

RADIATION ONCOLOGY OF LUNG
CANCER IN THE 21ST CENTURY –
A VIEW FROM BUILDING X

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*RADIATION ONCOLOGY OF LUNG CANCER IN THE 21ST CENTURY –
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ABOUT THE AUTHOR

Branislav Jeremic obtained his medical degree at the University of Belgrade, Serbia. He followed this with a radiation oncology residency – finishing it in 1987 at the age of 29 – after which he obtained his PhD degree in neuro-oncology at the University of Kragujevac, Serbia in 1992.

Having expressed an early interest in pursuing an academic career; he occupied various posts leading to the post of full Professor at the University of Kragujevac, Serbia. He embarked on clinical research in lung, head and neck, and brain tumours, mostly investigating optimisation of concurrent radiation therapy and chemotherapy in locally advanced disease. He designed and executed more than 30 clinical trials in this setting, which resulted in more than 190 peer reviewed papers in major oncological journals worldwide.

He frequently visits various leading institutions around the world and is frequently invited as Visiting Professor (Harvard, Mayo Clinic) and lecturer worldwide. For his intriguing ideas he was granted prestigious fellowships and awards, such as those from the Japanese Society for the Promotion of Science and the Alexander von Humboldt Foundation, including the Friedrich Wilhelm Bessel Prize. As staff radiation oncologist of the International Atomic Energy Agency (IAEA) he shared with other staff and the director of the IAEA the Nobel Peace Prize in 2005 and was responsible for organising the resulting continental (African) event in Cape Town in 2006.

Since December 2012, he occupies the position of Professor and Head of the Division of Radiation Oncology at the Stellenbosch University. He is married to Aleksandra, an electronic engineer, with whom he has one daughter, Marta, herself a freshman student of medicine. His extra-curricular activities include dedication to travel, wine, art and jazz, with emphasis on John Coltrane and late harvest sweet wine.

RADIATION ONCOLOGY OF LUNG CANCER IN THE 21ST CENTURY – A VIEW FROM BUILDING X

INTRODUCTION

Lung cancer continues to be the major cancer killer in both sexes world-wide (1). Approximately 1.6 million new cases of lung cancer are diagnosed each year (2). While the number of cases continues to increase in many places around the world, the overall cure rate from lung cancer is modest (approximately 17%) because the majority of patients present with advanced stage at diagnosis. This is irrespective of refinements in histological aspects, better diagnostic and staging tools – including massive influence of positron emission tomography (PET) scanning – and a sharp shift towards molecular oncology already finding its way to clinics. The most recent update of staging by the International Association for the Study of Lung Cancer (IASLC) provided an important addition to the issue (3). Therefore treatment paradigm may be seen as even more important nowadays, since it ultimately should match pre-treatment advances. Although many treatment modalities are employed in lung cancer, each of which continues to develop, we will concentrate on the non-surgical ones, namely radiation therapy (RT) and drug therapy, which includes both chemotherapy (CHT) and targeted therapy used in both non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). This article focuses on current aspects of non-surgical treatments in lung cancer since they are the domain of expertise of oncologists at the Division of Radiation and Clinical Oncology of the Stellenbosch University and its affiliated Tygerberg Hospital which is housed in a facility known as “Building X”. Ultimately, the goal is to confront worldwide state-of-the-art treatment in this disease with local/national realities, identifying both obstacles and opportunities in this setting.

TECHNOLOGY

In recent decades computerised techniques and software had a significant impact on radiation oncology. With the advent of computed tomography (CT) and magnetic resonance imaging (MRI) radiation oncologists were able to move away from “classic” two-dimensional (2D) to three-dimensional (3D) planning. Increasing

software capabilities enabled more focused irradiation of tumours and less irradiation to surrounding normal tissues. This also meant that with better RT field shaping, an increase in the RT dose delivered to tumours became possible. In lung cancer, numerous such studies in 3D RT showed promise (4, 5) which led to better local control and overall survival.

Translating existing knowledge and techniques into routine clinical use can present significant challenges, but is essential for improving the effectiveness of RT and improving local control and survival (6). Over the last two decades a convergence of technologies has helped to shape modern day RT, including four-dimensional RT (4DRT) for lung cancer and the use of PET-CT in treatment planning of irradiation of lung cancer. Four-dimensional lung RT makes it possible to identify and account for breathing related tumour and organ at risk (OAR) motion during RT planning and delivery. This concept is not new as the movement of lung tumours and surrounding structures was also appreciated during treatment simulation in the 2DRT era. However, at a time when the prognosis for many patients with lung cancer remains poor, many technical advances have failed to enter routine clinical use, even once the available technology has been acquired (7, 8). Although the explanations for this will likely vary between healthcare systems, one probable reason is that useful developments in RT are sometimes seen as difficult to implement, or perceived as too complex or time consuming for day to day use. Frequently, a lack of resources is implicated (7); however, all too often a systematic and focused approach to change and implementation may be lacking (9). Under such conditions the risk is high that technology implementation projects will fail, deliver below expectation or take a very long time to complete, adversely affecting their ability to impact positively on patient outcomes.

Another aspect of treatment planning in lung cancer, widely accepted as “new standard” in well-chosen cases, includes PET-CT-based treatment planning. The burgeoning PET and PET-CT literature clearly shows

that an estimate of disease extent based on PET is very frequently different from and is usually more accurate than an estimate made using CT alone. In a growing number of studies in the literature, PET- or PET-CT-based RT planning has been compared with planning using CT alone, using each patient as their own control. Comparisons between RT treatment plans or tumour volumes made with and without the assistance of PET have been made. PET-based RT planning has been shown to have an especially high impact on patients with atelectasis. On CT scans, atelectatic lung and tumour tissues typically have similar densities. The lack of contrast makes it impossible for the radiation oncologist to do anything other than guess where the boundary between tumour and lung lies. However, when CT information is supplemented by FDG-PET information, especially in the form of a fused PET-CT image, it is often very easy to determine the boundary between normal tissue and tumour, thereby attaining tumour coverage with the least exposure of uninvolved lung. Prospective and retrospective trials in which PET and PET/CT have been used for RT planning in lung cancer have shown a clinically significant impact of PET, although most studies were small. It is currently impossible to quantify the benefit of PET-based planning, but it is reasonable to assume that a treatment plan made using a more accurate estimate of tumour extent is going to be a better one.

So, where does this leave things? Our own department, which operates within the serious constraints of a public healthcare system, aims to create an environment that is receptive to the rapid adoption of new technologies and techniques that can make a specific treatment possible, permit the delivery of potentially toxic treatment with a lower predicted risk or enable greater efficiency. Technology is an enabler but the most important component of the treatment chain remains the radiation and how, when and where it is used. These aspects are taken into account by practicing principles of evidence-based oncology (EBO) with clearly delineated institutional diagnostic and treatment protocols. While taking into account worldwide achievements, accumulated evidence after investigating patterns of practice in this setting was considered an important additive to the decision-making process (10). It enabled identification of professional, scientific but also non-medical reasons that needed to be taken into account. As a result, adaptation to the limited resource setting of developing countries was considered as an absolute prerequisite for meaningful implementation of the RT approach in circumstances where access to RT seemed to be of paramount importance (11). After purchasing a Big Bore CT scanner (Philips, The Netherlands) we became capable of using information gathered during the

scanning process (including synchronisation of breathing cycles with tumour movements in 3D fashion) to create target volumes (that include such movements) being now more closely shaped than without it. This should result in better target coverage and less normal tissue being exposed to irradiation, hence better therapeutic ratio. This became standard procedure for all patients treated with curative intent, similar to the experiences worldwide the past decade. The next step would include 4D treatment delivery, once novel linear accelerators become available coupled with 4D irradiation, which currently available linear accelerators in Building X do not have. In addition, the sophisticated new Big Bore CT scanning process enables implementation of another important RT technique, known as intensity modulated radiation therapy (IMRT).

BIOLOGY

Lung carcinoma is a disease which is characterised by several genetic and molecular biological changes which contribute to carcinogenesis by the activation of oncogenes or inactivation of tumour suppressor genes. In the past 20 years we have substantially increased our knowledge in this field as well as enhanced our skills in detecting these changes. Various groups of factors, proteins, genes and proto-oncogenes as well as small molecules have been identified and related to different processes. This has largely helped more sophisticated histological refinements, ultimately leading to recent histological classifications. Knowledge gathered eventually also lead to the engineering of specific drugs to be used in clinics. Due to their “targeted” nature, they have all been frequently grouped among “targeted agents” to differentiate them from more classically used, systemic drug therapy (also known as chemotherapy). It was assumed that this “targeted” nature would allow for more specific (hence, better) effectiveness and, consequently, less toxicity. Some of the most investigated molecular abnormalities are listed in Table 1.

MOLECULAR ABNORMALITIES IN LUNG CANCER CELLS

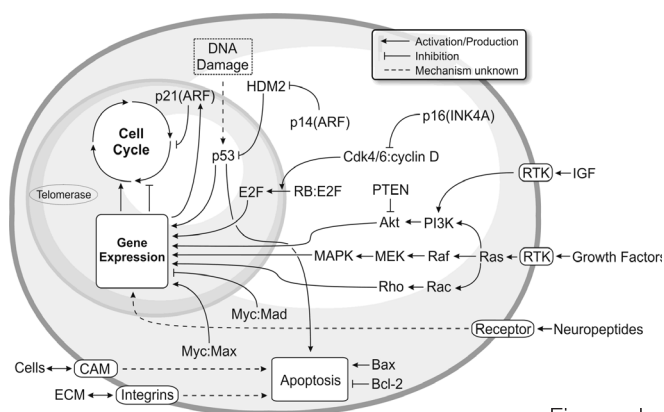


Figure 1

Growth Signals	NSCLC	SCLC
Ras	25	<1
Akt	70-90	65
Myc	20- 60	20-30
EGFR	50	0-50
HER2/neu	30	30
c-Kit	30- -40	50
Neuropeptides	~50	~50
IGF	~90	~90
Tumor Suppressor Genes		
RB	15- -30	>90
p16(INK4A) inactivation	50-70	0-20
3p deletions	70	90
FHIT inactivation	40-70	70
RASSF1A silencing	50	90
Apoptosis		
p53	40-50	60-75
Bcl-2	20-35	71
Replicative Potential		
Telomerase	80-100	80-100
Angiogenesis		
VEGF	75	75
COX-2	>70	Not reported
Metastasis		
N-CAM1, non-adhesive	Not reported	90
Laminin-5 inactivation	20-60	68-85

Table 1

In spite of booming clinical research in this field and approval by the FDA in the USA for several classes of targeted agents, molecular events on cellular level are still not completely demystified (see Figure 1). This represents a serious call for more preclinical research in lung cancer, largely considered vitally dependent on incorporation of novel biological aspects in existing treatment paradigms.

CLINICAL SCIENCE

Lung cancer has been and still is one of the major battlegrounds in clinical oncology. The highest level of EBO, i.e. prospective randomised clinical trials and meta-analyses, is continuously shaping the existing knowledge and influencing the decision-making process. As such, they exist in all lung cancer stages and both histological forms investigated.

In early stage (I-II) NSCLC, RT has traditionally been used in patients technically operable, but deemed medically inoperable due to existing comorbidities, producing

median survival times (MSTs) of 24 to 36 months and five-year survivals of 25–35% (12–17), though still significantly inferior to surgical reports. However, patients treated with RT alone are deemed as “very unfavourable” (comorbidities, understaging, clinical staging) and hence, not directly comparable to their surgical counterparts. Finally, when one takes into account cancer-unrelated deaths and correct the outcomes by using cancer-specific or cause-specific survival as an endpoint, RT results become much better (18). Recent decades also brought novel RT technologies into this setting. First 3DRT (4, 5) and then stereotactic body radiation therapy (SBRT) have been used with increasing frequency in medically inoperable patients with stage I-II NSCLC. Initial single-institutional reports on SBRT were followed by a number of prospective phase II studies around the globe which all showed excellent results (local control, 80–95%; three-year survival, 60–70%) irrespective of the technique and dose-fractionation parameters used (19–22). These encouraging results were coupled with retrospective reports from various institutions directly comparing surgical to RT cohorts of patients. These reports (23, 24) showed similarity in overall results (local control, overall survival, toxicity) and called for more formal comparison, using prospective randomised trial settings. Two on-going studies in the USA comparing surgery to RT should shed more light on the problem of preferred treatment option in patients with stage I-II NSCLC.

In locally advanced (stage III) NSCLC, three recent meta-analyses (25–27) reconfirmed findings of previous clinical trials that concurrent RT-CHT is superior to RT alone (28, 29) and sequential RT-CHT (30, 31), establishing it as the standard treatment in the last decade. While some studies indicated that concurrent RT-CHT can have more side-effects (32, 34), those studies used high-dose RT and concurrently given high-dose CHT. When, on the other side, high-dose RT was combined with low-dose (mostly given daily) CHT, side-effects became much less frequent (28, 29). Importantly, this particular approach (concurrent RT and low-dose CHT) achieved the best overall results with MSTs of more than 20 months and an overall five-year survival rate of more than 20%. Furthermore, concurrent RT-CHT proved to be an effective and low-toxic approach in the most “favourable” subgroup of patients with stage IIIA NSCLC in which several attempts to optimise outcome failed when surgery was included. Data from prospective randomised trials showed that concurrent RT-CHT was not inferior to neoadjuvant RT-CHT followed by surgery (35, 35) and, as recently shown (37, 38), exclusive and concurrent RT-CHT can produce results (MST, 38 months; five-year survival, 41%) which seem better than those produced in any of the surgical studies done so far.

In spite of being staged as locally advanced (non-metastatic) NSCLC, some patients are deemed incurable from the outset, mostly those with bulky tumours and unfavourable clinical characteristics (e.g. poor performance status, pronounced weight loss). In this patient population, RT has been frequently used to palliate existing symptoms and, if possible, prolong life. Until the first study from the UK Medical Research Council (MRC) was published in 1991 (39), a typical course was 30 Gy in 10 fractions (fx). Since then, several randomised phase III trials (40–47) compared a short-course RT (8 or 10 Gy/1fx or 17 Gy/2fx or 16 Gy/2fx) to a normo-fractionated RT ranging 20–50 Gy. In two trials (45, 46) the effect on symptoms was in favour of the higher dose; otherwise the effect on disease-related symptoms were equal. In three trials (41, 43, 46) the survival was in favour of the high-dose arm; 39 Gy/13fx, 30 Gy/10fx and 30 Gy/10fx, respectively. One trial (47) reported a survival benefit for 16 Gy/2fx versus 20 Gy/5fx. In another trial (44), 17 Gy/2fx was compared with two high-dose arms; 42 Gy/15fx and 50 Gy/25fx, with no difference in MST found. Five randomised phase III studies (48–52) have compared different normo- to high-dose regimens. Nearly all had stage III localised disease with WHO performance status (PS) 0–2. One study reported better palliation in the high-dose arm (66). Four studies provided data on survival, being equal in three and better for the high-dose arms in one (51). The latter study (51) is a particularly interesting one since it compared 40 Gy/10fx (split) to 50 Gy/25fx to “wait and see”. The survival in this “wait and see” arm was inferior compared to the two actively treated arms. While effect on symptoms and palliative effect may be similar regardless of dose and fractionation, trend of more rapid relief of symptoms in favour of hypofractionation is observed with no major difference in MST being observed. To investigate the issue whether some patients with localised stage III disease may benefit from a protracted high-dose RT, a MRC study (51) was undertaken which focused only on stage III disease with good PS. It compared 17 Gy/2fx (arm 1) with 39 Gy/13fx (arm 2). The MST increased from 7 to 9 months in arm 2 ($p > .05$), with 1- and 2-year survival rates of 31 and 9% versus 36 and 12% in arm 1 and arm 2, respectively. Another study (44) compared strict low-dose to 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) (53) showed three- and five-year survival rates in the three arms (17 Gy/2fx, 42 Gy/15fx, 50 Gy/25fx) of 1, 8 and 6%, versus 0, 4 and 3%, respectively. 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 PS and less weight loss could be treated with a protracted fractionated regimen of 30–45 Gy. General observation from all of these studies can be extrapolated to patients with stage IV disease which can also safely be treated with a hypofractionated schedule. While palliative RT aims to treat symptoms from intrathoracic tumours, in otherwise symptom-free patients immediate RT may have unnecessary side-effects and may not prevent development of later symptoms (54, 55). A “wait and see” procedure is therefore advocated until the patient becomes symptomatic.

Systemic therapy remains the mainstay of treatment of metastatic NSCLC. It is also frequently used in poor-risk stage IIIB NSCLC patients presenting with no intrathoracic symptoms of the disease. Combination CHT with a platinum-based regimen (cisplatin or carboplatin) has emerged as standard therapy the past few decades (56) and improvements in overall survival and quality of life have been demonstrated over best supportive care alone (57). Carboplatin-based regimens have a favourable tolerability over cisplatin-based regimens (58, 59). Despite the marginally higher response rate with cisplatin-based regimens, carboplatin-based regimens have found wide applicability in routine care. Recent improvements in anti-emetic therapy, however, made cisplatin-based regimens more tolerable. A number of randomised clinical trials have established the superiority of platinum-doublets over single-agent therapy (60–62). 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 (58, 60, 63–66). The use of triplets has generally resulted in higher toxicity without improved efficacy and has therefore largely been abandoned (67). With the currently available platinum-based two-drug regimens, the MST and one-year survival rate are 8–11 months and 30–40% in patients with a good PS (68). Choice of systemic therapy based on the histological subdivision of NSCLC is a new paradigm. It was shown that cisplatin-pemetrexed combination was associated with increased efficacy in non-squamous NSCLC (69). In patients with adenocarcinoma, the median survival with the cisplatin-pemetrexed regimen was 12.6 m vs. 10.9 m with cisplatin-gemcitabine ($p < .05$). 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. Until recently, four to six cycles CHT formed the “standard of care” for patients with advanced NSCLC (70, 71). Extension

of the same treatment failed to demonstrate any evidence of benefit. However, success of maintenance therapy with pemetrexed or erlotinib administered as single agents in stable/responding patients to front-line regimen have shifted the treatment paradigm in favour of this approach (72, 73). The meta-analysis of maintenance therapy studies demonstrates a significant improvement in progression-free survival and a modest improvement in overall survival (74). Continued controversy among lung cancer care providers exists regarding the optimal patient type for maintenance therapy and the choice of agent (continuation of the same agent vs. switching to a new agent). For now "switch maintenance" has been established until new data becomes available. Patients with poor or declining PS should not be offered maintenance therapy (94). EGFR (epidermal growth factor receptor) tyrosine kinase inhibitors (TKIs) (gefitinib, erlotinib, cetuximab) have all been investigated in metastatic NSCLC. While EGFR mutation was shown to be the main predictor of outcome with EGFR TKIs (76), studies (77–79) excluded a role for combination of EGFR TKIs in combination with CHT. Of 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 ECOG 4599 (80) trial tested six 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 m. 12.3 m, $p = .003$). The safety and efficacy of bevacizumab has also been documented when used in combination with other commonly used platinum-based doublets used for the treatment of advanced NSCLC (81). Of VEGF (vascular endothelial growth factor) receptor inhibitors, when combined with CHT, sorafenib (82, 83) and vandetanib (74) were tested with modest improvements in outcome, suggesting only a possible role of various VEGF receptor inhibitors with more clinical trial testing.

In the SCLC domain, in limited disease (LD), two meta-analyses that appeared more than two decades ago (85, 86) showed small but significant improvement in two-year and three-year survival rates, averaging 5–7% with combined RT-CHT. Importantly, the widespread use of cisplatin/etoposide, and its low toxicity when combined with RT, made more effective use of concurrent RT and platinum-based CHT, which is nowadays considered as the standard treatment in LD SCLC. In addition, almost 15 years ago meta-analysis (87) established the necessity to incorporate prophylactic cranial irradiation (PCI) as a mandatory part of the combined treatment. Due to its pronounced chemosensitivity, there are many

CHT agents which achieve response rates of $\geq 30\%$ in SCLC. They include cisplatin, carboplatin, etoposide, cyclophosphamide, doxorubicin, methotrexate and vincristine (88). In a phase III study, cisplatin/etoposide appeared superior to cyclophosphamide, epirubicin and vincristine in a randomised study. The five-year survival rates were 5% and 2% in the two treatment arms, respectively ($p = .0004$) (89). The use of cisplatin/etoposide in this disease has been additionally supported by a systematic review using 36 randomised trials which have tested single-agent 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 (90). Approaches to intensify the dose of CHT by giving higher doses (91), occasionally including granulocyte colony-stimulating factor support (92) or by decreasing the interval between the cycles of CHT (93) or even using bone marrow support (94), all showed promising results. However, they were always and unequivocally accompanied with high toxicity, which prevented it becoming standard treatment approach. Investigation of the place and role of third-generation drugs (e.g. topotecan, paclitaxel) showed they had no impact on survival (95, 96). When timing of combined RT and CHT is considered, some studies (97, 98) suggested that RT delayed until the fourth cycle of CHT (97) or later may be superior to initial RT or suggested no difference when compared to early RT and CHT (98). More recent studies using cisplatin/etoposide (99–101) showed clear superiority for early administration of RT (concurrently given during the first or second cycle of CHT) since it was capable of achieving five-year survival rates of $> 20\%$, whilst late RT usually obtained only about 10%. Recently, several meta-analyses and systematic reviews (102–104) brought somewhat conflicting results which were largely resolved by Jeremic (105) who performed "meta-analysis of the meta-analyses", who showed that early hyperfractionated RT and four courses of CHT based on cisplatin-etoposide should be practiced as standard approach. Regarding RT dose and fractionation, total doses were usually about 50 Gy, given daily, but 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 (106), 45 Gy given in 30 fractions in three weeks (1.5 Gy b.i.d. fractionation) was compared with the same dose given once daily, both with concurrent cisplatin-etoposide CHT. The survival was significantly better in the b.i.d. arm (five-year survival rate, 26% versus 19%). Hypofractionated RT regimens were also used, thought to cause more damage to SCLC cells (101). Currently, two major clinical trials investigating this issue are recruiting patients

(CONVERT of the EORTC in Europe and CALGB 30610/RTOG 0538 in the USA) by directly comparing the same hyperfractionated regimen with either the conventional or concomitant boost regimen.

For decades, clinicians and investigators considered platinum-etoposide CHT 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 five-year survival rates of 1–3% (107, 108). While up to 90% of patients eventually respond following initial courses of CHT, most of patients unfortunately relapse. Therefore, various approaches aiming intensification of the treatment were attempted. Unfortunately, maintenance CHT after four to six initial cycles with or without adding the third-generation drug (95, 109, 110) and higher doses of CHT (94, 111) did not prove to be beneficial in this setting. Adding a third CHT agent or using targeted agents also did not result in any improvement. Recent findings of Slotman et al. (112), however, changed the practice in ED SCLC by showing that PCI offer significant brain-metastasis-free survival, relapse-free survival and overall survival in patients after achieving any response after induction CHT. It is now accepted worldwide as standard treatment option in responding patients with ED SCLC. The case for curative RT 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 complete response, RT had not been systematically investigated in this setting. The systemic character of ED SCLC may also obscure possible effects of RT on survival (if previously established on a local level). The role of RT was evaluated in a prospective randomised trial by Jeremic et al. (108). After three cycles of CHT, complete patient re-evaluation and restaging was performed and patients were then randomised to receive either RT and concurrent CHT, followed by PCI (group I) or continue with four additional cycles of cisplatin-etoposide and PCI (group II). The MST was 17 vs. 11 months ($p = .041$), and five-year survival rates were 9.1 and 3.7% for groups I and II, respectively. This study (108) was the very first to show that RT may play a substantial role in the treatment of ED SCLC. Emerging reports worldwide confirm this observation. Both Yee et al. (113) and Zhu et al. (114) provided confirmatory data of the study of Jeremic et al. (108). Recently, Ou et al. (115) retrospectively analysed the data from Southern California to document the use of RT in ED SCLC in 35.1% patients. The two-year survival rate and MST were 9.3% and 8 months, respectively; significantly better than corresponding figures in patients who did not receive RT (3.8% and 4 months, respectively; $p < .0001$). Two large on-going studies (RTOG in the USA and CREST in

Holland) will provide further insight into this issue.

REALITIES vs. OPPORTUNITIES

Technological and biological advances in the field of non-surgical treatment of lung cancer and current standards of care in this disease must, however, be placed into the context of both existing realities and opportunities of the Division of Radiation Oncology of Stellenbosch University and its affiliated Tygerberg Hospital. Realities include the following:

1. Limited resource setting of a developing country:
 - a. Only three linear accelerators (LINACs) exist to treat more than 2000 new cancer patients annually, the oldest LINAC being more than 25 years old; hence, both limited access to RT (with resulting long waiting lists) and lack of modern RT techniques available on modern LINACs
 - b. Limited access to modern drugs, which are deemed “too expensive” (not cost-effective), although majority of them (e.g. paclitaxel) are not so, since they already exist in generic forms
 - c. Limited available space in the Division (Building X) for active or supportive treatment of lung cancer patients
2. Poor awareness of lung cancer and poor healthcare infrastructure:
 - a. Frequent delay in both diagnosis and referral
 - b. Usual advanced disease at presentation (advanced NSCLC or ED SCLC); hence, a substantial number of patients are treated palliatively
 - c. Strong dependence on transport aspects of cancer patients, resulting in “missing” appointments and missing treatment days (of RT and/or CHT), including frequent observation of “patient lost to follow-up”
 - d. Lack of appropriate communication with peripheral oncologists and non-oncologists in the process of follow-up and, if necessary, treatment of cancer- unrelated diseases and conditions

Opportunities include the following:

1. Improvement in existing logistics and infrastructure at SU/TBH:

- a. Weekly Multidisciplinary (Lung) Disease Team (MDT) meetings with presentation of new cases in front of a panel of various lung cancer specialists
- b. Updated (as of February 2013) lung cancer diagnostic and therapeutic protocols (in collaboration with other SU/TBH services)
- c. Newly formed Lung Cancer Group with various specialists working professionally and scientifically on the lung cancer problem
- d. A list of professional and scientific meetings proposed to be organised on national and international level (starting in October 2013)
- e. Initial efforts aiming to address the need for a lung cancer database
- f. Improved collaboration with existing non-clinical services of SU/TBH (e.g. radiobiology, pharmacology)

2. Partially available new and modern technology:

- a. Introduction of a Big Bore CT scanner exclusively dedicated to treatment planning purposes with available "gating" component, helping better delineation of the tumour volumes during breathing cycles; however, "gating" is available only for tumour delineation (planning) process and not for treatment
- b. Introduction of PET-CT in treatment planning of lung cancer patients, with or without "gating"
- c. Introduction of IMRT in selected cases, with or without "gating"

3. Identification of priority areas in the research of lung cancer:

- a. Existing equipment would pinpoint to the 4D in planning of RT of lung cancer as well as using PET-CT in 3D and 4D treatment planning of lung cancer and eventually to IMRT
- b. Existing type of patients would pinpoint research focusing upon:

- i. Patients with atelectasis
 - ii. Patients with HIV and/or TB
 - iii. Patients with poor performance status (e.g. PS3)
 - iv. Short fractionation RT regimen and short (low-toxic) CHT
 - v. Recurrent cancers treated with either protons and/or novel drugs
4. Publication of papers in national and international journals

CONCLUSIONS

Lung cancer is one of the major cancer types seen at SU/TBH and definitely the deadliest one. In spite of serious limitations, opportunities clearly exist for a systematic and orchestrated approach in clinic, education and research in this field. Working on this problem on interdisciplinary and interprofessional level remains the main objective for oncology at SU/TBH, with expertise and dedication as necessary ingredients for overall success.

REFERENCES

1. Jemal A, Center MM, DeSantis C, et al. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010;19:1893–1907.
2. Jemal A Sr, Xu J, Ward E. Cancer statistics. *CA Cancer J Clin* 2010 July.
3. Goldstraw P, Crowley J, Chansky K, et al. The IASLC lung cancer staging project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncology* 2007;2:706–714.
4. Graham MV, Purdy JA, Emami B, et al. Preliminary results of a prospective trial using three-dimensional radiotherapy for lung cancer. *Int J Radiat Oncol Biol Phys* 1995;33:993–1000.
5. Robertson JM, Ten Haken RK, Hazuka MB, et al. Dose escalation for non-small-cell lung cancer using conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1079–1085.
6. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: A population-based time-trend analysis. *J Clin Oncol* 2010;28:5153–5159.
7. Mayles WP. Radiotherapy Development Board. Survey of the availability and use of advanced radiotherapy technology in the UK. *Clin Oncol (R Coll Radiol)* 2010;22:636–642.
8. Routsis D, Staffurth J, Beardmore C, et al. Radiotherapy Development Board. Education and training for intensity-modulated radiotherapy in the UK. *Clin Oncol (R Coll Radiol)* 2010;22:675–680.
9. Kotter JP. Leading change: Why transformation efforts fail. *Harv Bus Rev* 1995;73:59–67.
10. Kepka L, Danilova V, Saghatelian T, et al. Resources and management strategies for the use of radiotherapy in the treatment of lung cancer in Central and Eastern European countries: Results of an International Atomic Energy Agency (IAEA) survey. *Lung Cancer* 2007;56:235–245.
11. Macbeth FR, Abratt RP, Cho KH, et al. Lung cancer management in limited resource settings: Guidelines for appropriate good care. *Radiother Oncol* 2007;82:123–131.
12. Dosoretz DE, Katin MJ, Blitzer PH, et al. Radiation therapy in the management of medically inoperable carcinoma of the lung: Results and implications for future treatment strategies. *Int J Radiat Oncol Biol Phys* 1992;25:3–9.
13. Kupelian PA, Komaki R, Allen P. Prognostic factors in the treatment of node-negative non-small-cell lung carcinoma with radiotherapy alone. *Int J Radiat Oncol Biol Phys* 1996;36:607–613.
14. Sibley GS, Jamieson TA, Marks LB, et al. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: The Duke experience. *Int J Radiat Oncol Biol Phys* 1998;40:149–154.
15. Rosenthal SA, Curran WJ Jr, Herbert SH, et al. Clinical stage II non-small-cell lung cancer treated with radiation therapy alone. The significance of clinically staged ipsilateral hilar adenopathy (N1 disease). *Cancer* 1992;70:3410–3417.
16. Jeremic B, Shibamoto Y, Acimovic LJ, et al. Hyperfractionated radiotherapy alone for clinical stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 1997;38:521–525.
17. Jeremic B, Shibamoto Y, Acimovic LJ, et al. Hyperfractionated radiotherapy for clinical stage II non-small-cell lung cancer. *Radiother Oncol* 1999;51:141–145.
18. Jeremic B, Classen J, Bamberg M. Radiation therapy alone in technically operable, medically inoperable early stage (I/II) non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;54:119–130.

19. Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small-cell lung cancer: A 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666–670.
20. Nagata Y, Negoro Y, Aoki T, et al. Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2002;52:1041–1046.
21. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation. Results of a phase I study in medically inoperable stage I non-small-cell lung cancer. *Chest* 2003;124:1946–1955.
22. Zimmermann F, Geinitz H, Schill S, et al. Stereotactic hypofractionated radiation therapy for stage I non-small-cell lung cancer. *Lung Cancer* 2003;48:107–114.
23. Yendamuri S, Komaki RR, Correa AM, et al. Comparison of limited surgery and three-dimensional conformal radiation in high-risk patients with stage I non-small-cell lung cancer. *J Thorac Oncol* 2007;2:1022–1028.
24. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol* 2010;28:928–935.
25. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181–2190.
26. O'Rourke N, Roqué I, Figuls M, et al. Concurrent chemoradiotherapy in non-small-cell lung cancer. *Cochrane Database Syst Rev* 2010;6:CD002140.
27. Liang HY, Zhou H, Li XL, et al. Chemo-radiotherapy for advanced non-small-cell lung cancer: Concurrent or sequential? It's no longer the question: A systematic review. *Int J Cancer* 2010;127:718–728.
28. Jeremic B, Shibamoto Y, Acimovic LJ, et al. Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. *J Clin Oncol* 1995;13:452–458.
29. Jeremic B, Shibamoto Y, Acimovic LJ, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: A randomized study. *J Clin Oncol* 1996;14:1065–1070.
30. Furuse K, Nishikawa H, Takada Y, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
31. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small-cell lung cancer: Randomized phase III trial RTOG9410. *J Natl Cancer Inst* 2011;103:1452–1460.
32. Lee JS, Scott C, Komaki R, et al. Concurrent chemoradiation therapy with oral etoposide and cisplatin for locally advanced inoperable non-small-cell lung cancer: Radiation Therapy Oncology Group protocol 91-06. *J Clin Oncol* 1996;14:1055–1064.
33. Komaki R, Scott C, Ettinger D, et al. Randomized study of chemotherapy/radiation therapy combinations for favorable patients with locally advanced inoperable non-small-cell lung cancer: Radiation Therapy Oncology Group (RTOG) 92-04. *Int J Radiat Oncol Biol Phys* 1997;38:149–155.
34. Byhardt RW, Scott CB, Ettinger DS, et al. Concurrent hyperfractionated irradiation and chemotherapy for unresectable non-small-cell lung cancer. Results of Radiation Therapy Oncology Group 90-15. *Cancer* 1995;75:2337–2344.

35. Van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442–450.
36. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. *Lancet* 2009;374:379–386.
37. Jeremic B, Milicic B, Milisavljevic S. Radiotherapy alone versus radiochemotherapy in patients with favorable prognosis clinical stage IIIA non-small-cell lung cancer (NSCLC). *Clin Lung Cancer* 2013;14:172–180.
38. Mac Manus MP, Everitt S, Bayne M, et al. The use of fused PET/CT images for patient selection and radical radiotherapy target volume definition in patients with non-small-cell lung cancer: Results of a prospective study with mature survival data. *Radiother Oncol* 2013;106:292–298.
39. Medical Research Council Lung Cancer Working Party. Inoperable non-small-cell lung cancer (NSCLC): A Medical Research Council randomised trial of palliative radiotherapy with two fractions or ten fractions. *Br J Cancer* 1991;63:265–270.
40. Medical Research Council Lung Cancer Working Party. A Medical Research Council randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. *Br J Cancer* 1992;65: 931–941.
41. Medical Research Council Lung Cancer Working Party. Randomised trial of palliative 2-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small-cell lung cancer and good performance status. *Clin Oncol* 1996;8:167–175.
42. Rees GJG, Devrell CE, Barley VL, et al. Palliative radiotherapy for lung cancer: Two versus five fractions. *Clin Oncol (R Coll Radiol)* 1997;9:90–95.
43. Bezzak A, Dixon P, Brundage M, et al. Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC.15). *Int J Radiat Oncol Biol Phys* 2002;54:719–728.
44. Sundstrøm S, Bremnes R, Aasebø U, et al. Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: A national phase III trial. *J Clin Oncol* 2004;22:801–810.
45. Erridge SC, Gaze MN, Price A, et al. Symptom control and quality of life in people with lung cancer: A randomised trial of two palliative radiotherapy fractionation schedules. *Clin Oncol* 2005;17:61–67.
46. Kramer G, Wanders SL, Noordijk EM, et al. Results of the Dutch National Study of the palliative effect of irradiation using two different treatment schemes for non-small-cell lung cancer. *J Clin Oncol* 2005;13:2962–2970.
47. Senkus-Konefka E, Dziadziuszko R, Bednaruk-Mlynski E, et al. A prospective randomised study to compare two palliative radiotherapy schedules for non-small-cell cancer (NSCLC). *Br J Cancer* 2005;92:1038–1045.
48. Simpson JR, Francis ME, Perez-Tamayo R, et al. Palliative radiotherapy for inoperable carcinoma of the lung: Final report of a RTOG multi-institutional trial. *Int J Radiat Onc Biol Phys* 1985;11:751–758.
49. Teo P, Tai TH, Choy D, et al. A randomized study on palliative radiation therapy for inoperable non-small-cell carcinoma of the lung. *Int J Radiat Onc Biol Phys* 1987;14:867–871.
50. Abratt RP, Shepherd LJ, Mameena Salton DG. Palliative radiation for stage 3 non-small-cell lung cancer. A prospective study of two moderately high dose regimens. *Lung Cancer* 1995;13:137–143.

51. Reinfuss M, Glinski B, Kowalska T, et al. Radiothérapie du cancer bronchique non á petites cellules de stade III inoperable asymptomatique. Résultats définitifs d'un essai prospectif randomisé. *Cancer Radiother* 1999;3:475–479.
52. Nestle U, Nieder C, Walter K, et al. A palliative accelerated irradiation regimen for advanced non-small-cell lung cancer vs conventionally fractionated 60 Gy: Results of a randomized equivalence study. *Int J Radiat Oncol Biol Phys* 2000;48:195–203.
53. Sundstrøm S, Bremnes R, Brunsvig P, et al. Palliative thoracic radiotherapy in locally advanced non-small-cell lung cancer: Can quality-of-life assessments help in selection of patients for short- or long-course radiotherapy? *J Thorac Oncol* 2006;1:816–824.
54. Falk S, Girling DJ, White RJ, et al. Immediate versus delayed palliative thoracic radiotherapy in patients with unresectable locally advanced non-small-cell lung cancer and minimal thoracic symptoms: Randomised controlled trial. *BMJ* 2002;325:465–468.
55. Sundstrøm S, Bremnes R, Brunsvig P, et al. Immediate or delayed radiotherapy in advanced non-small-cell lung cancer (NSCLC)? Data from a prospective randomised study. *Radiother Oncol* 2005;75:141–148.
56. Bunn PA Jr. Chemotherapy for advanced non-small-cell lung cancer: Who, what, when, why? *J Clin Oncol* 2002;20(18 Suppl):235–335.
57. Rapp E, Pater JL, Willan A, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer – Report of a Canadian multicenter randomized trial. *J Clin Oncol* 1988;6:633–641.
58. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
59. Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: A Southwest Oncology Group trial. *J Clin Oncol* 2000;19:3210–3218.
60. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: A Southwest Oncology Group study. *J Clin Oncol* 1998;16:2459–2465.
61. Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2000;18:122–130.
62. Lilenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: The cancer and leukemia group B (study 9730). *J Clin Oncol* 2005;23:190–196.
63. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-arm cooperative study in Japan. *Ann Oncol* 2007;18:317–323.
64. Fossella F, Pereira JR, Von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group. *J Clin Oncol* 2003;21:3016–3024.
65. Scagliotti GV, Parikh P, Von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.

66. Belani CP, Lee JS, Socinski MA, et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small-cell lung cancer. *Ann Oncol* 2005;16:1069–1075.
67. Alberola V, Camps C, Provencio M, et al. Cisplatin plus gemcitabine versus a cisplatin-based triplet versus non-platinum sequential doublets in advanced non-small-cell lung cancer: A Spanish Lung Cancer Group phase III randomized trial. *J Clin Oncol* 2003;21:3207–3213.
68. Ramalingam S, Belani CP. State-of-the-art chemotherapy for advanced non-small-cell lung cancer. *Semin Oncol* 2004;31(1 Suppl 1):68–74.
69. Eismann U, Oberschmidt O, Ehnert M, et al. Pemetrexed: mRNA expression of the target genes TS, GARFT and DHFR correlates with the in vitro chemosensitivity of human solid tumors. *Int J Clin Pharmacol Ther* 2005;43:567–569.
70. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. *J Clin Oncol* 2002;20:1335–1343.
71. Smith IE, O'Brien ME, Talbot DC, et al. Duration of chemotherapy in advanced non-small-cell lung cancer: A randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. *J Clin Oncol* 2001;19:1336–1343.
72. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: A randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432–1440.
73. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–529.
74. Soon YY, Askie LM, Boyer MJ. Duration of chemotherapy for advanced non-small-cell lung cancer: A systematic review and meta-analysis of randomized trials. *J Clin Oncol* 2009;27:3277–3283.
75. Belani CP, Ghazal H, Ramalingam SS, et al. Phase III study of maintenance gemcitabine (G) and best supportive care (BSC) versus BSC, following standard combinatin therapy with gemcitabine-carboplatin (G-Cb) for patients with advanced non-small-cell lung cancer (NSCLC). *J Clin Oncol* 2010;28(15s).
76. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
77. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: A phase III trial-INTACT 2. *J Clin Oncol* 2004;22:785–794.
78. Jänne PA, Wang X, Jones D, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol* 2012;30:2063–2069.
79. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): An open-label randomised phase III trial. *Lancet* 2009;373:1525–1531.
80. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
81. Patel JD, Hensing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for non-squamous non-small-cell lung cancer. *J Clin Oncol* 2009;27:3284–3289.

82. Scagliotti G, Novello S, Von Pawel J, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:1835–1842.
83. Spigel DR, Burris HA, Greco FA, et al. Randomized, double-blind, placebo-controlled, phase II trial of sorafenib and erlotinib or erlotinib alone in previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2011;29:2582–2589.
84. Herbst RS, Sun Y, Eberhardt WE, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): A double-blind, randomised, phase 3 trial. *Lancet Oncol* 2010;11:619–626.
85. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618–1627.
86. Warde P, Payne D. Does thoracic radiation improve survival and local control in limited-stage small cell carcinoma of the lung? *J Clin Oncol* 1992;10:890–895.
87. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;341:476–484.
88. Sandler AB. Chemotherapy for small-cell lung cancer. *Semin Oncol* 2003;30:9–25.
89. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: Results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol* 2002;20:4665–4672.
90. Mascaux C, Paesmans M, Berghmans T, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small-cell lung cancer with methodology assessment and meta-analysis. *Lung Cancer* 2000;30:23–36.
91. Cohen MH, Broder LE, Fossieck BE, et al. Intensive chemotherapy of small-cell bronchogenic carcinoma. *Cancer Treat Rep* 1977;61:349–354.
92. Ardizzoni A, Tjan-Heijnen VCG, Postmus PE, et al. Standard versus intensified chemotherapy with granulocyte colony-stimulating factor support in small-cell lung cancer: A prospective European Organization for research and treatment of cancer – Lung Cancer Group phase III trial – 08923. *J Clin Oncol* 2002;20:3947–3955.
93. Steward WP, Von Pawel J, Gatzemaier U, et al. Effects of granulocyte colony-stimulating factor and dose-intensification of V-ICE chemotherapy in small-cell lung cancer: A prospective randomised study of 300 patients. *J Clin Oncol* 1998;16:642–650.
94. Leyvraz S, Pampallona S, Martinelli G, et al. A threefold dose intensity treatment with ifosfamide, carboplatin, and etoposide for patients with small-cell lung cancer: A randomized trial. *J Natl Cancer Inst* 2008;100:533–541.
95. Schiller JH, Adak S, Cella D, DeVore RF, Johnson DH. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593 – A phase III trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19:2114–2122.
96. Mavroudis D, Papadakis E, Veslemes M, et al. A multicenter randomized clinical trial comparing paclitaxel-cisplatin-etoposide versus cisplatin-etoposide as first-line treatment in patients with small-cell lung cancer. *Ann Oncol* 2001;12:463–470.
97. Perry MC, Eaton WL, Propert KJ, et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. *N Engl J Med* 1987;316:912–918.

98. Work E, Nielsen O, Bentzen S, et al. Randomized study of initial versus late chest irradiation combined with chemotherapy in limited-stage small-cell lung cancer. *J Clin Oncol* 1997;15:3030–3037.
99. Jeremic B, Shibamoto Y, Acimovic LJ, et al. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer. *J Clin Oncol* 1997;15:893–900.
100. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: Results of the Japan Clinical Oncology Group study 9104. *J Clin Oncol* 2002;20:3054–3060.
101. Murray N, Coy, Pater J, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. *J Clin Oncol* 1993;11:336–344.
102. Huncharek M, McGarry R. A meta-analysis of the timing of chest irradiation in the combined modality treatment of limited-stage small-cell lung cancer. *Oncologist* 2004;9:665–762.
103. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol* 2004;22:4837–4845.
104. Pijls-Johannesma MC, De Ruyscher D, Lambin P, Rutten I, Vansteenkiste JF. Early versus late chest radiotherapy for limited-stage small-cell lung cancer. *Cochrane Database Syst Rev* 2005;1:CD004700.
105. Jeremic B. Timing of concurrent radiotherapy and chemotherapy in limited-disease small-cell lung cancer: “Meta-analysis of meta-analyses”. *Int J Radiat Oncol Biol Phys* 2006;64:981–982.
106. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:264–271.
107. Bunn PA Jr, Cohen MH, Ihde DC, et al. Advances in small-cell bronchogenic carcinoma: A commentary. *Cancer Treat Rep* 1977;61:333–342.
108. Jeremic B, Shibamoto Y, Nikolic N, et al. The role of radiation therapy in the combined modality treatment of patients with extensive disease small-cell lung cancer (ED SCLC): A randomized study. *J Clin Oncol* 1999;17:2092–2099.
109. Splinter TAW. Chemotherapy of small-cell lung cancer (SCLC): Duration of treatment. *Lung Cancer* 1989;5:186–196.
110. Bunn PA Jr. Clinical experience with carboplatin (paraplatin) in lung cancer. *Semin Oncol* 1992;19(Suppl 2):1–11.
111. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994;12:2022–2034.
112. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357:664–672.
113. Yee D, Butts C, Reiman A, et al. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small-cell lung cancer. *Radiother Oncol* 2012;102:234–238.
114. Zhu H, Zhou Z, Wang Y, et al. Thoracic radiation therapy improves the overall survival of patients with extensive-stage small-cell lung cancer with distant metastasis. *Cancer* 2011;117:5423–5431.
115. Ou S-H, Ziogas A, Zell JA. Prognostic factors for survival in extensive stage small-cell lung cancer (ED-SCLC). The importance of smoking history, socioeconomic and marital statuses, and ethnicity. *J Thorac Oncol* 2009;4:37–43.

