11

Radiation Therapy in Management of Small-Cell Lung Cancer

Erkan Topkan and Cem Parlak
Baskent University Adana Medical Faculty,
Department of Radiation Oncology
Turkey

1. Introduction

Worldwide, lung carcinoma (LC) is the commonest and deadliest form of cancer in men and women, exceeding the mortality of prostate, breast, and colorectal cancers combined (Jemal et al., 2009). Irrespective of histologic subtype, more than 90% of all LC is strongly associated with cigarette smoking (Alavanja et al., 2002), and the risk significantly increases with the number of cigarettes smoked per day, degree of inhalation, age at initiation, and life-long cumulative exposure (Tyczynski et al., 2003). Although survival at 5-year is less than 15%, yet, there exists no single proven chemopreventive measure reducing the risk of LC development, except for cessation of cigarette smoking.

Histologically, non-small cell LC (NSCLC) and small-cell LC (SCLC) are the two commonest types of LC, constituting 85-90% and 10-15% of all cases, respectively (Rosenzweig et al., 2010). SCLC (previously called oat cell carcinoma) is relatively less common than NSCLC; however, because of a more aggressive growth pattern and clinical course, its treatment is more challenging. Although there is no significant difference in outcome by histologic subtype, the World Health Organization classification subdivides SCLC into three cell types; pure or classic, variant cell, and mixed (Brambilla et al., 2001). SCLC displays a high propensity to metastasize, and usually a remarkable but temporary responsiveness to chemotherapy and radiotherapy (RT). Although some may be cured, most patients succumb to disease because of rapid development of drug resistance and resultant disease progression. Median survival for metastatic SCLC is only 10 months, which is interestingly very similar to patients with relatively much more drug resistant NSCLC of similar stage (Chute et al., 1997). Despite great improvements in imaging, pathology, genetics, chemotherapy, and RT techniques, this did not translate into the clinical outcomes, thus, the current overall survival rate for SCLC patients is not different than that was 20 years before (Chute et al., 1997).

This chapter has been designated to focus specifically on treatment of SCLC patients, with specific emphasises on the technical basis and outcomes of current RT and concurrent chemoradiotherapy (C-CRT). Therefore, readers interested in more comprehensive information about the epidemiology, etiology, preventive measures, pathologic and genetic basis and surgical treatment of SCLC are referred to excellent reviews available in this book.

2. Staging

Management of SCLC begins with the accurate staging of the disease. Historically, using the Veteran's Administration Lung Study Group (VALG) criteria (Zelen, 1973), staging of SCLC was simplified to include two stages: limited stage SCLC (LS-SCLC), and extensive stage SCLC (ES-SCLC). LS-SCLC is defined as the disease confined to the ipsilateral hemithorax which can be safely encompassed within a tolerable single radiation port. Involvement of ipsilateral supraclavicular lymph node region is also included in limited-stage disease. In contrast; patients with ES-SCLC have disease that is beyond the ipsilateral hemithorax. Besides the hematogenous spread, involvement of contralateral supraclavicular lymph node region and/or presence of malignant pleural- and/or pericardial effusion are included in extensive-stage disease. Only less than one third of SCLC patients present with limited-stage disease, while remaining two thirds have extensive-stage disease, and are treated with palliative chemotherapy.

The revised American Joint Committee on Cancer (AJCC) staging system implemented the TNM staging for NSCLC, but its use for SCLC was also recommended in sixth and seventh editions (Edge, 2010; Greene, 2002). Recent study by Vallieres et al., constituting of 349 patients with resected SCLC confirmed the utility of TNM-based pathologic staging in terms of survival outcomes. But, because of being restricted to only 5% SCLC patients presenting with an operable disease at presentation, TNM-based staging has not been routinely adopted two tired VALG staging system (LS-SCLC and ES-SCLC) in this group of patients (Vallieres et al., 2009).

3. Prognostic factors

Despite paramount improvements in imaging and treatment modalities, prognosis of patients with SCLC is still unacceptably poor with median survival ranges of only 15-20 months for LS-SCLC and 8-13 months for ES-SCLC (Lally et al, 2007). Furthermore, 5-year survivors are reported to be only in the respective ranges of 10-13% and 1-2%, emphasizing the futility of the condition (Lassen, 1995; Tai, 2003). A number of factors have been assigned to carry prognostic importance for patients with SCLC but the most important tumor related factor is the VALG stage (LS-SCLC versus ES-SCLC). In LS-SCLC, early stage disease that corresponds to TNM stage 1 carries the best prognosis specifically in the absence of elevated serum lactate dehydrogenase levels (Byhardt, 1986; Lassen, 1995). Similar to other tumor sites, weight loss and poor performance status are significant predictors of unfavorable outcome (Paesmans et al., 2000). Likewise, men fare poorer than women (Lally et al, 2007). In ES-SCLC, the number of organ sites and site of involvement are also strongly associated with prognosis (Albain et al, 1991). Compared to other sites, involvement of bone marrow, liver, or central nervous system signify unfavorable disease course.

Compared to NSCLC, SCLC is more frequently associated with paraneoplastic syndromes either via antibody-mediated tissue destruction or via ectopic hormone production (Lally et al, 2007). Although, some debate exists, unlike antibody-mediated paraneoplastic syndromes, ectopic hormone production is generally accepted as a predictor of poor outcome. Favorable prognosis linked to antibody-mediated paraneoplastic syndromes may be related with presence of a fully competent immune system, indicating the need for exploration of immunotherapy adjunct to standard treatment approaches in this patients group.

4. Treatment for limited-stage small cell lung carcinoma

4.1 Chemotherapy

In LS-NSCLC, chemotherapy trials conducted in the 1970s improved survival from weeks to months. Over the following three decades, several studies have shown that combination chemotherapy regimens were clearly more efficacious than single agent regimens. Response rates of 70%-85%, with complete response of 20%-30%, are encouraging but virtually almost every patient relapses (Lally et al, 2007). Results of randomized investigations and meta-analysis for the most active regimen indicated the superiority of etoposide plus cisplatin (EP) combination over the other tested combinations (Fukuoka, 1991; Pujol, 2000; Roth, 1992; Sundstrom, 2002). Therefore, the EP combination has become the standard care chemotherapy combination in United States and Europe since 1980s. Although cisplatin is the backbone of chemotherapy, carboplatin may be substituted for cisplatin in older patients or in those with renal insufficiency without an apparent efficacy loss (Okamoto et al., 2005).

Chemotherapy combinations constituting a variety of newer agents, like irinotecan, have been tested in an effort to improve current outcomes in LS-SCLC. However, these agents do not appear to be more active than older counterparts. Irinotecan, which was the most promising of them, has been tested in three randomized phase 3 trials (Hanna, 2006; Lara, 2009; Noda, 2002). The first trial by Noda et al. demonstrated the superiority of cisplatin plus irinotecan (IP) over the standard EP combination in a Japanese Clinical Oncology Group (JCOG) trial (Noda et al., 2002). However, two subsequent trials launched in United States could not validate these results (Hanna, 2006; Lara, 2009). In both trials response and survival rates in patients treated with investigational IP were found to be equivalent to standard EP. The potential benefit of adding a third agent to standard EP has also been extensively investigated. Higher response rates at a cost of significantly increased toxicity were achieved, with no notable improvement in median survival duration over EP alone (Loehrer, 1995; Mavroudis, 2001; Niell, 2005; Pujol, 2001).

Based on these results, the current standard for the first line chemotherapy in this group of patients is 4 to 6 cycles of EP combination, and further treatment with either maintenance therapy or four cycles of topotecan following standard EP regimen has not been proved to improve outcomes (Schiller, 2001; Sculier, 1998).

4.2 Thoracic radiotherapy

Before the introduction of chemotherapy in the 1970s, thoracic radiotherapy (TRT) was the mainstay of treatment for LS-SCLC. However, management of LS-SCLC with chemotherapy alone results in unacceptable rates of intrathoracic failures, ranging from 75 to90% (Faivre-Finn et al. 2005). In this setting, integration of TRT to chemotherapy reduces these failures up to 30 to 60%. Impact of such a decrease in intrathoracic failures has been extensively investigated by two meta-analyses (Pignon, 1992; Warde & Payne, 1992). In the first one, Warde and Payne (Warde & Payne, 1992) analyzed 11 randomized studies including 1911 patients, and reported a significantly longer overall survival with the combination of TRT and chemotherapy than with chemotherapy alone, with an absolute benefit of 5.4% at 2-year ($p<0.001$). In the other meta-analysis, Pignon et al. (Pignon et al., 1992) included 13 trials consisting of 2103 LS-SCLC patients. Combination of TRT and chemotherapy again resulted in an absolute survival advantage of 5.4% at 3-year compared to chemotherapy alone ($p=0.001$). Based on the results of these two meta-analyses combination of TRT and chemotherapy became the established standard of care in LS-SCLC.

TRT delivered both sequentially and concurrently with chemotherapy has been intensively assessed. Although sequential treatment approach has the theoretical benefits by chance of irradiating smaller target volumes with resultant reduced toxicity rates, the associated longer overall treatment time potentially increases the risk of accelerated tumor repopulation and development of treatment-resistant clones. In this context, concurrent use of chemotherapy and TRT does not only reduce the risk for accelerated repopulation but also offers a chance for better locoregional control by utilizing the radiosensitizing efficacy of chemotherapeutic agents. Nevertheless, despite such potential benefits, because of increased risk for higher rates of acute toxicity with concurrent chemoradiotherapy, sequential use of chemotherapy and TRT may be more feasible in elderly patients or those with larger tumors.

Data on the optimum radiotherapy dose and fractionation come mostly from retrospective and phase 2 prospective studies. The results from non-randomized studies indicate a notable increase in local control when the dose of TRT is increased from 35 to 40 Gy, and a slightly further gain with 50 Gy. Laboratory studies have suggested that typical SCLC cell lines have radiation survival curves with little shoulders indicating that accelerated fractionation schemes would, therefore, be advantageous (van Meerbeeck et al., 2011). In 1999, two different cooperative groups randomized patients to once-a-day versus twice-a-day TRT with concurrent chemotherapy, as depicted in Table 1 (Bonner, 1999; Turrisi, 1999). In the study by Bonner et al., authors reported the North Central Cancer Treatment Group (NCCTG) experience, and concluded that there was no difference in survival with twice-daily TRT versus once daily counterpart (Bonner et al., 1999). However, this study has been criticized because of using split-course RT schedule which is currently an established factor to increase the chance for accelerated repopulation, and therefore, affect treatment outcomes in an unfavorable fashion. In the landmark study by Turissi et al. (Int-0096), authors reported the long-term outcomes of 358 patients enrolled onto the cooperative group study of Eastern Cooperative Oncology Group/ Radiation Therapy Oncology Group (ECOG/RTOG) with the diagnosis of LS-SCLC. Results of this study demonstrated that twice-daily 45 Gy (1.5 Gy BID) and concurrent CRT was significantly superior over conventionally fractionated TRT scheme (Turrisi et al., 1999). Based on the results of this latter study, the current standard of care for medically fit LS-SCLC became the 45 Gy (1.5 Gy BID) TRT and concurrent EP. Nonetheless, because of the higher frequency of dose limiting ≥ Grade 3 esophagitis in twice-daily TRT scheme, 54 Gy (1.8 Gy per fraction) in 30 days and concurrent EP is also a common and acceptable treatment scheme.

Carcinoma and Leukemia Group B (CALGB) conducted two phase 2 trials to investigate the potential benefit of a higher dose of 70 Gy given in 35 fractions within 7 weeks (Bogart, 2004; Miller, 2007). In the first study, median survival, 2-year survival rate, and ≥ Grade 3 esophagitis rate were 22 months, 48%, and 21%, respectively (Bogart et al., 2004). In the second study respective rates were 20 months, 35%, and 30% (Miller et al., 2007). Based on the promising results of these two trials, two ongoing randomized Phase 3 trials were conducted to compare standard Turissi protocol with escalated doses of conventionally fractionated TRT. Results of these two landmark trials summarized in Table 2, will address the question whether the higher doses delivered by once daily scheme in 7-week, could compensate for the longer interval between the initiation of treatment and the end of TRT, in the expense of increased risk for accelerated tumor cell repopulation.

In treatment of LS-SCLC, another issue of interest is whether TRT should be administered early or late during the chemotherapy course. This question has been addressed by a number of trials with no firm conclusions (Gregor, 1997; Jeremic, 1997; Murray, 1993; Perry,

	ECOG/RTOG		P	NCCTG		P
Study Arms	Chemo + TRT	Chemo + twice daily TRT		Chemo + TRT	Chemo + twice daily TRT	
Number	176	182	-	133	130	-
Total cycles of CTX	4	4	-	6	6	-
Cycles of concurrent CTX	2	2	-	2	2	-
Median survival (mo)	18.6	20.3	0.04	21	21	0.49
2-year survival (%)	42	44		47	45	
3-year survival (%)	-	-		34	29	
5-year survival (%)	16	26		-	-	
≥Grad 3 Esophagitis	33 (16%)	67 (32%)	<0.001	7 (5.3%)	16 (12.3%)	0.05
≥Grad 3 Pulmonary toxicity	8 (4%)	14 (5%)	0.97	6 (4.5%)	8 (6.2%)	>0.05

Table 1. Limited-stage small cell lung cancer with daily versus twice-daily TRT

Study	CTX	Standard arm	Experimental arm	Primary endpoint	Expected enrollment
CONVERT	4xEP	45 Gy/30 fx, 3 week, BID, starting at second course	66 Gy/33 fx, 6.6 week, once-daily, starting at second course	Overall survival	532
RTOG0538/ CALGB30610	4xEP	45 Gy/30 fx, 3 week, BID, starting at first or second course	A: 70 Gy/35 fx, 7 week, once-daily B: 61.2 Gy/34 fx, 5 week, BID, starting at first course	Overall survival	712

Table 2. Benchmark ongoing trials of chemoradiotherapy for limited-stage small-cell lung carcinoma

1987; Skarlos, 2001; Takada, 2002; Work, 1997). In the landmark phase 3 ECOG/RTOG trial reported by Turissi et al., the shortening of total irradiation period from 5 weeks to 3 weeks was associated with an absolute 10% (16% versus 26%) increase in 5-year survival (Turrisi et al., 1999). Results of three other trials revealed a significantly superior survival advantage for early TRT over late TRT, confirming the findings of intergroup trial (Jeremic, 1997; Murray, 1993; Takada, 2002). The impact of timing of TRT relative to chemotherapy has also been addressed by various meta-analyses. De Ruysscher and colleagues conducted a meta-analysis of phase III trials combining TRT and platinum-based chemotherapy, and concluded that the most important predictor of 5-year survival was the interim between the start of any treatment until the end of RT (SER), with shorter SERs (<30 days) being associated with the highest 5-year survival rates (>20%) (De Ruysscher et al., 2006). With a subsequent meta-analysis, Pijls-Johannesma and colleagues evaluated the impact of timing of TRT by comparing early versus late TRT, by defining early TRT as within 30 days of beginning

chemotherapy. In presence of platinum-based chemotherapy, the 2- and 5-year survival rates were favoring early TRT, and this difference was significant only if the TRT was administered in a treatment period of less than 30 days. In this study, patient compliance was found to be of paramount importance, indicating the importance of patient selection in clinical trials (Pijls-Johannesma et al., 2007). In a relatively older meta-analysis by Fried et al., late TRT was defined as beginning 9 weeks after the initiation of chemotherapy or after the completion of third cycle of chemotherapy. Similar to other subsequent meta-analyses, this meta-analysis also demonstrated a statistically significant benefit of early TRT over late TRT in terms of 2-year overall survival. On subset analysis of studies that used hyperfractionated TRT, treatment with early versus late TRT revealed a survival benefit, but not when once-daily TRT was employed. Likewise, the survival benefit for early versus late TRT was observed uniquely in studies using platinum-based chemotherapy, which was not notable in studies using non-platinum-based chemotherapy (Fried et al., 2004). Results of the available studies and meta-analyses suggested an interaction between TRT and chemotherapy and, accelerated tumor cell repopulation was postulated to be triggered by the first dose of any effective cytotoxic agent (De Ruysscher et al., 2006). Therefore, to obtain the highest chance for local/regional control, the last clonogenic tumor cell should be killed by the end of TRT (van Meerbeeck et al., 2011). Hence, long-term survival decreases with increasing time between the initiations of any treatment and the completion of TRT.

In summary, current evidence recommends the early administration of 45 Gy (1.5 Gy, BID) with concurrent EP at systemic doses in medically fit LS-SCLC patients.

4.4 Radiotherapy techniques and treatment fields

Treatment for lung tumors, including SCLC, is complex. In order to ensure safe and effective RT, several issues must be considered: (a) accurate target volume delineation; (b) proximity of dose limiting normal structures (lung, spinal cord, esophagus, heart, brachial plexus, and liver); (c) anatomic slope of the chest surface; (d) inhomogenities resulting from the presence of nonuniform tissues on the way of RT; (e) frequent need for irregular field dose calculations; (f) respiratory motion of the targeted tumor and normal tissues such as lung, heart and liver, depending on the location of the primary tumor and involved lymphatic region(s).

The ultimate goal of any RT application is to deliver the prescribed dose homogenously (not cooler than 95% and not hotter than 107%) to the planned target volume and keep the dose to non-tumorous normal tissues as minimum as possible respecting their tissue architecture (serial versus parallel) and their radiation tolerance limits. In this setting, with the aid of imaging with anatomic computerized tomography (CT), functional 18-F-fluorodeoxyglucose positron emission tomography (PET), preferably fusion of both) and the use of 3–dimensional conformal RT, and novel 4-dimensional image-guided RT (IGRT), it is easier than before to achieve these goals. Additionally, the dose-volume histograms (DVH) created for each patient makes it possible to anticipate the potential early and late toxicity risks based on the organ of interest measures and, therefore, modify the treatment plans as necessitated.

There is considerable debate on the size of the RT portals of SCLC. Historically, RT portals were large, encompassing the primary tumor as well as both hilar, entire mediastinal and both supraclavicular lymph node regions with generous margins. This was believed to be necessary to ensure adequate coverage of gross disease prior to the routine use of CT- based RT planning. Although such large field plans may guarantee the irradiation of target volumes, they are also associated with increased acute and late toxicity rates and unplanned

treatment delays, which may negatively impact both quality of life measures and local/regional control rates and related survival outcomes. This issue is specifically argued when TRT is delayed after the completion of induction chemotherapy. Although some authors advocate generous portals encompassing the pre-chemotherapy volumes as stated above, others argue that only limited portals encompassing the pre-chemotherapy primary tumor and high-risk nodal areas with a 1-cm margin are adequate, since effective chemotherapy has the theoretical chance to cope with subclinical or microscopic disease eliminating the need for generous portals. This latter approach has the additional potential for decreased treatment related toxicity specifically when TRT is administered concurrently with chemotherapy. Treatment directed at pre- versus post-chemotherapy volumes is also an ongoing issue of conflict. The unique randomized trial that addressed this issue is the one conducted by the South West Oncology Group (SWOG). In this study, patients achieving a partial response after chemotherapy were randomized to pre- versus post-chemotherapy volume irradiation arms. Outcomes of this benchmark study did not indicate any superiority for pre-chemotherapy volume irradiation arm over post-chemotherapy irradiation counterpart, in terms of neither local/regional nor survival rates (Kies et al., 1987). This issue has latter been investigated by Liengswangwong et al. in a retrospective analysis. The authors were unable to find a benefit favoring pre-chemotherapy large-field TRT over post-chemotherapy limited-field TRT (Liengswangwong et al., 1994).

In NSCLC, elective irradiation of hilar and/or mediastinal lymphatic regions has gradually been replaced by treatment limited to nodes identified by CT or FDG –PET as being involved. For SCLC, evidence is scarce to support this approach. In a prospective study by De Ruysscher et al., authors limited the RT fields to only CT-positive mediastinal lymph nodes in a cohort of 27 patients with LS-SCLC. The authors reported an isolated regional recurrence rate of 11%, which was higher than similar studies using elective mediastinal irradiation. However, because of small sample size, no definitive conclusions can be drawn from this study (De Ruysscher et al., 2006). In a larger phase 2 study including 60 LS-SCLC patients, van Loon et al., irradiated only the lymph nodes that appeared to be involved on FDG-PET, and reported an isolated nodal failure rate of 3%, which awaits to be confirmed by further studies with larger cohorts (van Loon et al., 2010). A typical 3-D conformal RT plan used in our institution and associated DVH is shown in Figure 1.

4.5 Prophylactic cranial irradiation

Approximately 10-14% of SCLC patients have detectable brain metastases (BM) at the time of initial diagnosis (Hardy et al., 1990). During the course of disease, the incidence of BM increases up to more than 50%, which is far beyond in postmortem examinations (Hirsch, 1983; Nicholson, 2002). The incidence of BM is directly proportional with the survival time, indicating a potential for further increase with implementation of more effective treatment protocols (Komaki, 1981; van Oosterhout, 1996). Compared to patients with LS-SCLC, the risk for BM occurrence is higher for patients with ES-SCLC reaching 69% at 2- years of diagnosis (van Oosterhout, 1996; Yang GY & Matthews, 2000).

Impact of BM on socioeconomic issues and quality of life is significantly worse than the impact of failure at other metastatic sites. Patients with BM are often obliged to spend significant time hospitalized, and suffer loss of independence (Felletti et al., 1985). Despite cranial irradiation and/or chemotherapy, the treatment of clinically established BM is partially satisfactory with intracranial disease control rates of about 50% and overall survival of 4 to 6 months (Carmichael, 1988; Lucas, 1986; Postmus, 1989).

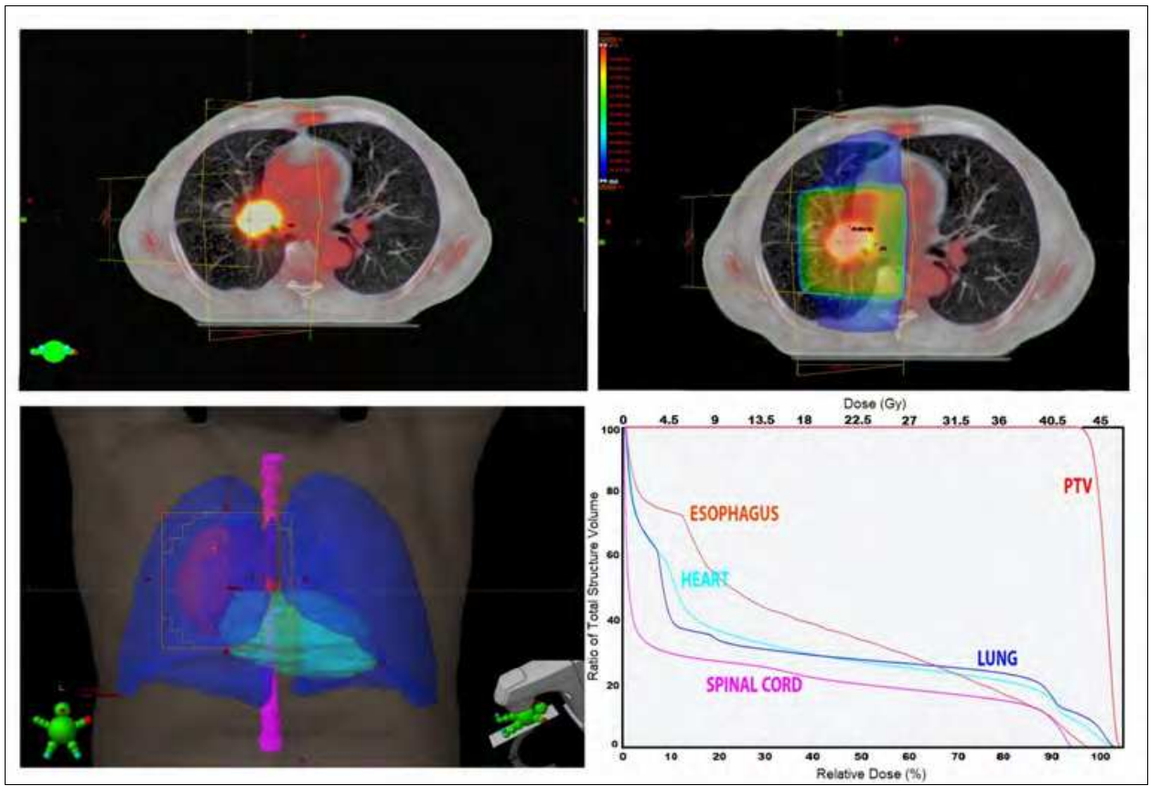


Fig. 1. An example of typical 3-D conformal RT plan and associated DVH.

Several randomized trials have been conducted to investigate the utility of prophylactic cranial irradiation (PCI) in prevention of BM development in patients with LS-SCLC. Logically, in patients with extracranial disease under control, PCI may eliminate the intracranial microscopic tumor cell deposits with relatively low radiation doses and, therefore, may increase the long-term survival. Results of two randomized controlled trials from France (PCI85) and United Kingdom (UK02) demonstrated a trend for better survival with PCI but neither could reach statistical significance (Arriagada, 1995; Gregor, 1997). Up till now, no individual randomized trial has conclusively demonstrated a survival benefit for PCI, which may be related with their deficiency in provision of sufficient power to detect moderate differences in survival.

To conduct a meta-analysis of trials using PCI and to make recommendations for clinical practice, the PCI Overview Collaborative Group was established. The meta-analysis reported by Auperin et al. in 1999 included individual data from patients enrolled on seven prospective randomized PCI trials. Trials eligible in the meta-analysis were limited to those, in which patients had been treated with systemic chemotherapy with/without TRT to a complete clinical response, and no known BM. PCI treatments were generally between 24 to 40 Gy, administered in 2-3 Gy per day. Results of this meta-analysis, for the first time, demonstrated a statistically significant survival advantage favoring PCI over non-PCI arm. The relative risk for death in the treatment group, as compared to control group, was 0.84 (95 CI, 0.73-0.97; P= 0.01), which corresponds to a 5.4% higher rate of survival at 3 years (20.7% versus 15.3%), and the survival advantage persisted over time. As a percent gain over control, this represents a 35% increase in the proportion of surviving patients. There was also significant difference in

disease-free survival at 3 years from 13.3% in the non-PCI group to 22.1% in the PCI group ($p<0.0001$). PCI was additionally associated with a 25.3% absolute decrease in the cumulative incidence of BM at 3 years, from 58.6% to 33.3% ($p<0.0001$) (Auperin et al., 1999). Results of this comprehensive meta-analysis have recently been confirmed by the review of data from Surveillance Epidemiology and End Results (SEER) reported by Patel et al. Of 7995 LS-SCLC patients included, 670 received PCI. Better overall and cause-specific survival were observed in patients treated with PCI, and corresponding 2- and 5-year survival rates were 23% and 11% without PCI and 425% and 19% with PCI (Patel et al., 2009).

Based on the results of meta-analysis by Auperin et al., PCI became the standard of care in patients with LS-SCLC demonstrating complete response following systemic and/or local/regional treatment (Auperin et al., 1999). However, an important concern about the use of PCI is the need for determination of an established non-toxic but effective fractionation scheme and total dose. Available data have shown that lower doses of PCI may be less effective in preventing CNS failures (Auperin, 1999; Gregor, 1997). Recently, Le Pechoux et al. published the results of benchmark international PCI trial evaluating radiation dose for PCI in LS-SCLC. The study randomized 720 LS-SCLC patients from 157 centers to one of two PCI arms: Arm-1 included patients receiving standard-dose PCI to 25 Gy in 2.5 Gy per fraction, and Arm 2 included patients receiving higher dose PCI to 36 Gy delivered in 2 Gy once daily or 1.5 Gy twice daily. No significant difference of BM incidence was reported between two study arms, but there was a significantly higher rate of cancer-related mortality in the higher dose arm as a result of unexplained finding of more deaths from extracranial disease progression (Le Pechoux et al., 2009). Based on the results of this study, 25 Gy delivered at 2.5 Gy per fraction per day remains the standard of care for PCI in LS-SCLC patients.

5. Treatment for extensive-stage small cell lung carcinoma

5.1 Radiotherapy

Combination chemotherapy is the mainstay in the management of ES-SCLC, but as intrathoracic disease control may be a significant challenge to overcome in a significant proportion of patients, role of consolidative TRT has been addressed in several trials. Jeremic et al. randomized patients with ES-SCLC, who responded completely at extrathoracic sites and at least partially at thorax, to consolidation TRT versus observation arms after 3 cycles of systemic chemotherapy. In experimental arm, TRT was administered in an accelerated hyperfractionated scheme of 54 Gy given in 1.5 Gy twice daily fractions concurrently with EP chemotherapy. The median and a 5-year overall survival in the TRT arm and no TRT arm were 17 versus 11 month and 9.1% versus 3.7%, respectively (Jeremic et al, 1999). However, the results of ongoing studies addressing the question of TRT both in Netherlands and in Canada should be awaited before its routine recommendation for patients with ES-SCLC.

5.2 Prophylactic cranial irradiation

Although the beneficial effects of PCI on prevention of BM occurrence and on augmentation of overall and disease-free survival have been well established in LS-SCLC patients, this issue had remained to be answered in ES-SCLC until the publication of the results of recent EORTC trial. In this benchmark study, patients with ES-SCLC who had a response to chemotherapy were randomized to PCI versus observation arms. The cumulative risk of symptomatic BM at 1-year and the 1-year survival rate were 14.6% versus 40.4% ($p<0.001$),

and 27.1% versus 13.3% (p=0.003), both favoring the PCI arm (Slotman et al., 2007). Following this study, similar to LS-SCLC, PCI became the standard of care in ES-SCLC patients except for those experience disease progression during chemotherapy.

6. Treatment related toxicity

Acute side effects of CRT often begin during the second or third weeks of treatment. Cessation of the tobacco abuse should be the first step in the management of SCLC patients to increase the efficacy of intended CRT as well as to decrease the incidence and severity of the treatment related side effects. Dermatitis may be seen but severe cases are rare. Prevention of trauma is the key for prevention of severe and difficult to treat dermatitis development. Aloe vera gel and perfume-free ointments can be safely used in mild to moderate dermatitis. Acute esophagitis is usually the dose limiting toxicity of mediastinal irradiation, which rarely progress to severe late esophagitis. In patients with mild to moderate swallowing difficulty, semisolid nutrition and liquid form analgesics may be beneficial. Although confirmation with randomized controlled Phase 3 trials are needed, based on the results of two recent retrospective series by Algara et al. and Topkan et al., prophylactic use of glutamine may be beneficial in preventing and reducing the severity of acute esophagitis (Algara, 2007; Topkan, 2009). Nonproductive dry cough may be seen if trachea and/or major bronchi is/are involved in the high dose radiation portals.

After the completion of TRT, radiation pneumonitis (RP) may be seen at 2 to 4 weeks. RP is a form of radiation-induced lung disease, mimicking bacterial pneumonia. Symptoms usually include non-productive dry cough, dyspnea, chest pain, palpitations, malaise, and occasionally fever. Rales can be noted on auscultation. Plain X-rays and CT are beneficial in demonstrating the extent of perivascular haziness and alveolar filling densities primarily within the radiation portal. Treatment of RP includes use of 60 mg/day prednisone for two weeks followed by gradual tapering at following 3 to 12 weeks. There is no evidence supporting the use of prophylactic use of glucocorticoids or antibiotics in preventing or reducing the severity of RP.

Late toxicities involve chronic esophagitis, pericarditis, myocarditis, pancarditis, spinal cord injury, radiation induced lung fibrosis, and secondary cancers. Incidence and severity of all these late toxicities depend on the total dose and dose per fraction, fractionation scheme, interim between subsequent fractions, volume of non-target organ exposed to specified doses of RT, and concurrent use of chemotherapy. Currently, excluding the symptomatic management measures, the best treatment method is prevention of toxicity in the presence of agents with at best limited healing efficacy. To achieve this, tolerance doses must be strictly respected. Specific for radiation-induced lung fibrosis, which may potentially be fatal, a recent study demonstrated promising efficacy of pentoxyfilline and alpha-tocopherol combination in reduction of fibrotic lung area up to 50% at median 24 months of drug use.

At long-term, potential neurocognitive toxicity of PCI is of great concern, since sequalae like severe memory loss, intellectual impairment or even dementia, ataxia, or seizures have been reported in retrospective studies with small size and questionable methodology. For example, neurocognitive assessments prior to chemotherapy and/or PCI are lacking despite the fact that almost 50% of SCLC patients have neurologic and neurocognitive impairments prior to onset of PCI (Arriagada, 1995; Gregor, 1997; Grosshans, 2008; Komaki, 1995). Neurocognitive impairment risk has been reported to strongly associate with daily fraction sizes of >3 Gy (Paumier & A Le Péchoux, 2010). In one study, Shaw et al. found that the risk for neurocognitive impairment following PCI was 2% and 10% at 2- and 5-year follow-ups,

respectively. Furthermore, the authors reported that all toxicities were seen with regimens using daily fraction sizes of >3 Gy (Shaw et al., 1994). Notably, two randomized studies with neurocognitive assessments in patients randomized to PCI versus non-PCI did not demonstrate any deterioration in neurologic functions at 30 months, and quality of life measures at baseline, at 6 and 12 months (Arriagada, 1995; Gregor, 1997). However, these findings do not mean that PCI has no potential toxicity and should be administered to every patient with the diagnosis SCLC, rather they impact the importance of patient selection based on neurocognitive tests for safer PCI applications.

7. Treatment algorithm for LS-SCLC and ES-SCLC

Our current instutitional treatment algorithm for LS-SCLC and ES-SCLC patients is as depicted in Figure 2.

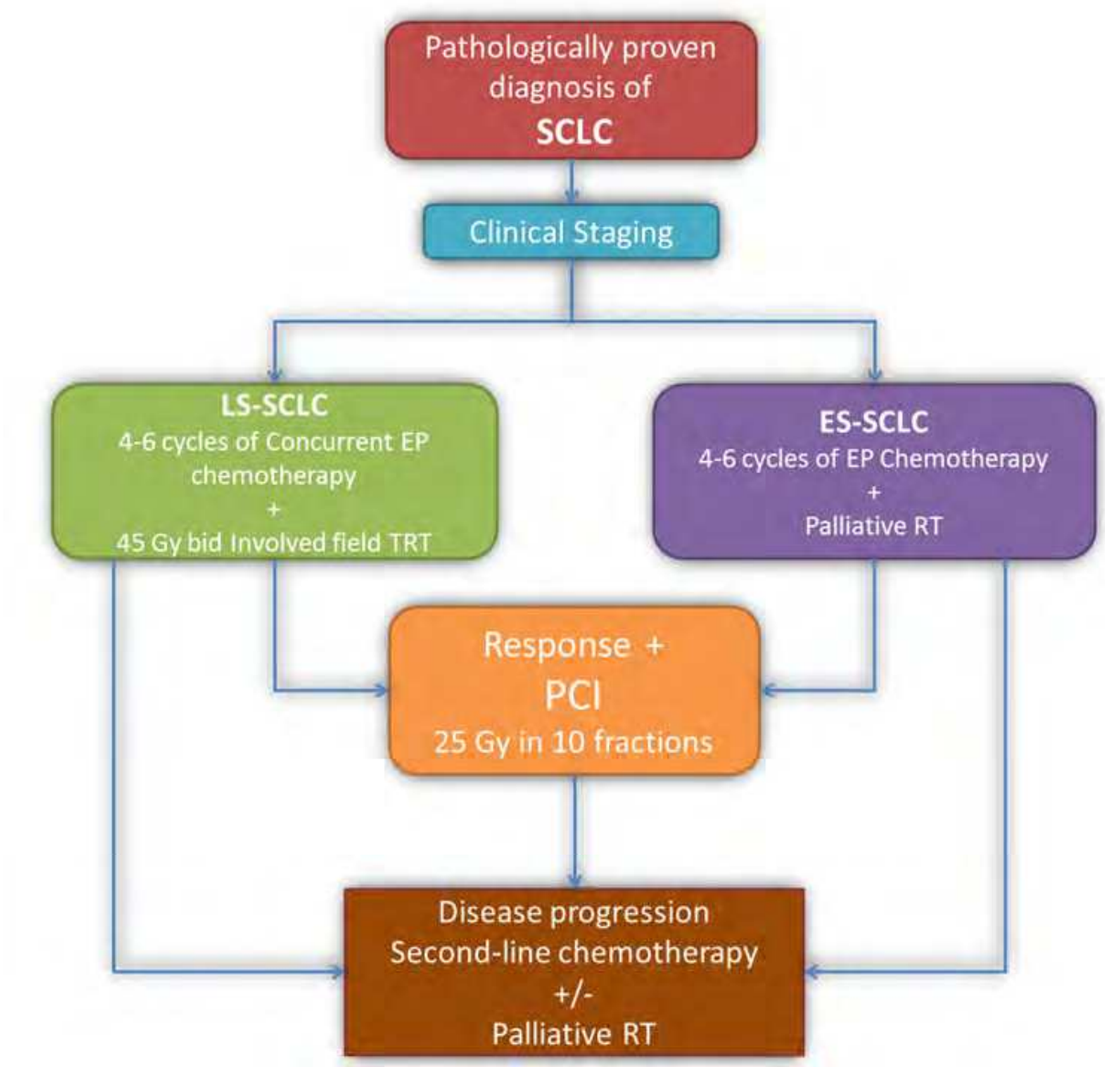


Fig. 2. Management Algorithm for LS-SCLC and ES-SCLC

8. Conclusion

Significant progress has been made in diagnosis and treatment of SCLC in the last 25 years, but, with an overall median survival time of 18 to 20 months, even in patients with limited-stage disease, it is still not possible to consider SCLC in the category of curable cancers. Despite this disappointing figure, mandating further research on this highly fatal disease, all improvements in LS-SCLC have been achieved by concurrent use chemotherapy and TRT (as early as possible), chemotherapy and PCI. For medically fit patients with ES-SCLC, combination chemotherapy followed by PCI (in non-progressive cases) is the standard of care, and further consolidation with TRT is currently under investigation. It is of paramount importance that patients with ES-SCLC be given the chance to participate in future trials for identification of a new and effective treatment combination, which may potentially offer a longer survival.

9. References

Alavanja, M.C. (2002). Biologic damage resulting from exposure to tobacco smoke and from radon: Implication for preventive interventions. *Oncogene*, Vol.21, No.48, (October 2002), pp.7365-7375.

Albain, K.S., Crowley, J.J., & Livingston, R.B. Long-term survival and toxicity in small cell lung cancer. Expanded Southwest Oncology Group experience. (1991). *Chest*, Vol.99, No.6, (June 1991), pp.1425-32.

Algara, M., Rodriguez, N., Vinals, P., Lacruz, M., Foro, P., Reig, A., Quera, J., Lozano, J., Fernandez-Velilla, E., Membrive, I., Dengra, J., & Sanz, X. (2007). Prevention of radiochemotherapy-induced esophagitis with glutamine: results of a pilot study. *Int J Radiat Oncol Biol Phys*, Vol.69, No.2, (October 2007), pp.342-349.

Arriagada, R., Le Chevalier, T., Borie, F., Riviere, A., Chomy, P., Monnet, I., Tardivon, A., Viader, F., Tarayre, M., & Benhamou, S. (1995). Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst*, Vol.87, No.3, (February 1995), pp.183-190.

Auperin, A., Arriagada, R., Pignon, J.P., Le Pechoux, C., Gregor, A., Stephens, R.J., Kristjansen, P.E., Johnson, B.E., Ueoka, H., Wagner, H., & Aisner, J. (1999). Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*, Vol.341, No.7, (August 1999), pp.476-484.

Bogart, J.A., Herndon, J.E., Lyss, A.P., Watson, D., Miller, A.A., Lee, M.E., Turrisi, A.T., & Green, M.R. (2004). 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys*, Vol.59, No.2, (June 2004), pp.460-468.

Bonner, J.A., Sloan, J.A., Shanahan, T.G., Brooks, B.J., Marks, R.S., Krook, J.E., Gerstner, J.B., Maksymiuk, A., Levitt, R., Mailliard, J.A., Tazelaar, H.D., Hillman, S., & Jett, J.R. (1999). Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. *J Clin Oncol,* Vol.17, No.9, (September 1999), pp.2681-2691.

Brambilla, E., Travis, W.D., Colby, T.V., Corrin, B., & Shimosato, Y. (2001). The new World Health Organization classification of lung tumors. Eur Respir J, Vol.18, No.6, pp.1059-68.

Byhardt, R.W., Hartz, A., Libnoch, J.A., Hansen, R., & Cox JD. (1986). Prognostic influence of TNM staging and LDH levels in small cell carcinoma of the lung (SCCL). *Int J Radiat Oncol Biol Phys,* Vol.12, No.5, (May 1986), pp.771-777.

Carmichael, J., Crane, J.M., Bunn, P.A., Glatstein, E., & Ihde, D.C. (1988). Results of therapeutic cranial irradiation in small cell lung cancer. *Int J Radiat Oncol Biol Phys*, Vol.14, No.3, (March 1988) pp.455-459.

Chute, J.P., Venzon, D.J., Hankins, B.S., Okunieff, P., Frame, J.N., Ihde, D.C., & Johnson, B.E. (1997). Outcome of patients with small-cell lung cancer during 20 years of clinical research at the US National Cancer Institute. *Mayo Clin Proc* Vol.72, No.10, (October 1997), pp.901-912.

De Ruysscher, D., Pijls-Johannesma, M., Bentzen, S.M., Minken, A., Wanders, R., Lutgens, L., Hochstenbag, M., Boersma, L., Wouters, B., Lammering, G., Vansteenkiste, J., & Lambin, P. (2006).Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol*, Vol.24, No.7, (March 2006), pp.1057-1063.

De Ruysscher, D., Bremer, R.H., Koppe, F., Wanders, S., van Haren, E., Hochstenbag, M., Geeraedts, W., Pitz, C., Simons, J., ten Velde, G., Dohmen, J., Snoep, G., Boersma, L., Verschueren, T., van Baardwijk, A., Dehing, C., Pijls, M., Minken, A., & Lambin, P. (2006). Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial. *Radiother Oncol*, Vol.80, No.3, (September 2006), pp.307-312.

Edge, S.B., Byrd, D.R., Compton, C.C., Fritz, A.G., Greene, F.L., & Trotti, A. (2010). *AJCC Cancer Staging Manual, 7th ed*.,ISBN: 0387884408, Springer, New York.

Faivre-Finn, C., Lorigan, P., West, C., & Thatcher, N. (2005). Thoracic radiation therapy for limited-stage small-cell lung cancer: unanswered questions. *Clin Lung Cancer,* Vol.7, No.1, (July 2005), pp.23-29.

Felletti, R., Souhami, R.L., Spiro, S.G., Geddes, D.M., Tobias, J.S., Mantell, B.S., Harper, P.G., & Trask, C. (1985). Social consequences of brain or liver relapse in small cell carcinoma of the bronchus. *Radiother Oncol,* Vol.4, No.4, (December 1985), pp.335-339.

Fried, D.B., Morris, D.E., Poole, C., Rosenman, J.G., Halle, J.S., Detterbeck, F.C., Hensing, T.A., & Socinski, M.A. (2004) Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol*, Vol.22, No.23, (December 2004), pp.4837-4845.

Fukuoka, M., Furuse, K., Saijo, N., Nishiwaki, Y., Ikegami, H., Tamura, T., Shimoyama, M., & Suemasu, K. (1991). Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *J Natl Cancer Inst*, Vol. 83, No.12, pp.855-861.

Greene, F.L., Page, D.L., Fleeming, I.D., Fritz, A., Balch, C.M., Haller, D.G., & Marrow M. (2002). *AJCC Cancer Staging Manual, 6th ed*. ISBN: 0387952713, Springer, New York.

Gregor, A., Drings, P., Burghouts, J., Postmus, P.E., Morgan, D., Sahmoud, T., Kirkpatrick, A., Dalesio, O., & Giaccone, G. (1997). Randomized trial of alternating versus sequential radiotherapy/chemotherapy in limited-disease patients with small-cell lung cancer: a

European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group Study. *J Clin Oncol*, Vol.15, No.8, (August 1997), pp.2840-2849.

Gregor, A., Cull, A., Stephens, R.J., Kirkpatrick, J.A., Yarnold, J.R., Girling, D.J., Macbeth, F.R., Stout, R., & Machin, D. (1997). Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer*, Vol.33, No.11, (October 1997), pp.1752-1758.

Grosshans, D.R., Meyers, C.A., Allen, P.K., Davenport, S.D., & Komaki, R. (2008). Neurocognitive function in patients with small cell lung cancer: effect of prophylactic cranial irradiation. *Cancer*, Vol.112, No.3, (February 2008), pp.589-595.

Hanna, N., Bunn, P.A., Langer, C., Einhorn, L., Guthrie, T., Beck, T., Ansari, R., Ellis, P., Byrne, M., Morrison, M., Hariharan, S., Wang, B., & Sandler, A. (2006). Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol*, Vol.24, (May 2006), No.13, pp.2038-2043.

Hardy, J., Smith, I., Cherryman, G., Vincent, M., Judson, I., Perren, T., & Williams, M. (1990). The value of computed tomographic (CT) scan surveillance in the detection and management of brain metastases in patients with small cell lung cancer. *Br J Cancer*. Vol.62, No.4, (October 1990), pp.684-686.

Hirsch, F.R., Paulson, O.B., Hansen, H.H., & Larsen, S.O. (1983). Intracranial metastases in small cell carcinoma of the lung. Prognostic aspects. *Cancer*. Vol.51, No.3, (February 1983), pp.529-533.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M.J. (2009). Cancer statistics, 2009. *CA Cancer J Clin*, Vol.59, No.4, (July 2009), pp.225-249.

Jeremic, B., Shibamoto, Y., Acimovic, L., & Milisavljevic, S. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study. *J Clin Oncol*, Vol.15, No.3, (March 1997), pp.893-900.

Jeremic, B., Shibamoto, Y., Nikolic, N., Milicic, B., Milisavljevic, S., Dagovic, A., Aleksandrovic, J., & Radosavljevic-Asic G. (1999). Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. *J Clin Oncol*, Vol.17, No.7, (July 1999), pp.2092-2099.

Kies, M.S., Mira, J.G., Crowley, J.J., Chen, T.T., Pazdur, R., Grozea, P.N., Rivkin, S.E., Coltman, C.A., Ward, J.H., & Livingston, R.B. (1987). Multimodal therapy for limited small-cell lung cancer: a randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders; and with wide-field versus reduced-field radiation in partial responders: a Southwest Oncology Group Study. *J Clin Oncol*, Vol.5, No.4, (April 1987), pp.592-600.

Komaki, R., Cox, J.D., & Whitson, W. (1981). Risk of brain metastasis from small cell carcinoma of the lung related to length of survival and prophylactic irradiation. *Cancer Treat Rep*,Vol.65, No.9, (September 1981), pp.811-814.

Komaki, R., Meyers, C.A., Shin, D.M., Garden, A.S., Byrne, K., Nickens, J.A., & Cox, J.D. Evaluation of cognitive function in patients with limited small cell lung cancer prior to and shortly following prophylactic cranial irradiation. *Int J Radiat Oncol Biol Phys*, Vol.33, No.1, (1995 August), pp.179-182.

Lally, B.E., Urbanic, J.J., Blackstock, A.W., Miller, A.A., & Perry, M.C. (2007) Small cell lung cancer: Have we made any progress over the last 25 years? *Oncologist*, Vol.12, No.9, (May 2007) pp.1096-1104.

Lara, P.N., Natale, R., Crowley, J., Lenz, H.J., Redman, M.W., Carleton, J.E., Jett, J., Langer, C.J., Kuebler, J.P., Dakhil, S.R., Chansky, K., & Gandara, D.R. (2009). Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol, Vol.27, No.15, (May 2009), pp.2530-2535.

Lassen, U., Osterlind, K., Hansen, M., Dombernowsky, P., Bergman, B., & Hansen, H.H. (1995). Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5 to 18+ years--an analysis of 1,714 consecutive patients. *J Clin Oncol*, Vol.13, No.5, (May 1995), pp.1215-1220.

Le Pechoux, C., Dunant, A., Senan, S., Wolfson, A., Quoix, E., Faivre-Finn, C., Ciuleanu, T., Arriagada, R., Jones, R., Wanders, R., Lerouge, D., & Laplanche, A. (2009). Prophylactic Cranial Irradiation (PCI) Collaborative Group. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol*, Vol.10, No.5, (May 2009), pp.467-474.

Liengswangwong, V., Bonner, J.A., Shaw, E.G., Foote, R.L., Frytak, S., Eagan, R.T., Jett, J.R., Richardson, R.L., Creagan, E.T., & Su, J.Q. (1994). Limited-stage small-cell lung cancer: patterns of intrathoracic recurrence and the implications for thoracic radiotherapy. *J Clin Oncol*, Vol.12, No.3, (March 1994), pp.496-502.

Loehrer, P.J., Ansari, R., Gonin, R., Monaco, F., Fisher, W., Sandler, A., & Einhorn, L.H. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. *J Clin Oncol*, Vol.13, No.10, (October 1995), pp.2594-2599.

Lucas, C.F., Robinson, B., Hoskin, P.J., Yarnold, J.R., Smith, I.E., & Ford, H.T. Morbidity of cranial relapse in small cell lung cancer and the impact of radiation therapy. *Cancer Treat Rep*, Vol.70, No.5, (May 1986), pp.565-570.

Mavroudis, D., Papadakis, E., Veslemes, M., Tsiafaki, X., Stavrakakis, J., Kouroussis, C., Kakolyris, S., Bania, E., Jordanoglou, J., Agelidou, M., Vlachonicolis, J., & Georgoulias, V. (2001). 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*. Vol.12, No.4, (April 2001), pp.463-470.

Miller, A.A., Wang, X.F., Bogart, J.A., Hodgson, L.D., Rocha Lima, C.M., Radford, J.E., Vokes, E.E., & Green, M.R. (2007). Phase II trial of paclitaxel-topotecan-etoposide followed by consolidation chemoradiotherapy for limited-stage small cell lung cancer: CALGB 30002. *J Thorac Oncol*, Vol.2, No.7, (July 2007), pp.645-51.

Murray, N., Coy, P., Pater, J.L., Hodson, .I, Arnold, A., Zee, B.C., Payne, D., Kostashuk, E.C., Evans, W.K., & Dixon, P. (1993). Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. Vol.11, No.2, (February 1993), pp.336-344.

Nicholson, S.A., Beasley, M.B., Brambilla, E., Hasleton, P.S., Colby, T.V., Sheppard, M.N., Falk, R., & Travis, W.D. (2002). Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. *Am J Surg Pathol*. Vol.26, No.9, (September 2002), pp.1184-1197.

Niell, H.B., Herndon, J.E., Miller, A.A., Watson, D.M., Sandler, A.B., Kelly, K., Marks, R.S., Perry, M.C., Ansari, R.H., Otterson, G., Ellerton, J., Vokes, E.E., & Green, M.R. (2005). Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *J Clin Oncol*, Vol.23, (Jun 2005), No.16, pp.3752-3759.

Noda, K., Nishiwaki, Y., Kawahara, M., Negoro, S., Sugiura, T., Yokoyama, A., Fukuoka, M., Mori, K., Watanabe, K., Tamura, T., Yamamoto, S., & Saijo, N. (2002). Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med, Vol.346, No.2, (January 2002), pp.85-91.

Okamoto, H., Watanabe, K., Kunikane, H., Yokoyama, A., Kudoh, S., Ishizuka, N., Fukuda, H., Tamura, T., & Saijo, N. (2005). Randomized phase III trial of carboplatin(C) plus etoposide (E) vs. split doses of cisplatin (P) plus etoposide (E) in elderly or poor-risk patients with extensive disease small cell lung cancer (ED-SCLC): JCOG9702. J Clin Oncol, Vol.23, (May 2005), Suppl.16, Abstract.7010.

Paesmans, M., Sculier, J.P., Lecomte, J., Thiriaux, J., Libert, P., Sergysels, R., Bureau, G., Dabouis, G., Van Cutsem, O., Mommen, P., Ninane, V., & Klastersky, J. (2000). Prognostic factors for patients with small cell lung carcinoma: analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. *Cancer*. Vol.89, No.3, (August 2000), pp.523-33.

Patel, S., Macdonald, O.K., & Suntharalingam, M. (2009). Evaluation of the use of prophylactic cranial irradiation in small cell lung cancer. *Cancer*, Vol.115, No.4, (February 2009), pp.842-50.

Paumier, A., & Le Pechoux, C. (2010). Radiotherapy in small-cell lung cancer: where should it go? Lung Cancer, Vol.69, No.2, (August 2010), pp.133-40.

Perry MC, Eaton WL, Propert KJ, Ware JH, Zimmer B, Chahinian AP, Skarin A, Carey RW, Kreisman H, Faulkner C, et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. N Engl J Med. 1987 Apr 9;316(15):912-8.

Pignon, J.P., Arriagada, R., Ihde, D.C., Johnson, D.H., Perry, M.C., Souhami, R.L., Brodin, O., Joss, R.A., Kies, M.S., & Lebeau, B. (1992) A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med*, Vol.327, No.23, (December 1992), pp.1618-1624.

Pijls-Johannesma, M., De Ruysscher, D., Vansteenkiste, J., Kester, A., Rutten, I., & Lambin P. (2007). Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials. *Cancer Treat Rev*, Vol.33, No.5, (August 2007), pp.461-73.

Postmus, P.E., Sleijfer, D.T., & Haaxma-Reiche, H. (1989). Chemotherapy for central nervous system metastases from small cell lung cancer: a review. *Lung Cancer,*Vol.5, pp.254-263.

Pujol, J.L., Carestia, L., & Daures JP. (2000). Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-

containing regimen versus a regimen without this alkylating agent. *Br J Cancer*, Vol.83, No.1, (July 2000), pp.8-15.

Pujol, J.L., Daures, J.P., Riviere, A., Quoix, E., Westeel, V., Quantin, X., Breton, J.L., Lemari, E., Poudenx, M., Milleron, B., Moro, D., Debieuvre, D., & Le Chevalier, T. Etoposide plus cisplatin with or without the combination of 4'-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutes multicenter phase III randomized study. *J Natl Cancer Inst,* Vol.93, No.4, (February 2001), pp.300-308.

Rosenzweig, K.E., Chen, C.P., Yom, S.S., & Krug, L.M. (2010). Tumors of the Lung, Pleura, and Mediastinum, In: *Leibel And Phillips Textbook Of Radiation Oncology*, Richard T. Hoppe, Theodore Locke Phillips, & Mack Roach III, (Ed.), pp. 737-771, Saunders, ISBN: 978-1-4160-5897-7, Philadelphia.

Roth, B.J., Johnson, D.H., Einhorn, L.H., Schacter, L.P., Cherng, N.C., Cohen, H.J., Crawford, J., Randolph, J.A., Goodlow, J.L., & Broun, G.O. (1992). Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol*, Vol.10, No.2, (February 1992), pp.282-291.

Schiller, J.H., Adak, S., Cella, D., DeVore, R.F., & Johnson, D.H. (2001). 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,*Vol.19, No.8, (April 2001), pp.2114-2122.

Sculier, J.P., Berghmans, T., Castaigne, C., Luce, S., Sotiriou, C., Vermylen, P., & Paesmans, M. Maintenance chemotherapy for small cell lung cancer: a critical review of the literature. *Lung Cancer*, Vol.19, No.2, (February 1998), pp.141-51.

Shaw, E.G., Su, J.Q., Eagan, R.T., Jett, J.R., Maksymiuk, A.W., & Deigert, F.A. (1994) Prophylactic cranial irradiation in complete responders with small-cell lung cancer: analysis of the Mayo Clinic and North Central Cancer Treatment Group data bases. *J Clin Oncol*, Vol.12, No.11, (November 1994), pp.2327-2332.

Skarlos, D.V., Samantas, E., Briassoulis, E., Panoussaki, E., Pavlidis, N., Kalofonos, H.P., Kardamakis, D., Tsiakopoulos, E., Kosmidis, P., Tsavdaridis, D., Tzitzikas, J., Tsekeris, P., Kouvatseas, G., Zamboglou, N., & Fountzilas, G. (2001). Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). *Ann Oncol,* Vol.12, No.9, (September 2001), pp.1231-1238.

Slotman, B., Faivre-Finn, C., Kramer, G., Rankin, E., Snee, M., Hatton, M., Postmus, P., Collette, L., Musat, E., & Senan, S. (2007). EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* Vol.357, No.7, (August 2007), pp.664-672.

Sundstrom, S., Bremnes, R.M., Kaasa, S., Aasebo, U., Hatlevoll, R., Dahle, R., Boye, N., Wang, M., Vigander, T., Vilsvik, J., Skovlund, E., Hannisdal, E., Aamdal, S., & Sundstrom. (2002). 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*, Vol.20, No.24, (December 2002), pp.4665-4672.

Tai, P., Tonita, J., Yu, E., & Skarsgard, D. (2003). Twenty-year follow-up study of long-term survival of limited-stage small-cell lung cancer and overview of prognostic and treatment factors. *Int J Radiat Oncol Biol Phys,* Vol.56, No.3, (July 2003), pp.626-633.

Takada, M., Fukuoka, M., Kawahara, M., Sugiura, T., Yokoyama, A., Yokota, S., Nishiwaki, Y., Watanabe, K., Noda, K., Tamura, T., Fukuda, H., & Saijo, N. 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,* Vol.20, No.14, (July 2002), pp.3054-3060.

Tyczynski, J.E., Bray, F., & Parkin D.M. (2003). Lung cancer in Europe in 2000: epidemiology, prevention, and early detection. Lancet Oncol, Vol.4, No.1, (January 2000), pp.45-55.

Topkan, E., Yavuz, M.N., Onal. C., & Yavuz, A.A. (2009). Prevention of acute radiation-induced esophagitis with glutamine in non-small cell lung cancer patients treated with radiotherapy: evaluation of clinical and dosimetric parameters. *Lung Cancer*, Vol.63, No.3, (March 2009), pp.393-399.

Turrisi, A.T., Kim, K., Blum, R., Sause, W.T., Livingston, R.B., Komaki, R., Wagner, H., Aisner, S., & Johnson, D.H. (1999). Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*, Vol.340, Vol.4, (January 1999), pp.265-271.

Vallieres, E., Shepherd, F.A., Crowley, J., Van Houtte, P., Postmus, P.E., Carney, D., Chansky, K., Shaikh, Z., & Goldstraw, P. (2009). The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol,* Vol.4, No.9, (September 2009), pp.1049-1059.

van Loon, J., De Ruysscher, D., Wanders, R., Boersma, L., Simons, J., Oellers, M., Dingemans, A.M., Hochstenbag, M., Bootsma, G., Geraedts, W., Pitz, C., Teule, J., Rhami, A., Thimister, W., Snoep, G., Dehing-Oberije, C., & Lambin, P. (2010). Selective nodal irradiation on basis of (18)FDG-PET scans in limited-disease small-cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys,* Vol.77, No.2, (June 2010), pp.329-336.

van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet. 2011 May 10. [Epub ahead of print]

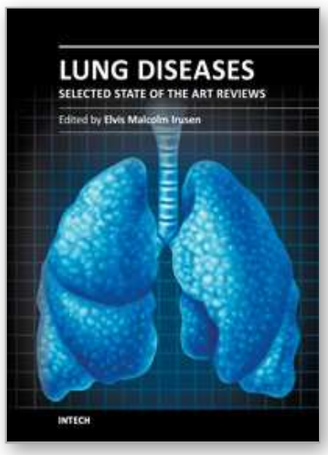
van Oosterhout AG, van de Pol M, ten Velde GP, Twijnstra A. Neurologic disorders in 203 consecutive patients with small cell lung cancer. Results of a longitudinal study. Cancer. 1996 Apr 15;77(8):1434-41.

Yang GY, Matthews RH. Prophylactic cranial irradiation in small-cell lung cancer. Oncologist. 2000;5(4):293-8.

Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol. 1992 Jun;10(6):890-5.

Work E, Nielsen OS, Bentzen SM, Fode K, Palshof T. Randomized study of initial versus late chest irradiation combined with chemotherapy in limited-stage small-cell lung cancer. Aarhus Lung Cancer Group. J Clin Oncol. 1997 Sep;15(9):3030-7.

Zelen, M. (1973). Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 3, Vol.4, No.2, pp.31-42.



Lung Diseases - Selected State of the Art Reviews
Edited by Dr. Elvisegran Malcolm Irusen

ISBN 978-953-51-0180-2
Hard cover, 690 pages
Publisher InTech
Published online 02, March, 2012
Published in print edition March, 2012

The developments in molecular medicine are transforming respiratory medicine. Leading clinicians and scientists in the world have brought their knowledge and experience in their contributions to this book. Clinicians and researchers will learn about the most recent advances in a variety of lung diseases that will better enable them to understand respiratory disorders. This treatise presents state of the art essays on airways disease, neoplastic diseases, and pediatric respiratory conditions. Additionally, aspects of immune regulation, respiratory infections, acute lung injury/ARDS, pulmonary edema, functional evaluation in respiratory disorders, and a variety of other conditions are also discussed. The book will be invaluable to clinicians who keep up with the current concepts, improve their diagnostic skills, and understand potential new therapeutic applications in lung diseases, while scientists can contemplate a plethora of new research avenues for exploration.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Erkan Topkan and Cem Parlak (2012). Radiation Therapy in Management of Small-Cell Lung Cancer, Lung Diseases - Selected State of the Art Reviews, Dr. Elvisegran Malcolm Irusen (Ed.), ISBN: 978-953-51-0180-2, InTech, Available from: http://www.intechopen.com/books/lung-diseases-selected-state-of-the-art-reviews/radiation-therapy-in-management-of-small-cell-lung-cancer

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen