant improvement in median PFS, though overall survival was not improved. In another study, vandetanib was added to pemetrexed for second-line therapy without significance.\cite{103} Vandetanib was also compared directly with erlotinib in a phase III study for advanced NSCLC and was noted to have comparable efficacy.\cite{104} Taken together, these results suggest a possible role of various VEGF receptor inhibitors.

SCLC

Small-cell lung cancer (SCLC) is a highly aggressive carcinoma and represents approximately 15 - 20% of all lung cancer cases.\cite{105} It is an entity of lung cancer that is biologically and clinically different from non-small-cell lung cancer. The World Health Organization (WHO) classification of a lung tumour, revised in 2004\cite{106} remains the cornerstone for lung cancer nomenclature. More than 4 decades ago, the Veterans Administration Lung Group had proposed dividing all SCLC into the two-stage system: limited disease (LD) and extensive disease (ED).\cite{107} The majority of clinicians and investigators still use it nowadays. The vast majority of patients (approximately two-thirds) fall into the ED SCLC, while LD SCLC occurs in approximately one-third of all SCLC. LD SCLC is defined as disease confined to the hemithorax of origin along with the involved regional lymph nodes (hilar and mediastinal), with or without ipsilateral supraclavicular lymph nodes. It can also be considered as a disease that can be incorporated within a single, tolerable TRT treatment field and may include patients with contralateral mediastinal or hilar lymph nodes. What has created confusion, and still does, is the term ‘tolerable TRT treatment field’. It was not always easy to denote and compare it between clinicians,
especially radiation oncologists. The most recent staging classification of SCLC\[107\] represents an important refinement in overall approach in SCLC, while stratification by stage I - III also was recommended in clinical trials of LD SCLC.

**Limited disease**

Although surgery has occasionally been practised in this disease, it never became the standard treatment option owing to lack of data support. In addition, SCLC is known as a radio- and chemosensitive tumour and both CHT and TRT were used alone in LD SCLC in the past. However, results of two meta-analyses that appeared more than 2 decades ago\[108,109\] summarised the data from prospective randomised trials showing small but significant improvement in 2-year and 3-year survival, averaging 5 - 7% and an improvement in local control rates with combined TRT-CHT. Importantly, the widespread use of cisplatin/etoposide and its low toxicity when combined with TRT made more effective use of concurrent TRT and platinum-based CHT, which is nowadays considered as the standard treatment in LD SCLC. In addition, almost 15 years ago meta-analysis\[110\] established the necessity to incorporate prophylactic cranial irradiation (PCI) as a mandatory part of the combined treatment.

Owing to its pronounced chemosensitivity, there are many CHT agents that achieve response rates of ≥30% in SCLC. They include cisplatin, carboplatin, etoposide, cyclophosphamide, doxorubicin, methotrexate and vincristine.\[111\] In a phase III study, the cisplatin/etoposide appeared superior to cyclophosphamide, epirubicin and vincristine in a randomised study. The 5-year survival rates were 5% and 2% in the two treatment arms, respectively \((p=0.0004)\). In subgroup analysis done for 214 patients with LD SCLC, this benefit was even more pronounced (5-year survival, 10% v. 3%; \(p=0.0001\)), while for patients having ED SCLC this benefit remained unreported.\[112\] The use of cisplatin/etoposide in this disease has been additionally supported by a systematic review using 36 randomised trials that have tested single agents, either cisplatin or etoposide, or both (doublet) against regimens not containing these agents. The significant improvement with use of these drugs in comparison with CHT with neither was demonstrated.\[113\] Furthermore, a meta-analysis of 19 trials that investigated the effects of CHT with or without cisplatin in more than 400 patients showed that patients receiving cisplatin had a survival advantage of 4.4% at 1 year.\[114\] In addition, there are long-known facts about the favourable toxicity profile of cisplatin/etoposide regimens\[106\] in combination with TRT.

Some studies advocated treatment of patients for the duration of their life. Only one study demonstrated a survival advantage for LD SCLC,\[115\] while numerous studies showed either no advantage at all\[116-122\] or even showing detrimental effects of continuous CHT.\[123\] Additionally, some studies investigated the optimal number of induction CHT courses. Here, no survival benefit was seen for 8 cycles of cyclophosphamide/etoposide/vincristine compared with 4 cycles, when there was an option of a second-line CHT.\[124\] This was indirectly confirmed as early as 1996 by preliminary results of an Intergroup 0096 study that produced convincing results with only 4 cycles of cisplatin/etoposide and TRT.\[125\] Approaches to intensify the dose of CHT by giving higher doses including doxorubicin or alkylating-based CHT in the 1970s and 1980s,\[126-128\] cisplatin-based in the 1990s,\[129\] granulocyte colony-stimulating factor support,\[130\] by decreasing the interval between the cycles of CHT\[131,132\] or even using bone marrow support\[133\] all showed promising results but always and unequivocally accompanied with such high toxicity that prevented it becoming a standard treatment approach. Investigation of the place and the role of the third-generation drugs (e.g. Topotecan, Paclitaxel) showed they had no impact on survival.\[134-136\] As a summary, there was no firm basis to recommend either dose intensification or the integration of new drugs into actual regimens owing to the risk of severe toxicity and the lack of clearly demonstrated improvement in overall survival. This is especially so when one considers the lack of data for CHT combined with TRT.

Timing of combined TRT and CHT, and total dose and fractionation used, attracted most of the attention of researchers. When timing of combined RT and CHT is considered it is usually defined as either concurrent, sequential or alternating. While some of the initial studies showed promising results for alternating RT and CHT, this type of combined approach is mostly abandoned today. The main question with the remaining two modes of administration is simply whether any portion of TRT and CHT overlap and, if this is the case, when overlapping occurs. Early concurrent thoracic TRT and CHT studies used non-platinum regimens or alternated it with cisplatin/etoposide, while more recent ones were exclusively platinum-based regimens. Some studies\[137-139\] suggested that CHT delayed until the fourth cycle of CHT\[137\] or until day 120\[138\] may be superior to initial TRT or suggested no difference when compared with early TRT and CHT.\[139\] A likely explanation lies in marked reduction of CHT dose in trials\[137,139\] when TRT was applied early. More recent studies using cisplatin/etoposide\[140-141\] or cisplatin/etoposide alternating with cyclophosphamide/doxorubicin/vincristine\[142\] showed clear superiority for early administration of TRT (concurrently given during the first or the second cycle of CHT). Early concurrent TRT and cisplatin/etoposide chemotherapy was capable of achieving 5-year survival of >20%, while late TRT usually obtained only about 10%. Therefore, it became a common practice worldwide to offer TRT with curative doses as early as possible (cycle one or two of CHT). Recently, several meta-analyses and systematic reviews addressed this issue. However, while Huncharek and McGarry\[143\] observed significantly superior survival for early TRT and CHT,\[143\] Fried et al.\[144\] observed a significantly higher 2-year survival in the early group with a suggestion of a similar trend at 3 and 5 years, Pijls-Johannesma et al.\[145\] did not find any advantage for early TRT and CHT. These analyses\[143-145\] brought somewhat conflicting results that were largely resolved by Jeremic,\[146\] who performed 'meta-analysis of the meta-analyses,' identifying common findings in existing analyses. Overall, prevailing evidence is that nowadays, using a 'standard' approach consisting of hyperfractionated TRT and four courses of CHT based on cisplatin-etoposide, early administration seems favourable and should be practised as the standard approach. Reports showing that prolonged (e.g. 4 - 6 cycles) sequential administration of CHT followed by radical TRT is an inferior treatment approach when compared with early and concurrent TRT-CHT are unfortunately still occurring nowadays.\[147,148\]

Regarding TRT dose and fractionation, total doses used for LD SCLC were usually about 50 Gy, given daily, but have ranged from as low as 30 Gy to as high as 70 Gy. In addition, many recent studies have used some form of hyperfractionation (b.i.d.). In the
Intergroup study,[140] 45 Gy given in 30 fractions in 3 weeks (1.5 Gy b.i.d. fractionation) was compared with the same dose given once daily, both with concurrent cisplatin-etoposide CHT. While survival was significantly better in the b.i.d. arm (5-year, 26% v. 19%), this was however achieved with a somewhat higher incidence of acute toxicity. Beside hyperfractionation and conventional fractionation, hypofractionated RT regimens were also used, thought to cause more damage to SCLC cells.[142,150] Currently, two major clinical trials investigating this issue are recruiting patients. In a CONVERT trial, EORTC is evaluating 66 Gy using standard fractionation with the b.i.d. fractionation as used in the Intergroup study (45 Gy in 30 fractions in 15 treatment days in 3 weeks).[149] Similarly, joint CALGB 30610/RTOG 0538 is directly comparing the same control Intergroup regimen with two experimental arms, either conventional (QD) or concomitant boost regimen (CB). The better of the two experimental arms (CB) is then being directly compared with hyperfractionated regimen. Mature data from these trials should hopefully give better perspective about the fractionation issue. Other regimens of b.i.d. irradiation (e.g. 54 Gy in 36 fractions in 18 treatment days in 3.5 weeks) have been successfully implemented in practice concurrently with low-dose CHT.[140]

Extensive disease
For decades, clinicians and investigators considered platinum-etoposide CHT as the standard treatment option for patients with ED SCLC. As an exclusive treatment, it can offer the median survival time of 9 - 12 months and 5-year survivals of 1 - 3%.[151-153] While up to 90% of patients eventually experience objective response following initial courses of CHT, ED SCLC remains a disease with very poor prognosis. This is because most patients unfortunately relapse, leading to outcomes virtually unchanged since platinum-etoposide was introduced several decades ago. It is therefore not hard to see this disease as one of the most frustrating challenges in thoracic oncology. To combat poor prognosis in patients with this disease when treated with CHT alone, various approaches aiming intensification of the treatment have been attempted. Unfortunately, maintenance CHT after 4 - 6 cycles of initial CHT with or without adding the third-generation CHT drug[154,156,158] and higher doses of chemotherapy[133,156] did not prove to be beneficial in this setting. Other approaches such as adding the third CHT agent or using targeted agents did not result in any improvement.

In contrast stand findings of Slotman et al.,[157] who published the results of a trial that changed the practice in ED SCLC by showing that PCI offers significant brain metastasis-free survival, relapse-free survival and overall survival in patients after achieving any response after induction CHT. Similarly to the place and role of PCI in LD SCLC, it is now accepted worldwide as the standard treatment option in responding patients with ED SCLC.

The case for curative TRT in ED SCLC is still an unsolved issue and is under active investigation. Although patients treated with CHT alone in ED SCLC frequently experience chest relapses, even in case of previous CR, TRT had not been systematically investigated in this setting. Also, one must take into account the systemic character of ED SCLC. It may obscure possible effects of TRT on survival (established on a local level), especially in adequately chosen subgroups of patients suitable for ‘curative’ role of TRT. Simply said, patients with ED SCLC may have systemic progression so fast that any possible effect on local control, and subsequently survival, may not be observed due to the short lifespan of these patients. The role of TRT in possible improvement in local (intrathoracic) tumour control and its subsequent impact, if any, on overall survival in favourable patient populations, was evaluated in a prospective randomised trial by Jeremic et al.[155]

After 3 cycles of cisplatin-etoposide regimen, complete patient re-evaluation and restaging was performed and patients achieving CR (at local and distant levels) and those achieving partial response (PR) within the thorax accompanied with the CR elsewhere were then randomised to receive either a) TRT and concurrent low-dose daily CHT, followed by PCI and then by additional 2 cycles of CHT (group 1) or b) 4 additional cycles of cisplatin-etoposide and PCI (group II). Patients in group I achieved results that were significantly better than those in group I: the median survival time was 17 v. 11 months (p=0.041), and 5-year survival rates were 9.1% and 3.7% for groups I and II, respectively. Local recurrence-free survival was also better in group I than in group II, with median time to local recurrence of 30 and 22 months, respectively, and 5-year local recurrence-free survival of 20% and 8.1%, respectively (p=0.062).

The study by Jeremic et al.[155] was the very first prospective randomised study that evaluated curative TRT in ED SCLC. It showed that TRT may have an important place and may have a substantial role in overall treatment of patients with ED SCLC. Emerging reports worldwide confirm this observation. In a Canadian trial of Yee et al.[158] the median time to disease progression was 8.4 months and the median overall survival time was 13.7 months, while in the study of Zhu et al.[159] for TRT-treated group MST was 17.2 months, and 2- and 5-year survival was 36% and 10.1%, respectively (p=0.0001). Studies by Zhu et al.[159] and Yee et al.[158] should not only be seen as confirmatory data of the study of Jeremic et al.[155] but also as confirmatory of existing institutional practices among thoracic oncologists involved in the treatment of ED SCLC since the study of Jeremic et al.[155] This was recently brought to the evidence by the study of Ou et al.,[159] who retrospectively analysed the data from the Cancer Surveillance programmes of Orange, San Diego and Imperial counties in Southern California that indicated the use of TRT in ED SCLC in 35.1% of patients. The 1-year, 2-year, and median overall survival were 27.8%, 9.3% and 8 months and were significantly better than corresponding figures in patients who did not receive TRT (16.2%, 3.8% and 4 months, respectively; p<0.0001). Two large ongoing studies (RTOG in the US and CREST in Holland) will add additional insight into the issue of place and role of TRT in ED SCLC.

Conclusion
Lung cancer has represented an active field of clinical research for many years. Treatment approaches have greatly improved over time, but unfortunately dismal treatment outcomes persist. It is expected that novel surgical and radiation oncology technologies as well as new drugs may help improve outcomes in patients with lung cancer. This should preferably be achieved using clinical trials as a vehicle to provide a high level of evidence, enabling its fast implementation in clinical practice worldwide.
References


Poor inhaler technique is a common problem resulting in inadequate drug delivery and decreased asthma control.¹