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CLINICAL PRACTICE GUIDELINES

European Lung Cancer Working Party Clinical Practice Guidelines. Small Cell Lung Cancer: IV. Limited disease

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ABSTRACT

The present guidelines on the management of limited disease small cell lung cancer (SCLC) were formulated by the ELCWP in April 2007. They are designed to answer the following seven questions: 1) What is the definition of limited disease? 2) Should chest radiotherapy be provided and what are the benefits? 3) What is the optimal timing and mode of administration of chest irradiation? 4) Which are the optimal radiotherapy parameters: dose, fractionation, target volume? 5) What is the optimal chemotherapy regimen for limited disease SCLC? 6) Should prophylactic cranial irradiation be provided, when and for which patients? 7) What is the additional role of thoracic surgery in early SCLC?

INTRODUCTION

This is the fourth of a series of five articles, reporting clinical practice guidelines for lung cancer, formulated by the European Lung Cancer Working Party (ELCWP). These articles consecutively present the recommended treatment of early (resectable) stages of non-small cell lung cancer (NSCLC) [1], locoregionally advanced NSCLC [2], metastatic NSCLC [3] and small-cell lung cancer (SCLC) of limited and extensive stage. The rational of the reasons and methodology used for those guidelines have been previously reported [1].

After an extensive discussion, a consensus was reached among members of the Group to formulate the guidelines of treatment of limited small cell lung cancer on the basis of seven predefined essential questions: 1) What is the definition of limited disease? 2) Should chest radiotherapy be provided and what are the benefits? 3) What is the optimal timing and mode of administration of chest irradiation? 4) Which are the optimal radiotherapy parameters: dose, fractionation, target volume? 5) What is the optimal chemotherapy regimen for limited disease SCLC? 6) Should prophylactic cranial irradiation be provided and when and for which patients? 7) What is the additional role of thoracic surgery in early SCLC?

These questions have been extensively discussed during a meeting organised in

October 2006 in Ostend in Belgium. The present consensus has been definitively approved by the Group in a final meeting in Brussels, in April 2007.

METHODOLOGY

Guidelines were established on the basis of the various data published in the literature: clinical trials, systematic reviews and meta-analyses, guidelines from medical societies or groups. Literature was identified and analysed by the evidence-based medicine group of the ELCWP. The quality of published guidelines was assessed with the use of the AGREE instrument [4;5], allowing elimination of the worst ones and use of the best available ones for the establishment of our own guidelines. The following guidelines were selected: ASCO (American Society of Clinical Oncology) [6,7], BTS (British Thoracic Society) [8], Cancer Care Ontario Practice Guidelines [9,10], Royal College of Radiologists (RCR) [11], American College of Chest Physicians (ACCP) [12] and FNCLCC (Fédération Nationale des Centres de Lutte contre le Cancer) [13]. Selection was based on the assessment of the literature previously performed by the ACCP [14] and it was completed by the analysis using the AGREE instrument of other guidelines that had not been taken into consideration by the ACCP. This approach allowed adding to the list the guidelines of FNCLCC and ACCP.

Concerning limited disease small cell lung cancer specifically, guidelines were available only by Cancer Care Ontario, Royal College of Radiologists and ACCP.

QUESTIONS AND GUIDELINES

QUESTION 1: WHAT IS THE DEFINITION OF LIMITED DISEASE?

Two main systems can be used to define the extent of disease: the International Staging System (ISS) with TNM according to the last version published in 1997 by the UICC [15] or the two-stage system developed by the Veterans Administration Lung Cancer Study Group (VALCSG) (limited or extensive disease) [16]. In the latter, patients with limited disease (LD) have involvement restricted to the ipsilateral hemithorax which can be included within a single radiation port. The International Association for the Study of Lung Cancer [17] includes also in the definition of limited disease the presence of contralateral hilar and/or ipsilateral and/or contralateral supraclavicular nodes and/or of pericardial and/or ipsilateral pleural effusion, regardless of the cytology.

In published guidelines, the Royal College of Radiologists [11] defines limited disease as a disease confined to one hemithorax, including involvement of ipsi-and/or contralateral hilar, mediastinal or supraclavicular node while ACCP [18] recommends the VALCSG definition.

ELCWP GUIDELINES:

The disease should be staged according to both ISS 97 and VALCSG definitions. The definition of limited disease should be improved, taking into account the tumour size and the volume that can be treated according to dose-volume histograms by the current radiotherapy techniques with a tolerable toxicity.

QUESTION 2: SHOULD CHEST RADIOTHERAPY BE PROVIDED AND WHAT ARE THE BENEFITS ?

Chest irradiation is recommended in all published guidelines for limited disease SCLC. For RCR [11], it has to be given as consolidation in case of complete response to chemotherapy in order to improve local control and survival. For Ontario Cancer Care [9] and for ACCP [19], radiotherapy is required in order to improve local control and survival.

The evidence comes from 15 randomised trials [20-33] summarized in table 1. It should be noted that in none, modern radiotherapy techniques or modern chemotherapy were used and that chest radiotherapy was administered according to various modalities (concomitant, sequential, ...). It was associated with a statistically significant survival benefit in only a few trials. Nevertheless, as shown by two meta-analyses performed on the data provided by the literature [34;35] and by one meta-analysis performed with the individual patients data of the randomised trials [36], there was a significant benefit in terms of both survival and local control. The benefit of survival at three years was estimated to be 5.4% [36]. For local control, the OR (odd ratio) for treatment benefit was 3.02 with an intrathoracic tumour control improved by 25.3% [34].

ELCWP GUIDELINES:

Chest radiotherapy has to be administered at some time in the course of treatment (see question 3) in order to improve both survival and local control.

QUESTION 3: WHAT IS THE OPTIMAL TIMING AND MODE OF ADMINISTRATION OF CHEST IRRADIATION?

The timing of chest irradiation has been the topic of many guidelines. The RCR [11] recommends chest radiotherapy as consolidation in all cases of complete response to chemotherapy. The Ontario Cancer Care Program [9] also recommends this treatment but without precise guidelines due to conflicting results for early versus late irradiation and for concurrent versus sequential administration.

Four meta-analyses have specifically addressed this problem [37-41]. Their main results are shown in table 2. All are based on published papers, taking into account 7 or 8 randomised trials for a total of more than 1500 patients and using different definitions for early and late irradiation. All but one [41] are in favour of early irradiation, although in the De Ruysscher

TABLE 1. Randomised trials comparing chest radiotherapy with chemotherapy to chemotherapy alone in small cell lung cancer.

Reference	Chemotherapy	RT Gy	N pts	MST CT+ RT	MST CT	p
Fox, 1980 [20]	VAC x 10	sequential 40	73	68w	62w	NA
Souhami, 1984 [21]	VAC~CPA-MTX x 12	sequential 40	130			NA
Osterlind 1986 [22]	CPA-MTX-VCR-CCNU x 18 m	concomitant 40	145	42w	52w	0.05
Ohnoshi, 1986 [23]	CPA-MTX-VCR-PCZ~VP16-ADR x 6	sequential 40	50	12m	15m	NS
Bunn, 1987 [24]	CPA-MTX-VCR ~ CDDP-ADR-VCR x 8	concomitant 40	96	15m	11m	0.03
Perry, 1987 [25]	VAC-VP16 x 18 m	concomitant 50	489	14m	14m	0.001
Kies, 1987 [26]	VAC-MTX-VP16 ~ CDDP-VP16 x 6	sequential 48	93			0.86
Nou, 1988 [27]	VAC-MTX ~ CPA-MTX-VCR-CCNU x 24	sequential 40	56	15m	15m	NS
Birch I, 1988 [28]	VAC x 6	fractioned 40	291	54w	46w	0.04
Birch II, 1988 [28]	VAC x 6	fractioned 45	369	45w	51w	0.12
Kraft, 1990 [29]	VAC x 6	sequential 50	91	13m	10m	0.02
Carlson, 1991 [30]	CPA-CCNU-VCR-CDDP ~ VP16-ADR-MTX x 7-10	sequential 55	48	20m	19m	0.91
Johnson, 1993 [31]	VAC x 6	concomitant 45	369	14m	13m	0.08
Lebeau, 1993 [32]	CPA-ADR-CCNU ~ VP16-ADR-CDDP x 8	sequential 46	35			0.96
Joss, 1994 [33]	ADR-VP16-CDDP or CPA-VP16-ADR or MTX-VCR-CPA ~ ADR-VP16-CDDP	sequential 45	118	363d	316d	0.86

RT: radiotherapy; N: number; pts: patients; CT: chemotherapy; MST: median survival time; w: week; m: month; d: day; NA: not available; NS: non significant; VAC: vincristine + adriamycine + cyclophosphamide; CPA: cyclophosphamide; MTX: methotrexate; VCR: vincristine; PCZ: procarbazine; VP16: etoposide; ADR: adriamycine; CDDP: cisplatin.

TABLE 2. Meta-analyses concerning the timing of chest irradiation.

Reference	Methodology	Outcome	N trials	N pts	Result
Fried, 2004 [37]	Systematic review	2 yr survival	7	1524	S for 2-year survival in favour early RT
Huncharek, 2004 [38]	Isolated	2 yr survival	8	1574	S in favour early RT
De Ruysscher, 2006 [39;40]	Systematic review	2 yr & 5 yr survival	7	1514	NS*
Spiro, 2006 [41]	Isolated	overall survival	8	1849	NS

N: number; yr: year; RT: radiotherapy; pts: patients; S: significant; NS: non significant. *see comment in the text

et al meta-analysis, statistically significant 5 years survival improvement is only obtained in favour of radiotherapy when it was finished within 30 days after the start of chemotherapy and if chemotherapy was cisplatin-based [40]. This result was obtained by analysing four randomised trials [39]. Early irradiation was not associated with better local control rate but with a higher incidence of severe oesophagitis. In a subgroup meta-analysis. taking into account the completion or not of the planned chemotherapy, Spiro et al demonstrated that survival was improved by early irradiation only if full chemotherapy cycles were provided [41].

Published individual randomised trials [25,41-47] are summarised in tables 3 and 4. These trials are very heterogeneous in terms of design. In those directly comparing early versus late administration (table 3), some used concurrent treatments [25,41-44,47], others sequential treatment [45] and the last one compared initial concurrent chemotherapy to a late sequential approach [46]. Three were associated with significantly better survival in favour of the early concurrent arm [43,44,46]. Two trials (table 4) tested alternating chemotherapy and irradiation with, for the control arm, a late sequential approach [48] or a concurrent approach during the third course [49]. None was associated with significant difference in survival.

ELCWP GUIDELINES:

The trend is in favour of early concurrent chemo-radio-

TABLE 3. Randomised trials testing early versus late chest irradiation for small cell lung cancer.

Reference	Chemotherapy	Radiotherapy	Arm	n pts	MST	p
Perry, 1987 [25;42]	CPA-VCR- ADR/VP16	50 Gy/25x/5 w	- initial (d1) concurrent	125	13.1 m	NS
			- late (# 4) concurrent	145	14.6 m	
Murray, 1993 [43]	CPA-VCR-ADR ~ CDDP-VP16	40 Gy/15x/3 w	- initial (w 3) concurrent	155	21.2 m	0.008
			- late (>#6) concurrent	153	16 m	
Jeremic, 1997 [44]	CDDP-VP16	54 Gy (2x/d)/	- initial (d1) concurrent	52	34 m	0.05
		36x/18d/3,6 w	- late (w 6) concurrent	51	26 m	
Work, 1997 [45]	CDDP-VP16 ~ ADR-CPA- VCR	40-45 Gy split	- initial (d1) sequential	99	10.5 m	NS
		2x11x/ 2 w	- late (> #6) sequential	100	12 m	
Skarlos, 2001 [47]	Carboplatine – VP16	HFRT 48 Gy	-initial (cycle 1) concurrent	42	17 m	NS
		1,8 Gy bid 15x	-late (cycle 4) concurrent	39	17 m	
Takada, 2002 [46]	CDDP-VP16	HFRT 45 Gy/	- initial (d2) concurrent	114	27.2 m	S
		30x/19d	- late (d 84) sequential	114	19.7 m	
Spiro, 2006 [41]	CPA-VCR-ADR ~ CDDP-VP16	40 Gy/15x/2 w	- early (#2) concurrent	159	13.7 m	NS
			- late (#6) concurrent	166	15.1 m	

N: number; pts: patients; MST: median survival time; w: week; m: month; d: day; NS: non significant; S: significant; CPA: cyclophosphamide; VCR: vincristine; VP16: etoposide; ADR: adriamycine; CDDP: cisplatin; HFRT: hyperfractionated radiotherapy; #: cycle

TABLE 4. Randomised trials testing alternating chemotherapy and radiotherapy for small cell lung cancer.

Reference	Chemotherapy	Arm	Radiotherapy	N pts	MST	p
Gregor, 1997 [48]	CPA-ADR-VP16 (x5)	- alternating	12 Gy (in 5x) d15 #2, 3, 4, 5	169	14 m	NS
		- sequential (after CT)	50 Gy/20x/4w	165	15 m	
Lebeau, 1999 [49]	CPA-ADR-VP16-VDS	- concurrent	3rd cycle: 50 Gy	82	13 m	NS
		- alternating	2nd, 3rd, 4th cycles: 20, 20 & 15 Gy	74	14 m	

N: number; pts: patients; MST: median survival time; w: week; m: month; d: day; NS: non significant; CPA: cyclophosphamide; VDS: vindesine; VP16: etoposide; ADR: adriamycine; #: cycle; CT: chemotherapy.

therapy. Early treatment means radiotherapy performed during the 30 days following the start of chemotherapy. This trend has to be confirmed by randomised trials.

QUESTION 4: WHICH ARE THE OPTIMAL RADIOTHERAPY PARAMETERS: DOSE,FRACTIONATION. TARGET VOLUME?

Only two societies have provided guidelines on this topic. The RCR [11] recommends a dose biologically equivalent to 45-50 Gy with a fractionation of 2 Gy per day and using CT-planned irradiation with lung correction; the Ontario Cancer Care Program [9] proposes a chest irradiation of at least 40 Gy in 15 fractions over 3 weeks without hyper-fractionation.

There are no meta-analysis and very few randomised trials available. Two (table 5) have tested hyperfractionation radiotherapy, one as early concurrent [50] and another as late concurrent [51]. Only the trial of Turrisi provides significant results but the problem is that the irradiation doses in the two arms are not biologically equivalent. In the Bonner trial, the hyperfractionated arm used a split-course schedule. There is only one randomised trial having specifically tested the dosage of chest irradiation [52] in a late sequential approach and with low doses of irradiation. Patients received 25 Gy in 10 fractions over 3 weeks or 37.5 Gy in 15 fractions over 3 weeks. Despite randomisation of 168 patients, no survival benefit was observed.

ELCWP GUIDELINES:

The dose of chest irradiation should be at least 45 Gy using a conventional fractionation or a biologically equivalent dose. EORTC Radiotherapy Group recommendations [53] should be respected for treatment planning and execution of radiotherapy as proposed in the ELCWP guidelines for unresectable non-metastatic non-small cell lung cancer [2].

TABLE 5. Randomised trials testing hyperfractionated radiotherapy for small cell lung cancer.

Reference	Chemotherapy	Arm	Radiotherapy	N pts	OR	SM	p
Turrisi, 1999 [50]	CDDP-VP16 (x4) early concurrent	- standard	45 Gy/ 1.8 per d/ in 5 w	206	87%	19 m (16% 5 yr)	0.04
		- bifractionated	45 Gy/ bid/ 30x in 3 w	211	87%	23 m (26% 5 yr)	
Bonner, 1999 [51]	CDDP-VP16 (x6) late concurrent	- standard cycles 4-5	50.4 Gy 1.8/d in 28 x	132		20.6 m (21% 5 yr)	NS
		- bifractionated cycles 4-5	48 Gy in 32x with split	130		20.6 m (22% 5 yr)	

N: number; CT: chemotherapy; OR: objective response; pts: patients; MST: median survival time; w: week; m: month; d: day; yr: year; NS: non significant; VP16: etoposide; CDDP: cisplatin.

QUESTION 5: WHAT IS THE OPTIMAL CHEMOTHERAPY REGIMEN FOR LIMITED SCLC?

Only the Ontario Cancer Care Program proposes specific guidelines for chemotherapy in LD SCLC [10]. The regimen should be cisplatin plus etoposide or the same regimen alternating with VAC (vincristine + adriamycine + cyclosphosphamide), as an alternative. No anthracycline should be administered concurrently to chest irradiation. Standard dosage should be used according to the usual schedules summarized in a table of the publication. Etoposide should be given over 3 to 5 days. The optimal duration of chemotherapy is uncertain but not beyond 6 cycles.

A meta-analysis performed by our Group [54] has shown that for any stage of SCLC, the combination of cisplatin plus etoposide is associated with significantly better survival than combinations without those drugs or with etoposide alone. In a subgroup analysis of a randomised trial with concurrent chemo-radiotherapy [55], survival was significantly better in limited disease when chemotherapy consisted of cisplatin plus etoposide rather than epirubicin plus cyclophosphamide plus vincristine, with respective median survival times of 14.5 months and 9.7 months (214 patients, p=0.001).

ELCWP GUIDELINES:

A combination of cisplatin and etoposide is recommended in the management of limited disease small cell lung cancer with chest irradiation because this regimen is associated with better survival, its concomitant administration with chest irradiation is not-contraindicated in terms of toxicity and it has been used in the most recent significant trials performed in LD SCLC.

QUESTION 6: SHOULD PROPHYLACTIC CRANIAL IRRADIATION BE PROVIDED? WHEN AND FOR WHICH PATIENTS?

Three societies recommend, in their guidelines, prophylactic cranial irradiation (PCI) in cases with complete response to treatment [11;56;57].

Two meta-analyses of the randomised trials performed in the eighties and early nineties on PCI have been published [58;59] As it is shown in table 6, both have demonstrated a survival benefit when PCI is restricted to patients with complete response to chemo(radio)therapy. There is also a benefit in terms of prevention of occurrence of brain metastases. Figure 1 shows the results obtained by our meta-analysis of the trials of which the data allowed survival aggregation.

Five published trials were performed in complete responders [60-64]. The definition of CR was provided in only two. It was described in one study [60], as the disappearance of all signs and symptoms of disease, including normalization of all abnormal biomarkers lasting for a minimum of 30 days with

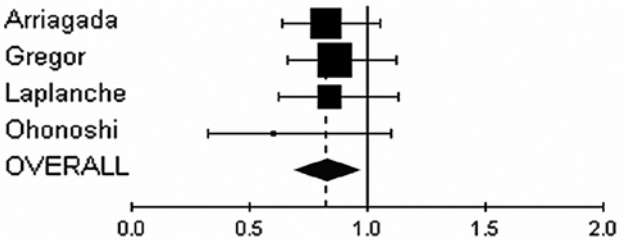

FIGURE 1. Results of the ELCWP meta-analysis [59] of the studies evaluating the role of PCI in SCLC on survival when patients are in CR: HR: 0.82 (95% CI: 0.71-0.96).

TABLE 6. Meta-analyses performed on the role of prophylactic cranial irradiation in SCLC.

Reference	Methodology	Outcome	N trials	N pts	Survival results
Auperin, 1999 (58)	Individual patients data	Overall survival	6 (CR)	987	S in favour PCI
Meert, 2001 (59)	Systematic review	Overall survival	11 (global)	1518	NS
			6 (CR)	865	S in favour PCI

N: number; pts: patients; CR: complete response; PCI: prophylactic cranial irradiation; S: significant; NS: non significant.

a work-up where all previously positive suspicious tests had to be repeated and in the other [62], as the disappearance of all tumour confirmed by the chest film and microscopic and histological evaluation at the time of bronchoscopy with a work-up including brain CT scan and all previously positive suspicious tests.

ELCWP GUIDELINES:

Prophylactic cranial irradiation can be proposed in patients with limited disease small cell lung cancer, in cases with complete response to treatment if the response assessment and the assessment work-up are similar to those used in the relevant trials and if a similar definition of complete response is used.

QUESTION 7: WHAT IS THE ADDITIONAL ROLE OF THORACIC SURGERY IN EARLY SCLC ?

For RCR [11], thoracic surgery is not routinely recommended as primary therapy. In cases of biopsy excision of a peripheral nodule, chemotherapy has to be administered. For ACCP [65], surgery can be offered in case of very limited disease (stage T1-2 N0) and has to be followed by platinum-based chemotherapy. Two old randomised trials are available (table 7), one testing radiotherapy versus surgery [66] and the other testing the additional role of surgery after induction chemotherapy [67]. Both were performed in patients with bulky SCLC and none showed a benefit of surgery. Many small series published encouraging results with surgery [68]. Two indications can be stated: solitary pulmonary nodules [69-71] and central very limited disease (N0 or N1) [70;72]. Surgery may also be proposed as salvage therapy in rare cases of residual disease due to non-small cell lung histology in the context of a mixed tumour [73].

ELCWP GUIDELINES:

The additional role of surgery in limited disease SCLC is controversial. It has nevertheless some potential indications such as: the peripheral nodule, stage I (T1 N0, T2 N0) disease (called very limited disease) and residual disease after induction chemo(radio)therapy in the case of histological mixed tumour. Surgery should be performed using the guidelines recommended for non-small cell lung cancer. When surgery is initially performed, adjuvant chemotherapy should be administered. For centrally localized SCLC, surgery should only be performed in the context of a clinical trial.

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TABLE 7. Randomised trials testing thoracic surgery for limited disease small cell lung cancer.

Reference	Arm	Design	N pts	OR	MST	p
Fox, 1973 [66]	- surgery		82		199 d	
	- radiotherapy	Minimum 30 Gy	84	48%	300 d	
Lad, 1994 [67]	- surgery	5 cycles induction chemotherapy with CPA + VCR + ADR	70	83%		NS
	- no surgery		74			

N: number; pts: patients; MST: median survival time; d: day; NS: non significant; CPA: cyclophosphamide; VCR: vincristine; ADR: adriamycine; OR: objective response

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