clinical practice guidelines

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Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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introduction

Lung cancer represents the leading cause of cancer mortality worldwide, accounting for ∼1.2 million deaths each year.

Improving survival in lung cancer is a major challenge for modern oncology considering that 5-year survival remains <15%, across all stages of disease and with <7% of patients alive 10 years after diagnosis.

Because of the difficulties in significantly improving survival in locally advanced and metastatic non-small-cell lung cancer (NSCLC), diagnosis and treatment of early stages theoretically represent the most consistent possibility of modifying the outcome of NSCLC in terms of disease-free and overall survival.

lung cancer screening and staging

The large majority of NSCLC patients present with symptoms in a late advanced stage and diagnosis occurs mostly in locally advanced or metastatic disease with a very poor rate of cure. The issue of lung cancer screening has consequently a strong rationale, to increase the detection of early NSCLC potentially cured by surgery. Earlier controlled trials, using standard radiography and sputum cytology failed to demonstrate any survival benefit for early detection in the interventional arm versus controls. Subsequently using more sensitive screening modalities such as low-dose CT scanning (LDCT) several authors have demonstrated the possibility of detecting approximately three times as many small lung nodules in comparison with chest X-ray and of finding early stage lung cancers.

Three independent analysis of six prospective CT screening studies suggest a potential mortality reduction benefit of ∼20%. In a large collaborative study the International Early Lung Cancer Action Program Investigators screened 31 567 asymptomatic persons at risk for lung cancer with LDCT scanning from 1993 to 2005, suggesting that the stage I detection rate on 484 diagnosed lung cancers and 10-year survival rate could both exceed 80%.

At the same time, however, an analysis of three prospective trials on 3246 persons suggested that the use of LDCT could not reduce significantly the mortality from lung cancer.

Major concerns still remain about the potential over-diagnosis and follow-up of the number of detected nodules as well as about cost and healthcare policy questions of lung cancer screening; it is necessary to await the completion and maturation of some prospective randomized trials such as the one designed and conducted by the National Cancer Institute (USA), the National Lung Screening trial comparing spiral CT and chest X-ray screening for early lung cancer detection to definitively evaluate the relevance of screening in early diagnosis of NSCLC. At the moment it is clear that chest X-rays cannot be recommended for screening of lung cancer.

recommendation IA

Low-dose CT scan cannot yet be used for screening of lung cancer unless in a clinical trial.

recommendation IIC

Accurate staging procedures are critical to define optimal therapeutic strategies and prognosis in early stages NSCLC.

Recently a new lung cancer staging system has been published by the International Association for the Study of Lung Cancer (IASLC), based upon data regarding TNM descriptors which have been intensively validated internally and externally. CT scan and positron emission tomography (PET) are widely used on a systematic basis to define the mediastinum nodal status which remains a critical discriminant in NSCLC staging. Sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis are 51% [confidence interval (CI) 47%–54%] and 85% (CI 84%–88%); meanwhile sensitivity and specificity of PET scanning are 74% (CI 69%–79%) and 85% (CI 82%–88%), demonstrating that PET scanning is more accurate in mediastinum staging and has great relevance in the search for distant metastasis. Biopsy is

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mandatory to confirm CT and PET abnormal findings. In patients amenable for radical surgery with curative intent PET scanning is recommended for staging.

recommendation IA

In the case of abnormal results on PET scan with mediastinal lymph node enlargement a biopsy of mediastinal lymph node is recommended, through different invasive techniques for confirmation of the N2–N3 node status such as mediastinoscopy TBNA, EBUS-NA.

recommendation IA

surgery for stage I and II

Surgery remains the cornerstone of early stage NSCLC treatment, but only in stage pI is 5-year survival over 50% (ranging from 73% in stage pIA to 58% in stage pIB), with much room for improvement with systemic adjuvant or neoadjuvant approaches in stages II and III.

Lobectomy including systematic lymph node dissection is considered standard of care for stage I and II NSCLC resulting in a 5-year survival for pIA ranging from 69% to 89%, for pIB from 52% to 75%, for pIIA from 45% to 52% and 33% for pIIB. A pneumonectomy is rarely indicated in these stages. Operative mortality is reported to be 3.7% in average and ranges from 1% to 7.6%. In specialized centres mortality is expected to be clearly <2%.

Sublobar resection of small peripheral tumours includes anatomical segmentectomy and large wedge excision. The only randomized controlled study for stage I tumours found significantly higher local recurrences in the segmentectomy group with a trend, but not significant survival benefit for lobectomies. Further studies including a meta-analysis confirmed that 5-year survival is similar for stage I and therefore recommendations are that patients unfit for lobectomy should undergo a segmentectomy. Minimally invasive video-assisted (VATS) lobectomy is continuously more and more applied in many centres for tumours generally <5 cm. A recent meta-analysis reported similar locoregional recurrences for VATS compared with open lobectomy but a reduced systemic recurrence rate ($P = 0.03$) and improved 5-year survival rate ($P = 0.04$). The latter may be partially due to a selection bias in the VATS group. However, VATS lobectomy is associated with lower morbidity, shorter hospital stay and facilitates the delivery of adjuvant chemotherapy.

Radiotherapy is a reasonable opportunity for those patients not candidates for surgery because of medical comorbidities or refusing surgery. Local recurrence occurred at a median rate of 40% and median survival was reported as between 18 and 33 months. Results have been improved by modern techniques of radiotherapy, administered in larger doses, fewer fractions and smaller fields with three-dimensional conformal radiotherapy. Local recurrent rate has been reduced around 14.5%.

recommendations

For healthy patients with stage I–II lobectomy represents the treatment of choice [I, A]. Fractionated or conformal stereotactic radiotherapy should be offered to medically unoperable patients [I, B].

adjuvant chemotherapy in early stage NSCLC

Adjuvant chemotherapy has been considered a standard modality of cure after surgery in breast and colorectal cancer with the highest level of evidence and recommendation, but just in the last 10 years it has become a recommended treatment for early stage NSCLC. In 1995 a first meta-analysis of all randomized trials of adjuvant chemotherapy versus best supportice car (BSC) (or observation) performed on the basis of individual data, showed an absolute survival benefit of 4% at 5 years, for modern cisplatin-based chemotherapy regimens, with a non-statistically significant trend in survival benefit. In this meta-analysis it was clear that the survival benefit would result from the 11 trials of cisplatin-based regimens, whilst the previous use of alkylating agents was detrimental in comparison with observation.

The results of a 1995 *BMJ* meta-analysis prompted a number of randomized clinical trials which have been completed and published, for an accrual of >7000 patients, with conflicting results (Table 1). Two studies, one by ECOG with cisplatin–etoposide plus radiotherapy and one by ALPI-EORTC using the MIP regimen (mitomycin–ifosfamide–cisplatin), failed to show any survival benefit in comparison with observation in stage I–II–IIIA radically resected patients.

In the ECOG trial, the concomitant chemoradiotherapy potentially could have harmed the treated patients reducing the cisplatin dose intensity below an active threshold level. In the ALPI-EORTC trial, the choice of MIP regimen—at that time considered as a reference combination—could have negatively influenced dose intensity and survival.

A similar trial, the Big Lung Trial (BLT), was performed in the UK exploring the value of cisplatin-based chemotherapy versus observation in fully resected stage I–II–III NSCLC. This study enrolled only 381 patient without adequate power to detect any survival difference and included stages I–III, failing to show any benefit for the adjuvant treatment.

In 2004 the International Adjuvant Lung Cancer Trial (IALT) published the results of the largest adjuvant chemotherapy study ever done, in 1867 fully resected stage I–III NSCLC, randomized to receive three or four cycles of cisplatin combined with vinblastine, vinorelbine or etoposide versus observation; postoperative radiotherapy (PORT) was performed on the basis of individual centres' decision. This study was the first positive adjuvant trial with a statistical survival benefit in favour of chemotherapy in both disease-free and overall survival. In the IALT trial 37% of the patients had stage I, 24% stage II and 39% stage III, and stage III patients obtained the largest benefit from chemotherapy. A higher cumulative cisplatin dose (240 mg/m^2) and the application of PORT in stage III in the IALT trial, could explain the better outcome in comparison with the results of the ECOG, ALPI-EORTC and BIG trials. In a recent update, the IALT investigators reported that the survival benefit in favour of chemotherapy was non-significant after a median follow-up of 90 months, probably because of more non-cancer-related deaths in the chemotherapy-treated patients.

Table 1. Trials addressing the effect of platinum-containing adjuvant chemotherapy (published after 1994)

Reference/sponsor/year	Patients per arm POCT/control) (*n*)	P stage	Patients with pIII/pN2/adenocarcinoma (%)	Chemotherapy regimen	Chemotherapy compliance (%)/mortality (%)	Interval between resection and POCT planned/actual median (weeks)	Patients with PORT per arm (POCT/control) (%)	Difference in 5-year survival (%): POCT–no POCT	*P* value/HR/(95% CI)
BLT [22]/2003	192/189	I–IV[a]	34/21/37	3× PVd, PVn, PM, MVbP	64/NS	6/7	NS	–2	0.9/1.02 (0.75–1.35)
JCOG [20]/2004	59/60	IIIA	100/100/73	3× PVd	58/0	6/NS	0/0	–7.9	0.9/0.92 (0.58–1.44)
ALPI-EORTC [21]/2003	548/540	I–IIIA	28/25/37	3× MVdP	69/0.5	6/NS	65/82	1	0.6/0.96 (0.81–1.13)
IALT [23]/2004	932/935	I–III	39/26/40	3 of 4× PE, PVn, PVd, PVb	74/0.8	2–8/6	64/70	4.1	<0.03/0.86 (0.76–0.98)
NCIC-BR 10 [25]/2005	242/240	I–II	39/39/53	4× PVn	65/0.8	6/6	0/0	15	0.04/0.69 (0.52–0.91)
CALGB [27]/2006	173/171	IB	0/0/61	4× CbT	84/0	4–8/NS	0/0	3	0.32 NV
ANITA [26]/2005	407/433	I–IIIA	35/NS/40	4× PVn	56/1.7	NS/NS	21/33	8.6	0.01/0.79 (0.65–0.95)
NATCH [28]	211/212	I–IIIA	–/26/	3× CbT	61/0	NS	NS	1.5	–/0.99

Cb, carboplatin; E, etoposide; M, mitomycin; P, cisplatin;T, paclitaxel; Vb, vinblastin; Vd, vindesin; Vn, vinorelbin; NS, not stated.
[a]Two patients had pIV.

The IALT results have been later confirmed in two similar trials, designed to evaluate the combination of cisplatin and weekly vinorelbine for up to 16 weeks as adjuvant treatment.

The National Cancer Institute of Canada designed its trial in 482 fully resected NSCLC stage IB–II, with a significant survival benefit, obtained only in stage II patients. Neutropenia grade III–IV was present in 88% and febrile neutropenia in 7% of the cases. In the chemotherapy arm median survival was significantly prolonged at 94 months as compared with 73 months in the observation groups; a preplanned subgroup analysis did not show improvement in overall survival for stage IB patients.

The same regimen has been also evaluated in a prospective, randomized study, carried out by the Adjuvant Navelbine International Trialist Association (ANITA) in 840 fully resected stage IB–III patients: in these study postoperative radiotherapy was planned in node-positive patients and 232 patients received postoperative radiotherapy (33.% in the observation and 22% in the chemotherapy arm). A retrospective analysis showed that median survival was longer in patients with stage III–N2 disease both in the chemotherapy and the observation arm suggesting a positive role for adjuvant radiotherapy in stage III patients. The ANITA trial confirmed the poor compliance of the vinorelbine–cisplatin schedule with 86% of grade III–IV neutropenia and 9% of febrile neutropenia. After 76 months of median follow-up, the median overall survival was significantly longer in the chemotherapy arm but, at subgroup analysis the benefit was limited to stage II–III patients.

In 2005, the CALGB presented the preliminary results of a prospective randomized trial of adjuvant carboplatin–paclitaxel administered to fully resected patients with stage IB disease, showing a significant reduction at 4 years. Unfortunately, these results were not confirmed at 6-year follow-up, except in an unplanned subset analysis of patients with tumour size >4 cm. This finding opened a still unsolved controversy of whether patients with stage IB tumours should be treated with systemic adjuvant chemotherapy. In the new UICC 7 classification, T2 N0 tumours >5 cm in diameter will be reclassified as stage IIA instead of IB, which could solve this controversy.

The Spanish NATCH trial, designed to detect differences in outcome between preoperative chemotherapy, postoperative chemotherapy and surgery alone was recently reported. A total of 624 patients were randomized between surgery with or without adjuvant or neoadjuvant three cycles of carboplatin and paclitaxel. No difference in outcome was observed between the two arms, possibly due to the predominance of stage I patients.

meta-analyses (Table 2)

These last five large randomized trials have been pooled in an individual patient database LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis of 4584 patients, showing that adjuvant chemotherapy increases survival from 64% to 67% for stage IB, from 39% up to 49% for stage II and from 26% up to 39% for stage III NSCLC at a median follow-up of 5.1 years. The meta-analysis confirmed a potential detrimental effect of chemotherapy in stage IA.

Table 2. systematic reviews and meta-analyses addressing adjuvant chemotherapy

Reference	Intervention/control	Number of participants/ (number of studies)	Difference in 5 year survival (%)/(95% CI)	HR/95% CI	*P*-value	Remark
NSCLC-CG, 1995 [10]	Resectiion ± cisplatin–POCT	1394 (8)	+5 (–1; +10)	0.87 (0.74–1.02)	0.08	IPD
NSCLC-CG, 1995 [10]	Resection + PORT ± cisplatin–POCT	807 (7)	+2	0.98 (–14 to +17)	0.76	IPG
Sedrakyan, 2004 [32]	Resectie ± POCT	7200 (19)	NS	0.87 (0.81–0.93)	<0.0001	
	Resection ± cisplatin –POCT	4912 (12)	NS	0.89 (0.82–0.96)	0.004	NNT: 25
Hotta, 2004 [31]	Resection ± POCT	5360 (13)	NS	0.87 (0.80–0.94)	0.001	
	Resection ± cisplatin –POCT	3786 (8)	NS	0.89 (0.81–0.98)	0.012	
Berghmans, 2005 [51]	Resection ± POCT	7644 (17)	NS	0.84 0.78–0.89	NV	Systematic review
	Resection ± cisplatin –POCT	NV (16)	NS	0.86 (0.80–0.92)	NV	
Bria, 2005 [33]	Resection ± platinum –POCT	4612 (10)	3.9	0.92 (0.87–0.97)	NV	NNT: 21; pooled analysis
LACE, 2006 [29]	Resection ± cisplatin –POCT	4584 (5)	4.2	0,89 (0,82–0,96)	<0.005	IPD
NSCLC-CG, 2007 [30]	Resection ± cisplatin –POCT, no PORT	8147 (30)	4	0.86 (0.81–0.93)	<0.001	IPD
NSCLC-CG, 2007 [30]	Resection + PORT ± cisplatin–POCT	2763 (12)	4.43	0.90 (0.82–0.98)	0.02	IPG

NNT, number needed to treat; NS, not stated; POCT, postoperative chemotherapy; PORT, postoperative radiotherapy; IPD, individual patient data.

In 2007, the update of the 1995 NSCLC collaborative group's individual patient data meta-analysis, reviewing data of 8147 patients of 30 randomized trials, demonstrated a significant survival benefit for adjuvant cisplatin-based chemotherapy, with an absolute benefit of 4% (from 60% to 64%) at 5 years. On the basis of this level 1 evidence, there is a widespread consensus that cisplatin-based doublet adjuvant chemotherapy improves disease-free survival and 5-years overall survival in completely resected patients with stage II–IIIA NSCLC.

However, not all the NSCLC early stage patients are potential candidates to receive adjuvant chemotherapy: a significant proportion of NSCLC cases is diagnosed among patients >70 years and because of prolonged smoking exposure most of them present with relevant cardiovascular, pulmonary and metabolic comorbidities which can significantly reduce chemotherapy compliance and increase the side-effects of cisplatin-based treatment.

In current clinical practice, the best candidate for adjuvant chemotherapy is a relatively young patient, in good condition and without significant comorbidities, who undergoes a complete resection by lobectomy for an early stage NSCLC and recovers quickly from surgery. In the adjuvant setting an absolute benefit of 4%–5% in 5-year survival is considered worthwhile to recommend chemotherapy in current clinical practice after surgery in breast, colorectal and today also NSCLC. However, also in carefully selected patients compliance with chemotherapy in recent randomized trials seems to be moderate and a significant number of patients experience dose reduction, or delays or interruption of treatment. These data reopen the strategic question of whether the more appropriate systemic treatment of early stage NSCLC should consist of neoadjuvant or adjuvant chemotherapy.

recommendations

Three large randomized trials very similar in design and chemotherapy regimens showed a significant survival benefit for the treatment arm in stage II and III radically resected patients with HR ranging from 0.70 to 0.80 and 0.86. In all studies cisplatin-based doublets were used, mainly cisplatin–vinorelbine, with a cisplatin dose >80 mg/m^2 and the survival benefit was consistent across the trials for stage II–IIIA. Besides these studies a number of smaller trials addressing the same questions have been completed and published in these years showing similar results.

Subsequentially a meta-analysis based on individual patient data on 4584 patients has been published 13 years later than the first meta-analysis of the *BMJ*. It confirmed that adjuvant cisplatinum-based chemotherapy increases survival from 64% to 67% for stage IB NSCLC, from 39% to 49% for stage II NSCLC and from 26% to 39% for stage III NSCLC. These data have been substantially confirmed by three different literature-based meta-analyses recently published, exploring the magnitude of benefit of cisplatin-based adjuvant chemotherapy. On the basis of the LACE meta-analysis, of the update of the 1995 *BMJ* meta-analysis and of the single randomized published studies, the evidence in favour of adjuvant cisplatin-based chemotherapy has been confirmed and strengthened and constitute a rational basis for the ESMO

Clinical Practice Guidelines in favour of adjuvant chemotherapy in the stage II–III radically resected NSCLC patient with Recommendation IA.

neoadjuvant chemotherapy in stage I–IIA NSCLC

Neoadjuvant or preoperative chemotherapy is still considered an experimental modality of treatment mainly because it has been evaluated in only a small number of randomized trials and in a series of small phase II studies, exploring the safety and activity of different platinum regimens. Theoretically the neoadjuvant approach has a number of advantages: it can reduce the tumour volume and facilitate the control of micrometastatic diffusion or prevent it; the neoadjuvant treatment allows a careful evaluation of chemotherapy response giving critical information on tumour biology in adequate tumour samples: the compliance of chemotherapy in untreated patients is certainly better than after surgery and its dose intensity higher. On the other hand, its toxicities and a delay to surgery could be disadvantages, although up to now these issues seem to be scarcely relevant.

Two small randomized trials comparing neoadjuvant chemotherapy and surgery versus surgery alone in stage IIIA have raised considerable interest and had a profound impact in the scientific community and in clinical practice. These trials were designed to compare induction platinum-based chemotherapy (with different regimens) followed by surgery versus surgery alone. Roth et al. compared three cycles of cisplatin–etoposide and cyclophosphamide and surgery with surgery alone in stage IIIA in 60 patients, resulting in a 64-month median survival for the combined arm versus 11 months for the control arm with an impressive statistical benefit, which, however, vanished after 82 months of follow-up to 21 and 14 months of median survival, respectively, with borderline statistical significance. Similar results were obtained by Rosell et al. in which the poor outcome of the surgery arm could be attributed to a negative imbalance of biological prognostic factors. The study was prematurely interrupted on the basis of an interim analysis and showed a median survival of 22 months versus 10 months in favour of the (combined) experimental arm, but was also not confirmed in a subsequent identical larger trial from the same Spanish investigators. Pass et al. randomized 27 patients between surgical resection either preceded by cisplatin–etoposide chemotherapy or followed by radiotherapy and observed median survival times of 29 versus 16 months. The results of this trial are, however, difficult to interpret due to the asymmetry in randomization. Other small randomized series did not observe a difference in outcome between approaches with or without preoperative chemotherapy.

These earlier trials have a number of weaknesses in their design: a variable use of adjuvant chemo- and radiotherapy; the use of first- and second-generation drugs, some of which have been associated with a detrimental effect on survival and the use of the 1986 staging classification, in which stage III is even more heterogeneous than in the present one and inappropriate staging resulting in an imbalanced distribution of various stages in the two arms.

In 2001, the results of a French phase III randomized trial of induction mitomycin, ifosfamide, cisplatin chemotherapy in resectable stage IB, II and IIIA were reported. Three hundred and fifty-five eligible patients were randomized to surgery alone or combined modality therapy consisting of two cycles of chemotherapy followed by surgery. Responding patients received two additional cycles of adjuvant chemotherapy. The arms were well balanced for patient characteristics with the exception that fewer clinically N2 patients were assigned to the surgery-only arm (28% versus 40%). A non-significant excess of postoperative morbidity in the chemotherapy arm was seen (24/167 versus 22/171). Postoperative mortality was 7% in the chemotherapy arm and 5% in the surgery arm ($P = 0.38$). Median survival was improved by 11 months (37 versus 26 months) and at 4 years, there was a 9% increase in survival in the chemotherapy arm, but this did not achieve statistical significance. No difference was seen in local recurrence rates. A significant decrease in distant metastases was observed favouring the chemotherapy arm. Follow-up data on this trial, when minimal follow-up exceeded 60 months, showed that the 3- to 5-year survival differences were stable at ~10%. Statistically significant benefits in the N0–1 subgroup were confirmed with 5-year survival rates of 49% compared with 34% in the N2 subgroup.

At least five randomized trials have further explored the issue of neoadjuvant chemotherapy. A common feature of these trials is that they have all been confronted with accrual problems, leading in some studies to their early closure, when the results of randomized trials showing a benefit of adjuvant chemotherapy were published.

The Southwest Oncology Group trial S9900, was a phase III randomized study comparing induction paclitaxel/carboplatin chemotherapy for three cycles followed by surgery with surgery alone in clinical stage IB, II and IIIA NSCLC (excluding superior sulcus and N2 disease) (Table 3). Mediastinoscopy was performed whenever the mediastinal lymph node size exceeded 1 cm. PET imaging was not required. The study called for 600 patients to detect a 33% increase in median survival or 10% increase in 5-year survival but the accrual was prematurely suspended at a total of 354 patients. Of the patients randomized to chemotherapy, 79% completed three cycles of chemotherapy, 41% had radiographic response and 94% had complete resection. Eighty-nine per cent of patients on the control arm had complete resection. With a median follow-up of 53 months, median and 5-year survival rates were 75 versus 46 months, and 50% versus 43% for the chemotherapy–surgery and surgery-alone arms, respectively. Although the use of chemotherapy was associated with a 19% reduction in the risk of death, this difference did not achieve statistical significance. Progression-free survival trended in favour of neoadjuvant chemotherapy, with a median of 33 months versus a median of 21 months for immediate surgery.

In the European Intergroup trial MRC-LU 22 EORTC-08012 NVALT-2, 519 patients with resectable early stage NSCLC were randomized to either surgery alone or three cycles of platinum-based chemotherapy followed by surgery. Choice of chemotherapy regimen was at investigator's choice, as was the intensity of preoperative staging, resulting in only a quarter of the patients being staged with mediastinoscopy and/or PET

Table 3. Summary of four randomized trials comparing neoadjuvant chemotherapy with immediate surgery

Study/reference	SWOG 9900 [46]		European Intergroup Trial [47]		Ch.E.S.T. [49]		NATCH [28]	
	Immediate surgery	Neoadjuvant chemotherapy	Immediate surgery	Neoadjuvant chemotherapy	Immediate surgery	Neoadjuvant chemotherapy	Immediate surgery	Neoadjuvant chemotherapy
No. patients	167	169	261	258	141	129	210	199
Accrual interval	1997–2005		1999–2004		2000–2004		2000–2007	
Chemotherapy								
Regimen(s)		100% Carboplatin AUC 6 Paclitaxel 225 mg/m^2		Cisplatin–vinorelbin (45%) Cisplatin–gemcitabine (25%) Carboplatin–docetaxel (12%) Mitomycin–vindesin–cisplatin (12%) Mitomycin–ifosfamide–cisplatin (7%)		100 Cisplatin 75 mg/m^2 day 1 Gemcitabine 1250 mg/m^2 days 1,8		100 Carboplatin AUC 6 d1 Paclitaxel 200 mg/m^2 d1
Frequency		q 3 w × 3		q 3–4 w × 3		q 3 w × 3		q 3 w × 3
Compliance (%)		79		75		1		85
Patient and tumour characteristics								
Age (median)	64	65	63	62	63	61	64	65
Female gender (%)	32	36	28	28	11	22	12	24
c stage I (%)[a]	67	68	59	64	54	43	73	74
c stage II (%)[b]	32	33	35	28	43	52	25	23
c stage IIIA (%)	NA	NA	6	8	2	5	2	2
Squamous cell (%)	42	34	48	51	45	37	50	54
Response on chemotherapy								
Clinical objective response (%)		41 (CR: 3)		49 (CR: 4)		35		53
PD during chemo (%)		7[a]		6		6		5
Pathological CR (%)		<10		4		NA		10
Safety of chemotherapy								
Neutropenia (grade 3–4) (%)		48		NA		26		12.4
Myalgia/arthralgia (grade 3–4) (%)		6/7		NA				2.6
Mortality: number (%)		3		1				1 (0.5)
Surgical results								
Operated on (%)	96	97	93	91	96	85	95	91
Downstaging	NA	NA	18	31		NA		NA
Complete resection (%)	89	94	79	81	NA	NA	NA	NA
Pneumonectomy rate (%)	25	24	33	28	24	10	26	23
p stage I (%)	NA	NA	47	59	NA	NA	48	49

Table 3. (*Continued*)

Study/reference	SWOG 9900 [46]		European Intergroup Trial [47]		Ch.E.S.T. [49]		NATCH [28]	
	Immediate surgery	Neoadjuvant chemotherapy	Immediate surgery	Neoadjuvant chemotherapy	Immediate surgery	Neoadjuvant chemotherapy	Immediate surgery	Neoadjuvant chemotherapy
Pathological complete remission (%)		<10		4		NA		10
Operative mortality (%)	2.3	4	2	2	NA	NA	6	5
Outcome								
Progression-free survival, median (m)	21	33	25	26	35	48	25.1	31.5
Overall survival, median (m)	46	75	55	54	58	NR	49	55
Overall survival, 5 years (%)	43	50	45	44	NR	NR	44	46.6
HR (95% CI)	0.81 (0.6–1.1)		1.02 (0.8–1.3)		0.63 (0.42–0.93		0.96 (0.84–1.1)	
P-value	0.19	0.86	0.053		0.56			

scan. This trial was also prematurely closed for slowing accrual and its results reported. Of the patients randomized to chemotherapy, 75% completed three cycles of chemotherapy, 49% had radiographic response and 81% had complete resection. Seventy-nine per cent of patients on the control arm had a complete resection. With a median follow-up of 41 months, median and 5-year survival rates were 54 versus 55 months, and 44% versus 45% for the chemotherapy–surgery and surgery-alone arms, respectively. A peculiar finding is the inaccuracy of clinical staging: whereas 18% of the patients who were resected without neoadjuvant chemotherapy actually had a lower pathological than clinical stage, and 41% were likewise 'upstaged'. Patient quality of life seemed not to suffer from the use of chemotherapy and the delayed resection.

A Scandinavian randomized phase II trial reported in abstract a HR of 0.89 in favour of neoadjuvant chemotherapy. In the Ch.E.S.Trial, prematurely closed in August 2004, 236 patients with early stage NSCLC were randomized to either surgery alone or three cycles of cisplatin and gemcitabine followed by surgery. Preliminary 3-year survival data favour neoadjuvant chemotherapy, but should be confirmed at 5 years.

In the Spanish NATCH trial, 624 patients were randomly allocated to immediate surgery or to three cycles of neoadjuvant carboplatin and paclitaxel followed by surgery. No difference in outcome was observed between the two arms, with the exception of a non-significant trend towards improved disease-free survival with neoadjuvant chemotherapy which became significant in stage II T3 N1 at subgroup analysis. This trial confirmed the better compliance with preoperative chemotherapy (97%) as compared with adjuvant (61%) and showed similar resectability rates, surgical procedures and postoperative mortality across arms.

Besides their low power and accrual, these trials have two further weaknesses in common: the survival in their control arms treated with immediate surgery is better than initially estimated, confounding the underpowering caused by the early closure of these trials; stage I (clinical or pathological) accounted for >50% of the enrolment and hence of the better than expected survival. As the accumulated evidence in the adjuvant setting has not found a statistically significant survival benefit for adjuvant chemotherapy in stage I disease, the implication of this finding in the neoadjuvant setting might imply that a possible benefit for higher stages has been diluted by the majority of stage I cases.

meta-analyses (Table 4)

Two systematic reviews from published summary data of randomized chemotherapy trials in early stage NSCLC have been published. The meta-analysis by Berghmans et al. reported six randomized trials, including 590 patients, published between 1990 and 2003. The overall fixed-effect HR on survival was 0.69 (95% CI 0.57–0.84) in favour of the addition of neoadjuvant chemotherapy to surgery. A less extreme result was seen in the publication by Burdett et al. Data from seven randomized trials (published between 1990 and 2005), including 988 patients, were combined in a systematic review and meta-analysis. Preoperative chemotherapy improved survival with a HR of 0.82 (95% CI 0.69–0.97), equivalent to an

absolute benefit of 6% at 5 years. They furthermore found an incremental benefit by stage: stage IA: + 4%, stage IB: 6%; stage II–III: + 7%, but did not observe any interaction between the kind of platinum-containing regimen or the kind of adjuvant treatment (chemo- or radiotherapy). The exploratory nature of these subgroup analyses warrants an IPD approach, which is ongoing. Gilligan et al. added the mature results of the European Intergroup trial to the previous meta-analysis and observed a shift of the hazard ratio to 0.87, with loss of the significance of the improvement in outcome (Figure 1).

recommendations

The available outcome data trend in favour of neoadjuvant therapy, but the majority of individual trials did not find a statistically significant benefit. This could be due to the underpowering of the individual studies or contamination of the outcome by the use of adjuvant therapy in some of them. The data of both systematic reviews on the other hand show an overall effect which is significantly in favour of neoadjuvant treatment. The size of the observed effect is comparable to the one described in a similar meta-analysis of adjuvant chemotherapy. One must keep in mind that both patient populations are different, as only selected patients are offered adjuvant chemotherapy, after pathological staging. The lack of clinicopathological correlation observed in the European Intergroup trial illustrates the heterogeneity of patients enrolled on neoadjuvant trials.

Neoadjuvant chemotherapy results in a clinical downstaging in ~40%–60% of the patients and a pathological complete response rate in 5%–10%. As expected, compliance is better with neoadjuvant chemotherapy compared with adjuvant treatment: >90% of the patients are able to complete all three cycles of neoadjuvant chemotherapy, whereas the full planned adjuvant chemotherapy could only be administrated in 45%–60% of patients.

With the present status of knowledge, neoadjuvant regimens should be platinum based and at least three cycles of chemotherapy should be administered. As in advanced NSCLC, a two-drug combination of platinum and a third-generation drug seems preferable: preoperative cisplatin-based combination chemotherapy can be considered in patients with stage IIIA–N2 disease.

recommendation IIB

Table 4. Meta-analysis of outcome of peri-operative platinum-based chemotherapy in NSCLC

HR (95% CI)	Adjuvant chemotherapy	Neoadjuvant chemotherapy
Early evidence	0.86 (0.80–0.92)	0.66 (0.48–0.93) [50]
Recent evidence	0.89 (0.82–0.96)	0.88 (0.76–1.01) [51]

locally advanced NSCLC (stage III)

Locally advanced or stage III disease accounts for ~30% of patients with NSCLC. Treatment of stage III NSCLC remains a very difficult and controversial area mainly because of the large heterogeneity of different pathological conditions that are still included in stage III in the last update of the TNM classification of lung cancer. Locally advanced NSCLC has been for many years divided into stage IIIA with a 24% 5-year survival and stage IIIB with a worse prognosis and 5-year survival of 9%. Stage IIIA NSCLC represents a heterogeneous group of patients whose tumour extension is restricted to the affected lung (T3 N1), but also includes patients with metastatic disease to the ipsilateral mediastinal lymph nodes (T1–3 N2). Approximately 10%–15% of newly diagnosed cases with NSCLC will be classified as stage IIIA–N2. Their presentation ranges from apparently resectable tumours with occult nodal microscopic metastasis to unresectable, bulky multistation nodal disease. Taken into account this substantial heterogeneity, stage III NSCLC has been classified into six subsets (Table 5).

The poor survival with surgery alone has led to efforts to add chemo- and/or radiotherapy to the locoregional treatment. As mentioned in an above-mentioned meta-analysis, the subgroup of pIIIA patients (subsets 0–2) has a 17%–20% reduction in the risk of death with adjuvant chemotherapy, improving their 5-

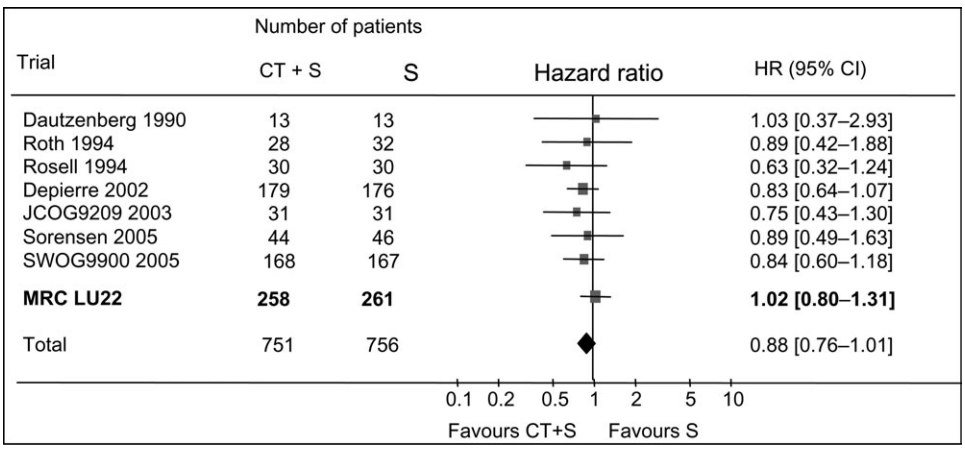

Figure 1. Twelve per cent relative survival benefit with the addition of neoadjuvant chemotherapy (1507 patients; HR = 0.88; $P = 0.07$), equivalent to an absolute improvement in survival of 5% at 5 years.

Table 5. subclassification of stage III

Subset	Definition
IIIA–0	T3 N1 or T4 N0–1 without N2 involvement
IIIA–1	Incidental nodal metastases found on final pathology examination of the resection specimen
IIIA–2	Nodal (single station) metastases recognized intraoperatively
IIIA–3	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)
IIIA–4	Bulky or fixed multistation N2 disease
IIIB	Nodal metastasis in N3 lymph nodes

year survival rate by 13%–15%. This benefit on overall survival was, however, smaller in an individual patient data meta-analysis of randomized trials addressing the benefit of adjuvant chemotherapy on surgery, but included an improved local recurrence-free interval and persisted when PORT was added to surgery. There is hence little controversy that adjuvant chemotherapy should be given to those resected patients presenting with pIIIA subsets 0–2.

PORT in pN2 patients has been shown to result in no clear difference in overall survival but a small reduction in local recurrence. Results from a subgroup analysis of a randomized trial addressing adjuvant chemotherapy and from a retrospective epidemiological study, however, indicates a benefit of PORT on overall outcome in stage IIIA. This issue is currently being prospectively studied in the LUNG-ART trial.

Twelve randomized trials have compared neoadjuvant chemotherapy followed by surgery versus surgery alone in patients with stage IIIA NSCLC with variable numbers of N2 involvement. A number of these trials have not yet been published as full papers. Table 6 summarizes the available evidence as pooled analyses of survival data of these trials. It can be concluded that a significant benefit in favour of neoadjuvant chemotherapy is present ranging at 5 years from 6% to 14% albeit weakened by confounding factors as the non-homogeneity of the patients included, the inadequate sample size and the variable addition of postoperative treatments. In the above-mentioned meta-analysis of neoadjuvant chemotherapy in patients with resectable NSCLC, the analysis by stage shows a 6%–7% absolute benefit in 5-year survival in cIIIA patients, improving their outcome from 15%–35% to 21%–42%. Specific data regarding the subset IIIA–N2 are, however, lacking.

Two randomized clinical trials have been completed in Europe and North America aimed at evaluating the role of the addition of surgical resection to an induction regimen in patients with clinically proven stage IIIA–N2 NCLC, considered functionally operable (Table 7). In the EORTC trial, patients with documented IIIA due to unresectable N2 (disease) NSCLC received as induction chemotherapy three cycles of platinum-based chemotherapy: 332 responding patients were then randomly allocated to receive surgery or radiotherapy, the latter consisting of at least 60 Gy to the primary tumour and 40–46 Gy to mediastinum; PORT was later given to 62 (40%) patients in the surgical arm. Median survival time and 5-year overall

Table 6. Pooled analyses of outcome of stage IIIA patients treated with surgery with and without peri-operative therapy

Reference	Pignon *et al.* [29]	Lim *et al.* [61]	Stewart *et al.* [10]	Le Péchoux *et al.* [62]	PORT [63]	Berghmans *et al.* [51]	Lim *et al.* [61]	Burdett *et al.* [50]
Type of perioperative therapy	± adjuvant chemotherapy	± adjuvant chemotherapy	± adjuvant chemotherapy	PORT ±adjuvant chemotherapy	± adjuvant radiotherapy	± neoadjuvant chemotherapy	± neoadjuvant chemotherapy	± neoadjuvant chemotherapy
Type of analysis	Pooled data	Pooled data	Individual patient data	Individual patient data	Pooled data	Pooled data	Pooled data	Individual patient data
No. trials in the analysis	5	22	15[a]	12	10	5	10	7
No. patients with IIIA/n patients with N2	1247/NA	NA	1020/NA	1596/NA	809/550	376/NA	NA	988/NA
HR (95% CI)	HR 0.83 (0.73–0.95)	HR 0.80 (0.74–0.87)	HR 0.92 (0.78–1.08)	HR 0.89 (0.81–0.97)	HR 0.97 (0.82–1.14)	HR 0.65 (0.41—1.04)	HR 0.81 (0.67–0.97)	HR 0.82 (0.69–0.97)
Absolute benefit at 5 year, % (95%CI)	13	15	3	4.4 (1–8)	3	Not specified	14	6–7

NA: not available.
[a]Only trials not containing tegafur/UFT.

survival rates were 16.4 months and 16% in the surgical arm, and 17.5 months and 14% in the radiotherapy arm. In the surgery arm only 50% resulted in complete resection due to the study design. The conclusions were that surgery did not improve overall or progression-free survival compared with radiotherapy in stage III A unresectable N2 patients responding to induction chemotherapy.

In the phase III randomized North American Intergroup Trial, 492 patients with pathologically documented stage IIIA–N2 NSCLC were randomly assigned to either concurrent chemoradiotherapy therapy (two cycles of cisplatin and etoposide plus radiotherapy interrupted at 45 Gy) followed by surgery (trimodality treatment), or the same chemoradiotherapy with uninterrupted definitive radiotherapy up to 61 Gy. Two additional consolidation cycles of cisplatin and etoposide were given in both groups. Overall survival was not significantly improved with the addition of surgery, even though progression-free survival was significantly better and local-only relapse rates were lower in patients who underwent trimodality treatment. The most probable reason for the observed lack of improved outcome with surgery relates to the exceedingly high mortality rate after pneumonectomy, mainly attributable to acute respiratory distress syndrome and other respiratory causes, and not observed in other centres or single institutional series. Other reasons might include an inadequate study power and the reduced delivery of the adjuvant chemotherapy in the surgical group. However, whether the consolidation chemotherapy had any effect in the non-surgical setting is unknown. The authors did an exploratory matching analysis between resected and not resected patients that led to the hypothesis that trimodality treatment could be beneficial if a complete resection with lobectomy is done after induction chemoradiotherapy, and if the increased surgical mortality associated with pneumonectomy is avoided. This type of analysis is, however, prone to bias because of the absence of matching for other possible prognostic factors such as gender, age and different biomarkers.

Although it is hazardous to make intertrial comparisons between the results of EORTC 08941 and InterGroup 0139, the following conclusions can be drawn.

- Both trials show equivalence in overall survival between surgery and thoracic radiotherapy. The operative morbidity and mortality is also higher than with radiotherapy in both trials, suggesting that for a similar outcome, a preference is to be given to the safest approach, regardless of the IIIA subgroup studied. Although this does not mean that surgery is not feasible or is inferior to radiotherapy, the results neither justify a presumption of superior efficacy of thoracic surgery in subgroups, nor a defeatism against radiotherapy. In the absence of high-quality comparative outcome studies, the available institutional expertise with both approaches and observed clinical outcomes should determine the local approach.
- The rate of pathological nodal downstaging is low, confirming the low accuracy of radiological response assessment (see further) and a low activity of the induction regimens used. The rate of complete pathological remission with neoadjuvant chemotherapy is lower than with chemoradiotherapy, confirming the results of other series. Interestingly, although mediastinal downstaging occurred in 48% of patients allocated to the trimodality treatment in the Intergroup trial, only 15% of them had a pathological

Table 7. Randomized trials in stage IIIA–N2 NSCLC comparing surgery and radiotherapy as locoregional modalities after induction chemo(radio)therapy

Study (reference)	EORTC 08941 [55]		Intergroup 0139 [56]	
Treatment arm	Induction chemotherapy + surgery	Induction chemotherapy + radiotherapy	Induction chemoradiotherapy + surgery	Chemoradiotherapy
Number of patients with IIIA–N2	167	166	202	194
Chemotherapy regimen	Platinum based	–	Cisplatin–etoposide	–
Radiotherapy total dose (Gray)	–	60	45	61
Rate of pneumonectomy/ (bi-)lobectomy/exploratory thoracotomy (%)	47/38/14	–	27/49/4	–
R0 resection rate(%)	50	–	71	–
Treatment related mortality rate (%)	4	<1	8	2
Pathological nodal downstaging rate (%)	41 (pN0–1)	–	38 (pN0)	–
Pathological complete response rate (%)	5	–	15	–
Median PFS (months)	9.0	11.3	12.8	10.5
Locoregional failure rate (%)	32	55	10	22
Median OS (months) with 95% CI	16.4 (13.3–19.0)	17.5 (15.8–23.2)	23	22.2
5 year SR (%) with 95% CI	15.7 (10–22)	14 (9–20)	27.2	20.3

PFS, progression-free survival; OS, overall survival; R0, microscopically radical resection; SR, survival.

complete response after 45 Gy of radiotherapy, suggesting an inappropriate dose of the latter to sterilize the primary tumour.
- In both trials local control with surgery is better than with radiotherapy, as the locoregional relapse rate in the EORTC study was higher with radiotherapy and progression-free survival was better in the Intergroup trial. Although this observation can be credited to the surgical resection only, it cannot be excluded that the administration of PORT in the EORTC trial and an imbalance in the consolidation chemotherapy in the Intergroup trial are responsible for this finding, as both modalities have been shown to reduce local control. This finding suggests a role for resection as consolidation after definitive chemoradiotherapy.
- Exploratory subgroup analyses of both trials show an improved outcome in patients who are downstaged, and/or in whom a complete resection can be obtained with a lobectomy, as compared with either operated patients without these features, or matched irradiated patients. This finding requires further validation in an adequately designed trial in which patients downstaged after definitive chemoradiotherapy are randomly allocated to either consolidation resection or not.

unresectable locally advanced stage III NSCLC

recommendations

In patients with stage IIIB or stage IIIA–N2 subset 4, several meta-analyses allow the following conclusions (Table 8).

1. Adding platinum-containing chemotherapy either at systemic doses preceding or at low radiosensitizing dose concomitant with chest radiotherapy in good performance patients significantly improves the outcome as compared with single modality chest radiotherapy with traditional dose and fractionation schedules (1.8–2.0 Gy per fraction per day to 60–70 Gy in 6–7 weeks), which yields poor survival rates and patterns of failure that are both locoregional and distant. Although the evidence was already observed in a previous meta-analysis, the latter did not specifically analyse for stage IIIA and for the sequence in which both modalities were administered.

recommendation IA

2. Concomitant chemoradiotherapy at systemic doses results in superior outcome to sequential chemoradiotherapy, at the cost of a moderately increased toxic morbidity—consisting mostly of grade 3–4 esophagitis—and is considered the present standard of care in selected patients. Hence 5-year survival rates of 15% in a mixed population of selected stage III patients seem achievable and are comparable to unmatched series using a surgical approach. Cisplatin–etoposide (or vinblastine or vinorelbine) and carboplatin–paclitaxel both at systemic doses should be considered as the reference regimens.
3. In all meta-analyses, the effect was observed to be independent of patient and tumour characteristics, substage (IIIA versus IIIB) and time period in which the trials were conducted.
4. Definitive-dose thoracic radiotherapy should be no less than the biological equivalent of 60 Gy, in 1.8- to 2.0-Gy fractions to the planning target volume (PTV). Ideally, this requires 3-dimensional (3D) conformal radiotherapy, a technique characterized by beam outlines that match the shape of the PTV.

recommendation IA

follow-up and surveillance of early stage NSCLC after curative intent treatment

Considerable controversy exists about the post-treatment management of patients with early stages NSCLC: how often

Table 8. Individual patient meta-analyses of outcome of stage IIIA patients treated with chemoradiotherapy

Comparison	Reference	Arms	No. patients with IIIA	HR (95% CI)
Radiotherapy versus radiotherapy combined with platinum-based chemotherapy	Rolland *et al.* [55]	Radiotherapy	449	0.91 (0.79–1.05)
		Platinum-based concomitant chemoradiotherapy	548	
Radiotherapy versus sequential chemoradiotherapy	Rolland *et al.* [55]	Radiotherapy	723	0.87 (0.78–0.97)
		Sequential chemoradiotherapy	741	
Radiotherapy versus combined chemoradiotherapy at sensitizing dose	Aupérin *et al.* [58]	Radiotherapy	490	0.81 (0.71–0.92)
		Concomitant chemoradiotherapy	592	
Sequential versus concomitant approach at systemic doses of chemotherapy	Aupérin *et al.* [59]	Sequential chemoradiotherapy	190	0.72 (0.58–0.90)
		Concomitant chemoradiotherapy	188	

and by which tests surveillance should be performed is still debatable mainly because of the lack of evidence that earlier treatment of recurrence leads to a better outcome. Guidelines from different scientific societies suggest only physical examination every 3 months (ASCO) or annual CT scan as stated from the American College of Radiology, NCCN and ACCP. However, a number of issues in the post-treatment time of early stage NSCLC need to be addressed, particularly treatment complications, recurrence of disease and metachronous, new primary tumours.

Treatment complications related to surgery, adjuvant chemotherapy or radiotherapy should be carefully evaluated for a frame time of 3–6 months.

recommendation IIC

According to the published literature, in lung cancer patients treated with curative intent in good performance status surveillance with physical examination and CT scan is recommended every 6 months for 2 years and then annually, coordinated by a multidisciplinary team.

recommendation IC

Despite some reports of better sensitivity, specificity and accuracy of PET/CT for earlier diagnosis of recurrence, this methodology is not yet recommended, mainly because there is no correlation between earlier detection of recurrence and survival benefit and an intensive surveillance programme is certainly more expensive.

recommendation IIC

Patients treated with curative intent should be encouraged and sustained in programmes to quit smoking.

recommendation IA

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