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CLINICAL PRACTICE GUIDELINES

European Lung Cancer Working Party Clinical Practice Guidelines. Non-small cell lung cancer: I. Early stages

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ABSTRACT

The present guidelines on the management of resectable non-small cell lung cancer (NSCLC) were formulated by the (ELCWP) in April 2005. They aim in answering the following eleven questions: 1) Is surgery the best therapy for a potentially resectable cancer? 2) How is complete resection defined? 3) Is systematic lymph node dissection necessary during surgery? 4) What is the role of radiotherapy after complete resection? 5) Should adjuvant or neoadjuvant chemotherapy be administered in clinical stages I or II? 6) Should adjuvant chemotherapy be administered in pathological stages I or II? 7) Is adjuvant therapy advisable after complete resection for pathological stage IIIA N2? If yes, of what type: chemotherapy, radiotherapy or chemotradiotherapy? 8) What are the indications for surgery after induction treatment, in clinical stages IIIA or IIIB? 9) In clinical stages IIIA or IIIB, is preoperative therapy required and of what type? 10) What type of treatment is indicated after an incomplete surgical resection? 11) What is the best regimen for (neo)adjuvant chemotherapy?

INTRODUCTION

European Lung Cancer Working Party (ELCWP) is a cooperative research group, actively engaged in the thoracic oncology field, for more than 25 years now. It has conducted and still continues to conduct a number of academic clinical trials for various stages and histological types of lung cancer. Published trials can be found at the Group's website (www.elcwp.org). The Group is also interested in evidence-based medicine and it has published, so far, a number of systematic reviews and meta-analyses. In recent years, many European countries created, by legal disposition, oncological networks and cancer care programmes. Members of ELCWP have therefore to integrate clinical research trials of the Group into developed local programmes. In order to optimise this enterprise and keep a common research programme, the members decided to formulate consensus clinical practice guidelines based on the available literature.

The following is the first of a series of five articles, reporting clinical practice

guidelines for lung cancer, formulated by the European Lung Cancer Working Party (ELCWP). These articles will consecutively deal with the treatment of early (resectable) stages of non-small cell lung cancer (NSCLC), locoregionally advanced NSCLC, metastatic NSCLC and small-cell lung cancer (SCLC) limited and extensive stages.

TREATMENT OF EARLY (RESECTABLE) STAGES OF NON-SMALL CELL LUNG CANCER

METHODOLOGY

During a meeting of the Group, organised in Mons, Belgium, in September 2004, and after an extensive discussion, a consensus was reached among members to base the formulation of guidelines of treatment of early (resectable) stages non-small lung cancer on eleven predefined essential questions:

1. Is surgery the best therapy of a potentially resectable lung cancer?
2. What constitutes a complete resection?
3. Is a systematic lymph node dissection necessary?
4. What is the role (if any) of radiotherapy after complete resection?
5. Is adjuvant or neoadjuvant chemotherapy indicated in clinical stage I or II?
6. Should adjuvant chemotherapy be administered in pathological stage I or II?
7. Should adjuvant therapy be advised after complete resection for pathological stage IIIA N2, and if yes, what type: chemotherapy, radiotherapy or radiochemotherapy?
8. What are the indications for surgery after induction treatment in clinical stage IIIA or IIIB? 9) In clinical stage IIIA or IIIB, if surgery is considered, is induction therapy required, and if yes, of what type?
10. What should be the postoperative treatment after incomplete surgical resection,
11. Which regimen should be advised as adjuvant or neoadjuvant chemotherapy?

For the purpose of answering the above questions, a thorough review of several sources of data published in the literature was undertaken. It included clinical trials, systematic reviews and meta-analyses, and guidelines from medical societies and scientific groups. Literature was identified and analysed by the evidence-based medicine group of the ELCWP. Where necessary, aggregation of randomised clinical trials was performed by the meta-analysis method as previously described [1-4]. The quality of published guidelines was assessed using the AGREE instrument [5-8], allowing elimination of the worst and use of the best of them as sources for the formulation of the ELCWP guidelines. Accordingly, the following guidelines were selected: ASCO (American Society of Clinical Oncology) guidelines [9,10], BTS (British Thoracic Society) guidelines [11], Cancer Care Ontario Practice Guidelines [12] (www.cancercare.on.ca/access_PEBC.htm), Royal College of Radiologists guidelines [13], American College of Chest Physicians (ACCP) guidelines [14] and FNCLCC (Fédération Nationale des Centres de Lutte contre le Cancer) guidelines [15]. Our selection was based on the results of a prior assessment of the literature performed by the ACCP [16], complemented by our own analysis, performed by using the AGREE instrument, of other guidelines not considered by ACCP. This approach allowed us to include the FNCLCC and ACCP guidelines.

The text of our recommendations produced in the above way has been presented, actively debated and definitively approved by the Group in a final meeting, in Brussels, in April 2005.

QUESTION 1: IS SURGERY THE BEST THERAPY FOR A POTENTIALLY RESECTABLE LUNG CANCER?

This question has already been addressed in various published guidelines. In 2000, the FNCLCC recommended surgery for stages I and II NSCLC as well as for some T4N0 [17]. It stated as reference values, a less than 2% operative mortality for lobectomies and less than 6% for pneumonectomies. Surgery was considered optimal therapy for local control in stage IIIA N2. In 2001, the BTS published, similar guidelines for stages I and II and some stages T4N0-1 [11]. It proposed surgery in combination with chemotherapy for some stages IIIA. According to BTS, only 5 to 10% of patients with stage I and II tumours should be considered inoperable. A similar approach was proposed, in 2001, by the Royal College of Radiologists [13]. Finally, in 2003, the ACCP recommended surgery alone and lobectomy or sleeve lobectomy, when possible, rather than pneumonectomy, for stages I [18] and II [19]. It proposed surgery only for stages III [20,21] as well as stages T4 N0-1 by virtue of satellite nodule.

For evident ethical reasons, no randomised controlled trials exist demonstrating the efficacy of surgery alone. The level of evidence is based on historical data [22]: The first lobectomies were performed in 1920 by Sauerbruck, a well-known German surgeon whose reputation soon waned as a result of his connections to Gebhart, a famous orthopaedist but also an SS General charged with the execution of medical experiments in the concentration camps. The first pneumonectomies were performed in the United States by Graham in 1930 while in 1950, Churchill from Harvard University reported a 12% 5 year survival for pneumonctomy and 19% for lobectomy. Today‘s cure rates are much higher. Mountain referring to the series on which the current staging system of lung cancer is based [23] has reported, 5 year-survival rates

of 61% in cIA stage (67% for pathological stages), 38% in cIB (57%), 34% in cIIA (55%), 24% in cT2N1 (39%) and 22% in cT3 N0 (38%).

More limited resections than lobectomy, such as segmentectomy and wedge resection, are possible, They have been tested in 2 randomised trials: The first, conducted by the Lung Cancer Study Group, in North America included 247 patients with clinical stage T1 N0 [24]. It has shown better results after lobectomy than after wedge resection, both in terms of locoregional relapses ($p=0.008$) and of 5 year survival ($p=0.08$). The second randomised trial including stage IA patients compared lobectomy using classical surgery versus video-assisted surgery [25]. It did not show significant difference between the two arms but because of the limited size of the study (100 patients) confirmation of results by further studies is required. A systematic review of the literature [26] showed that "sleeve" lobectomy, whenever possible, should be preferred instead of pneumonectomy because of better results in terms of survival and quality of life.

For carcinoma in situ (CIS) and microinvasive squamous cell carcinoma, the FNCLCC, the Royal College of Radiologists and the ACCP recommend endoscopic treatment (cryotherapy, photochemotherapy, electrocoagulation, brachytherapy) as first-line therapy [13,27]. In patients with stages I and II tumours, not suitable for surgery, the FNCLCC and the Royal College of Physicians recommend elective radiotherapy [27]. The ACCP proposes this approach only for stage I.

ELCWP GUIDELINES:

For stages I and II, treatment must at least include surgery (level of evidence: retrospective and prospective operated patients series); operation should remain an option in stage III. In order to improve cure rates, (neo)adjuvant chemotherapy is advisable (see questions 5 and 6).

If the patient cannot be operated on for other medical reasons or refuses surgery, then elective radiotherapy with or without chemotherapy is a valid option (level of evidence: retrospective series).

In case of CIS or microinvasive squamous cell carcinoma, curative endoscopic therapy (cryotherapy, photochemotherapy, electrocoagulation, brachytherapy) might be used in the context of a clinical trial with a very close follow-up but surgery remains the standard first-line treatment (level of evidence: prospective and retrospective series of patients).

QUESTION 2: WHAT CONSTITUTES A COMPLETE RESECTION?

There is no published guidelines on this topic. The ACCP [18] defines only the type of resection (lobectomy, segmentectomy, wedge resection).

The IASLC (International Association for the Study of Lung Cancer) in the context of the International Staging Committee (including two ELCWP members) has commissioned a sub-group to elaborate on the terms complete resection, incomplete resection and uncertain resection. These definitions, when finalised, will be useful.

ELCWP GUIDELINES:

Resection definition to be proposed by IASLC should be used in order to facilitate comparison of the results between different studies.

QUESTION 3: IS A SYSTEMATIC LYMPH NODE DISSECTION NECESSARY?

There are three published guidelines on this topic. According to FNCLCC, homolateral mediastinal dissection is recommended. BTS also suggests the performance of nodal dissection in every case, mainly for the purpose of establishing a precise pathological staging [11]. According to ACCP, a systematic lymph node dissection has to be performed in every patient [18,19].

There are three published and two ongoing randomised trials comparing systematic dissection with lymph nodes sampling. Izbicki randomising 182 patients and Passlick randomising 94 patients, have both failed to show improvement of survival or of local relapse rate [28]. On the contrary, Wu, in a much larger study including 471 patients randomised between mediastinal lymphadenectomy and no mediastinal lymphadenectomy, demonstrated a significant improvement in 5 year-survival (48.2% versus 37%; $p<0.001$) and in local relapse rate (2.9% versus 4.8%) favouring lymphadenectomy [29].

ELCWP GUIDELINES:

Mediastinal lymphadenectomy has to be systematically performed in order to achieve a precise pathological staging, a very important information for prognosis and choice of further therapy (level of evidence: experts opinion and published guidelines consensus).

QUESTION 4: WHAT IS THE ROLE (IF ANY) OF RADIOTHERAPY AFTER COMPLETE RESECTION?

This question has been addressed in various guidelines. The FNCLCC reports that radiotherapy has no role in stage I and II. In stage III, it emphasises that radiotherapy with modern techniques may have a place [15]. According to the BTS and the Royal College of Physicians, thoracic irradiation is not recommended after complete resection [11,13]. Cancer Care Ontario recommends radiotherapy only for stage IIIA,

based on a case by case decision, emphasizing that the benefit in terms of survival has not been demonstrated. Finally, the ACCP recommends radiotherapy for stages II and III but only to reduce the risk of local relapse [19,20].

The evidence against post-operative chest irradiation after complete resection in early stages, comes from PORT meta-analysis based on nine randomised trials and showing a deleterious effect of radiotherapy [30,31]. The level of evidence is thus high but it should be noted that in all nine studies old radiotherapeutic techniques were used.

ELCWP GUIDELINES:

Today, postoperative radiotherapy is not recommended for stages I and II completely resected tumours (level of evidence: meta-analysis of 9 trials). Nevertheless, postoperative irradiation has to be further investigated using modern techniques.

For resected stage III disease, radiotherapy is advocated in combination with adjuvant chemotherapy (see question 7).

QUESTION 5: IS ADJUVANT OR NEOADJUVANT CHEMOTHERAPY INDICATED IN CLINICAL STAGE I OR II?

For clinical stages IB-II, the FNCLCC [17] recommends neoadjuvant (also called primary or induction) chemotherapy as an option. However, the Royal College of Physicians [13] and ACCP [18-19] recommend it only in the context of randomised clinical trials.

In the literature, there is no randomised controlled trial, comparing surgery alone with surgery followed by adjuvant chemotherapy for clinical stage I or II. On the contrary, there is some data about neoadjuvant chemotherapy from a subgroup analysis of a phase III randomised trial conducted by Depierre in France [32] using MIP combination (mitomycine + ifosfamide + cisplatin). For stages IB and II (N0, N1), there is a significant improvement of survival and cure rate.

ELCWP GUIDELINES:

For clinical stages IB and II, neoadjuvant chemotherapy can be advised, preferably in the context of a clinical trial (level of evidence: sub-group analysis of a prospective randomised controlled trial). Outside a trial, MIP combination should be used because this is the only regimen shown effective in controlled data.

For stage IA (small size tumours), due to a lack of controlled studies, there is no evidence for administration of preoperative chemotherapy.

For resected stage IB or II tumours, adjuvant chemotherapy is recommended if the clinical stage is confirmed by the pathological stagee (see question 6).

QUESTION 6: SHOULD ADJUVANT CHEMOTHERAPY BE ADMINISTERED IN PATHOLOGICAL STAGE I OR II?

The available guidelines of FNCLCC [17], Royal College of Radiologists [13] and ACCP [18-19] recommend adjuvant chemotherapy for resected stage I or II tumour only in the context of a clinical trial.

As summarised in table I, there are multiple randomised trials published on the topic We have identified eight trials [33,34-40] specifically performed in stage I and/or II, including two available as online presentation (wwww.asco.org) only [39,40] and four providing sub-group analysis for these stages [41-44]. Five of the studies report significant survival improvement by chemotherapy with regimens such as cisplatin + adriamycine + cyclophosphamide, cisplatin + etoposide, cisplatin + vinorelbine or carboplatin + paclitaxel or UFT. Patients with a pathological stage IA were often excluded form the randomisation.

Two previous meta-analyses have already shown a survival advantage with adjuvant chemotherapy [1,45] and their results have been confirmed by two recent meta-analyses [46,47]. None separates stages I and II from stage III. A Japanese meta-analysis, presented by Hamada at ASCO 2004 meeting and available online (www.asco.org/virtualmeeting), shows that UFT is associated with an improvement in long-term survival with the exception of small size tumours (<2cm). For the present guidelines, we have updated our prior meta-analysis (Berghmans and al, Lung Cancer, in press) and have specifically analysed the effect of chemotherapy in stages I and II for the trials where data were available in the literature. Results are shown in Figure 1 and are in favour of adjuvant chemotherapy whether or not the two not fully published trials [39,40] are considered.

ELCWP GUIDELINES:

Cisplatin-based chemotherapy, using one of the regimens shown effective in term of cure, is recommended after complete resection of a stage IB or II NSCLC (level of evidence: prospective randomised controlled trials and meta-analyses). There are not enough data to recommend this approach for small-size tumours (stage IA).

QUESTION 7: SHOULD ADJUVANT THERAPY BE ADVISED AFTER COMPLETE RESECTION FOR PATHOLOGICAL STAGE IIIA N2, AND IF YES, OF WHAT TYPE: CHEMOTHERAPY, RADIOTHERAPY OR RADIOCHEMOTHERAPY?

Published guidelines from ACCP [20], BTS [11] and the

TABLE I. Results of randomised clinical trials testing adjuvant chemotherapy in pathological stages I and II.

reference	n	stage	control arm	5 year survival	adjuvant arm	5 year survival	p	Stages I & II
SPECIFIC RANDOMISED TRIALS								
Niiranen, 1992 [33]	110	T1-3 N0	- (56 pts)	56%	CAP (54 pts)	67%	0.05	
Feld, 1993 [35]	269	T1N1 or T2N0	- (133 pts)	NA	CAP (136 pts)	NA	NS	
Wada, 1999 [62]	226	I - II	- (116 pts)	71.1%	CDDP-MMC-VDS then UFT (109 pts)	76.8%	NS	
Mineo, 2001 [34]	66	IB (T2N0)	- (33 pts)	45%	CDDP + VP16 (33 pts)	63%	0,04	
Endo, 2003 [37]	221	T1-2 & N0-1	- (110 pts)	75%	UFT 2 years (109 pts)	79%	NS	
Kato, 2004 [38]	980	I (adenoc)	- (488 pts)	85%	UFT (491pts)	88%	0.047	
Strauss, 2004 [39]	344	IB (T2N0)	- (171 pts)	59%	Paclitaxel – Carboplatine			
				(4 years)	(173 pts)	71%	0.028	
Winton, 2004 [40]	482	IB - II	- (239 pts)	54%	CDDP – VNR (243 pts)	69%	0.012	
SUBGROUP ANALYSIS OF RANDOMISED TRIALS								
Dautzenberg,	267	I, II, IIIA	RT (60%)	19%	ADR/CPA-VCR-CDDP	18%	NS	0.03
1995 [41]	130	N0N1	(129 pts)	34%	(138 pts)	17%	0.03	(deleterious)
	147	N2		6%		19%	0.03	
Chubu study,	309	I – III	- (154 pts)	58%	CDDP-ADR-UFT	62%	NS	NS
1995 [42]		(III: 25%)			(155 pts)			
Scagliotti,	1209	I-IIIA	(RT)		(RT) + CDDP-MMC-		0.59	NS
2003 [43]		(IIIA: 28%)	(540 pts)		VDS x 3 (548 pts)			
IALT, 2004 [44]	1867	I-III	RT (free)	40.4%	CDDP + (free) VDS,	44.5%	0.03	NS
		(III: 39%)	(935pts)		VBL, VNR, VP16			
					(932 pts)			

RT: chest irradiation; pts: patients; NS: non significant; NA: non available; CAP: cisplatin + adriamycine + cyclophosphamide; CDDP: cisplatin; MMC: mitomycin; ADR: adriamycine; VDS: vindesine; VBL: vinblastine; VNR: vinorelbine: CPA: cyclophosphamide; VP16: etoposide.

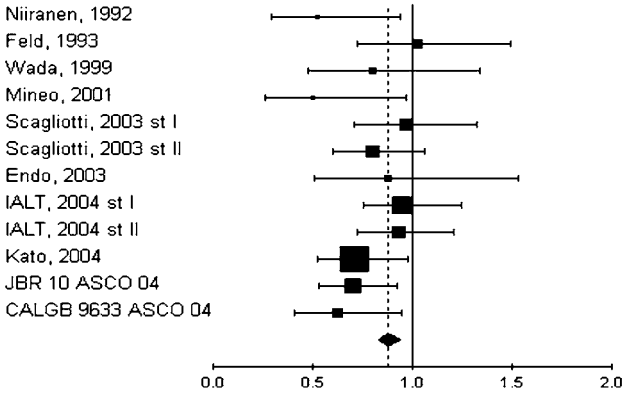

FIGURE 1. Meta-analysis of randomised trials testing the favourable effect of adjuvant chemotherapy in pathological stages I and II. (heterogeneity test: p = 0.11; random effect model: HR = 0.81 with 95% CI: 0.73 – 0.91).

Royal College of Radiologists [13] advise chemotherapy only in the context of a clinical trial. The ACCP recommends chest irradiation to improve local control while the Cancer Care Ontario Practice [12] acknowledging a lack of demonstrated benefit in survival, recommends a case by case decision.

There are only two randomised trials specifically in stage IIIA, testing a cisplatin + vindesine regimen after a resection considered as complete [48,49]. Both failed to show survival improvement. There are also five sub-group analyses of global trials (table II) testing adjuvant chemotherapy [41-44,50]. Two were associated with a benefit [41,44] using cisplatin-based regimens.

Apart from our own, none of the published meta-analyses refers specifically to the results for stage III. Five studies report aggregated data (Figure 2). Despite a trend in favour of adjuvant chemotherapy, statistical significance is not reached. A significant heterogeneity is present.

ELCWP GUIDELINES:

The presently available data do not allow the recommendation of adjuvant chemotherapy in every patient. Further trials are needed, testing the effect of the addition of chemotherapy to irradiation and assessing the impact of various cytotoxic drug regimens. Today, outside the context of a clinical trial, therapeu-

TABLE II. Results of randomised clinical trials testing adjuvant chemotherapy in pathological stages III.

reference	n	stage	control arm arm	5 year survival	adjuvant arm	5 year survival	p	Stages III
SPECIFIC RANDOMISED TRIALS								
Ohta, 1993 [48]	181	IIIA	-(91 pts)	41%	CDDP-VDS (90 pts)	35%	NS	
Tada, 2004 [49]	119	pN2 complete resection	-(60 pts)	36.1%	CDDP-VDS x 3 (59 pts)	28.2%	0.89	
SUBGROUP ANALYSIS OF RANDOMISED TRIALS								
Dautzenberg,	267	I, II, IIIA	RT (60%)	19%	ADR/CPA-VCR-	18%	NS	0.03
1995 [41]	130	N0N1	(129 pts)	34%	CDDP (138 pts)	17%	0.03	
	147	N2		6%		19%	0.03	
Chubu study,	309	I – III	-(154 pts)	58%	CDDP-ADR-UFT	62%	NS	NS
1995 [42]		(III: 25%)			(155 pts)			
Keller, 2000 [50]	488	II-IIIA	RT (50,4 Gy)	NA	RT + CDDP-	NA	0.56	NS
		(IIIA: 58%)	(242 pts)		VP16 x 4 (246 pts)			
Scagliotti, 2003 [43]	1209	I-IIIA	(RT)		(RT) + CDDP-MMC-		0.59	NS
		(IIIA: 28%)	(540 pts)		VDS x 3 (548 pts)			
IALT, 2004 [44]	1867	I-III	RT (free)	40.4%	CDDP + (free) VDS,	44.5%	0.03	S
		(III: 39%)	(935pts)		VBL, VNR, VP16 (932 pts)			

RT: thoracic radiotherapy; pts: patients; NS: non significant; NA: non available; CDDP: cisplatin; MMC: mitomycin; ADR: adriamycine; VDS: vindesine; VBL: vinblastine; VNR: vinorelbine: CPA: cyclophosphamide; VP16: etoposide.

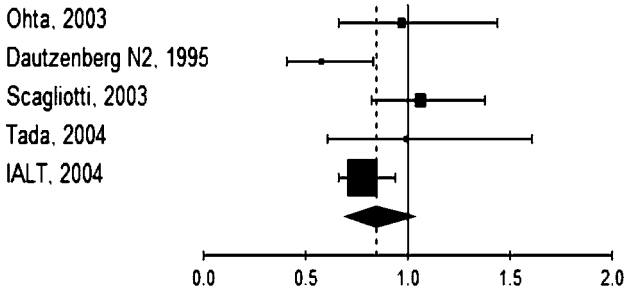

FIGURE 2. Meta-analysis of randomised trials testing adjuvant chemotherapy in pathological stage III. Results are in favour of treatment without reaching statistical significance (heterogeneity test: p = 0.07; random effect model: HR = 0.85 with 95% CI: 0.69 – 1.04).

tic decision has to be made on a case by case basis. It is highly recommended to include such patients into clinical trials.

QUESTION 8: WHAT ARE THE INDICATIONS FOR SURGERY AFTER INDUCTION TREATMENT IN CLINICAL STAGE IIIA OR IIIB?

The majority of published guidelines recommends a surgical approach only after multidisciplinary discussion and in the context of a clinical trial [11,13,17]. For Cancer Care Ontario Practice [12], preoperative chemotherapy followed by postoperative radiotherapy is recommended if resection is technically feasible and planned. According to ACCP [20,21], surgery is advisable if the objective is complete resection, the alternative being radiotherapy except for non N2 Pancoast tumours where induction radiochemotherapy is recommended [51]. In the latter situation, BTS also recommends a multimodal approach.

There is only one published small-size (45 patients) randomised trial testing the feasibility of surgery after induction chemotherapy in comparison to radiochemotherapy without resection [52].

A large randomised trial (392 patients) has been performed by the American Intergroup and showed no significant overall survival advantage for surgery compared with chest irradiation alone [53]. For Pancoast tumours, no prospective controlled study is available.

ELCWP GUIDELINES:

Treatment has to be multimodal, including chemotherapy and radical local therapy (level of evidence: experts opinion). Concerning local therapy, provided that complete resection is feasible, the choice between surgery (+radiotherapy) or radiotherapy alone will depend on the available facilities. Inclusion in clinical trials is highly advisable. For non N2 Pancoast tumours, induction chemoradiotherapy prior to surgery is recommended.

QUESTION 9: IN CLINICAL STAGE IIIA OR IIIB, IF SURGERY IS CONSIDERED, IS INDUCTION THERAPY REQUIRED, AND IF YES, OF WHAT TYPE?

Many published guidelines (FNCLCC, BTS, Royal College of Radiologists and AACP) advocate neoadjuvant chemotherapy in this situation with patients inclusion in a clinical randomised trial [11,13,17,20,21]. Cancer Care Ontario Practice recommends preoperative chemotherapy and postoperative radiotherapy [12].

The level of evidence consists of a series of small randomised trials mainly performed in stage IIIA [54-59] and of the sub-group analysis of Depierre's study [32]. All the data are summarised in table III. There are only two trials reporting statistically significant results in favour of induction chemotherapy. The ELCWP meta-analysis shows, in a significant heterogeneity context, a non significant trend in favour of induction chemotherapy (Figure 3).

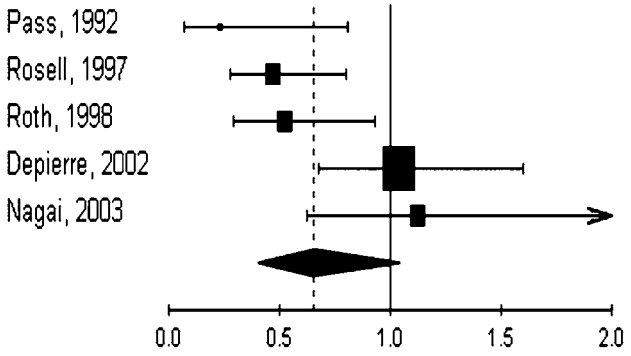

FIGURE 3. Meta-analysis of randomised trials testing neoadjuvant chemotherapy in clinical stage IIIA. Results are in favour of treatment without reaching statistical significance (heterogeneity test : p = 0.02; random effect model: HR = 0.65 with 95% CI: 0.41 – 1.04).

ELCWP GUIDELINES:

Induction chemotherapy complemented by postoperative radiotherapy and administered in the context of a clinical trial is highly recommended (level of evidence: experts opinion).

QUESTION 10: WHAT SHOULD BE THE POSTOPERATIVE TREATMENT AFTER INCOMPLETE SURGICAL RESECTION?

FNCLCC guidelines advocate full-dose external irradiation only for stage T3 N1 [17] while the Royal College of Radiologists and the ACCP recommend the same approach in every case [13,20].

There is only one randomised study on the above topic performed in the eighties [60]. It compared radiotherapy with or without chemotherapy using cisplatin + adriamycine + cyclophosphamide. Results did not show a difference in terms of survival.

ELCWP GUIDELINES:

These patients must be treated by radiochemotherapy as unresectable disease (level of evidence: experts opinion). If resection is incomplete at microscopic level, the patient should be reoperated or otherwise irradiation should be administered.

TABLE III: R-esults of randomised clinical trials testing neoadjuvant chemotherapy in clinical stage IIIA.

Reference	Treatment	n pts	IIIA	N2	T3	T3 N0-1	RO	MS (month)	p
	SPECIFIC RANDOMISED TRIALS								
Pass, 1992 [54]	1. CDDP-VP16	13	13	13	0	0	62%	29	NS
	2. Control	14	14	14	0	0	-	16	
Rosell, 1994 [55,56]	1. MMC-Ifo-CDDP(3x)								
	then surgery (+RT)	30	26	25	13	5	53%	26	S
	2. surgery (+RT)	30	21	19	16	11	-	8	
Roth, 1994 [57,58]	1. CPA-VP16- CDDP(6x)								
	then surgery (+RT if incomplete)	29	20	20	12	6	35%	64	S
	2. surgery (+RT if incomplete)	32	24	22	15	10	-	11	
Nagai, 2003 [59]	1. CDDP-VDS (3x) then surgery	31	31	31	3	0	28%	17	NS
	2. surgery	31	31	31	3	0	77%	16	
	SUBGROUP ANALYSIS OF RANDOMISED TRIALS								
Depierre, 2001 [32]	1. MMC-Ifo-CDDP x 2 then surgery	179	92	92			NA	NA	NS
	2. surgery	176	75	75			-	NA	

RT: thoracic radiotherapy; pts: patients; S: significant; NS: non significant; NA: non available; CDDP: cisplatin; MMC: mitomycin; Ifo: ifosfamide; VDS: vindesine; CPA: cyclophosphamide; VP16: etoposide.

QUESTION 11: WHICH REGIMEN SHOULD BE ADVISED AS ADJUVANT OR NEOADJUVANT CHEMOTHERAPY?

There is no published guidelines on this topic and there is no randomised trial comparing the various regimens. There is only one meta-analysis [61] performed in advanced disease demonstrating better response rates if the number of drugs used is higher (3>2>1).

ELCWP GUIDELINES:

If the patient is treated outside a clinical trial, one of the regimens shown to be effective in randomised trials is recommended (level of evidence: experts opinion). It is important to perform trials comparing various chemotherapeutic regimens as induction treatment and as adjuvant therapy.

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