

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

Protocol for Planning and Treatment

The process to be followed in non-surgical management of:

NON-SMALL CELL LUNG CANCER

Patient information given at each stage following agreed information pathway

1. DIAGNOSIS Haemoptysis; dyspnoea or worsening of previous dyspnoea; recurrent pneumonia; new cough or a change in a chronic cough; unexplained weight loss; chest wall pain; incidental finding on CXR performed for another reason.
2. STAGING As per UICC, TNM, 7 th Edition 2009 definitions
3. HISTOPATHOLOGY Wherever possible non-small cell carcinoma should be subclassified into specific histological type with EGFR status, as this will affect choices of chemotherapeutic agents and enable more accurate prognosis. It may not be possible to do this on cytology specimens of limited size hence large biopsies are encouraged. WHO subclassification of non-small lung cancer: Squamous cell carcinoma Adenocarcinoma (i) Acinar adenocarcinoma (ii) Papillary adenocarcinoma (iii) Broncho-alveolar carcinoma (iv) Solid carcinoma with mucus formation Large cell carcinoma Large cell with neuroendocrine features Adenosquamous carcinoma

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 1 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

4. INVESTIGATIONS

A full history and physical examination should precede any investigation.

Initial investigations should include full blood count, serum biochemistry and C reactive protein; a chest X-ray and CT thorax and upper abdomen.

Lung function testing (FEV1/FVC) should be performed.

Because lesions thought to be lung cancer radiologically are sometimes shown to be a benign process and because of the difference in treatment for non-small cell and small cell lung cancer, histological or cytological verification of the diagnosis should be obtained wherever possible.

Diagnostic procedures should be tailored to the individual patient and may include:

1. Review of old chest X-rays to exclude a long-standing benign lesion or determine the rate of progression of a malignant lesion.
2. Bronchoscopy, biopsy of endobronchial lesions, brushings and washings, post-bronchoscopy sputum cytology.
3. Percutaneous fine needle or core biopsy, or endoscopic bronchial or oesophageal ultrasound (EBUS / EUS), in selected cases where bronchoscopy unhelpful.
4. Excisional or needle biopsy of readily accessible secondary deposits
5. Once the diagnosis of non-small cell lung carcinoma has been established, steps are taken to stage clinically and assess the patient's suitability for surgery or radical chemo / radiation. This will include PET scanning and CT Brain and possibly mediastinoscopy to exclude operable metastases in mediastinal lymph nodes.

All patients should be discussed at the lung cancer MDT meeting to confirm staging and histological diagnosis and to determine an appropriate management plan which should be recorded in the patient's notes.

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 2 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

5. RADIOTHERAPY/ CHEMOTHERAPY

5.1 Adjuvant treatment following potentially curative resection

Adjuvant chemotherapy * CONSIDER CLINICAL TRIALS *

Rationale ⁽¹⁾

LACE meta-analysis showed absolute benefit of 5.4% in 5 year survival, most benefit being seen in higher stage patients ⁽¹⁾

Indications

Potentially curative resection
Final pathological stage II and III and selected stage IB (tumour > 4cm in size)
No previous chemotherapy or radiotherapy for current lung cancer
Ideally within 60 days of surgery (desirable gap 4-6 weeks, max 12 weeks unless exceptional circumstances)
No co-morbidities precluding chemotherapy
Good recovery from surgery

Regimen ⁽¹⁾

Cisplatin/vinorelbine 4 cycles

Day 1 Cisplatin 80mg/m² IV vinorelbine 25mg/m² IV

Day 8 Vinorelbine 60mg/m² PO, cycle 1 escalating to 80 mg/m² PO for all subsequent cycles

If cisplatin contraindicated due to poor renal function consider:

Day 1 Carboplatin AUC 5 (based on measured GFR) IV, vinorelbine 25mg/m² IV

Day 8 Vinorelbine 60mg/m² PO, cycle 1 escalating to 80 mg/m² PO for all subsequent cycles.

Adjuvant radiotherapy

Rationale ^(2,3,4,5)

Detrimental to survival in early stage disease but improves local control in positive margins. Controversy exists over N2 disease.

Indications

Involved surgical margins (<1mm)
N2-3 disease without a pathologically clear distant station
Sufficient lung function with respect to volume being irradiated

Dose

50Gy in 20 fractions over 4 weeks

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 3 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

5.2 Radical Treatment for Stage I and II (T1N0, T2N0, T1N1, T2N0, T3N0)

Radical radiotherapy alone

Rationale ⁽¹⁾

No randomised controlled trials but immediate radical XRT appears to give superior survival compared to palliative radiotherapy at time of symptoms.

Indications

PS 0, 1, and selected PS 2.

Stage I and II, confirmed on PET scan, which are medically inoperable or refusing surgery

Lung function sufficient with respect to overall volume to be irradiated.

Absence of brain metastases confirmed on CT brain

Dose

55Gy in 20 fractions over 4 weeks

5.3 Stage IIIA (solitary primary lesion i.e. no ipsilateral nodules) Stage IIIB (without pleural effusion)

Options are: * CONSIDER CLINICAL TRIALS *

Concurrent Chemo radiotherapy ^(1,2,3,)

Rationale

35% vs 16% 2 year survival; 21% vs 12% 4 year survival compared to radiotherapy alone ⁽³⁾

Indications

PS 0 or 1; disease stage confirmed on PET scan

Sufficient lung function with respect to overall volume to be irradiated (FEV1 = > 1.0 litres)

Adequate cardiac and renal function for chemotherapy

Disease volume that can be encompassed in a radical radiotherapy volume at the outset

Absence of brain metastases confirmed on CT brain

Chemotherapy

Day 1 Cisplatin 80mg/m² IV vinorelbine 25mg/m² iv (cycle 1 and 4)

Day 8 Vinorelbine 25mg/m² iv (cycle 1 and 4)

Day 1 Cisplatin 80mg/m² IV vinorelbine 15mg/m² iv (cycle 2 and 3 with radiotherapy)

Day 8 Vinorelbine 15mg/m² iv (cycle 2 and 3 with radiotherapy)

First cycle of chemotherapy to be commenced at earliest possible date, and radiotherapy to commence as close to d1 cycle 2 as possible.

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 4 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

NB Dose reduction of vinorelbine when concurrent with XRT; all given iv.

Radical radiotherapy

To start D1 cycle 2 of chemotherapy or as near as possible
60 to 66Gy in 30 to 33# over 6 to 6 and a half weeks ⁽⁴⁾

RADIOTHERAPY MUST BE BOOKED AT START OF CHEMOTHERAPY

Sequential chemo-radiotherapy (radical) ⁽⁵⁾

Rationale

Improved 2 year survival from 14% to 21% and reduced distant metastases compared to radical radiotherapy alone ⁽⁴⁾

Indications

PS 0 or 1; Staging confirmed on PET scan

Sufficient lung function with respect to overall volume to be irradiated (FEV1 = > 1.0 litres)

Adequate cardiac and renal function for chemotherapy

Disease volume that can be encompassed in a radical radiotherapy volume OR

Disease not encompassable in radical volume at presentation but it is hoped that volume will shrink to allow radical radiotherapy to be given after chemotherapy.

Absence of brain metastases confirmed on CT brain

Chemotherapy

Day 1 Carboplatin IV AUC6 (Cockcroft Gault) or AUC5 if EDTA GFR

Day 1 and 8 Gemcitabine 1200mg/m².

N.B. Consider Pemetrexed and Platinum for adenocarcinomas – see palliative section for regime.

Every 21 days for maximum 4 cycles. If no evidence of response on CT after 2 cycles (i.e. stable disease or progression) and still encompassable in a radiotherapy field, proceed directly to radiotherapy at this point. If disease remains or has become unencompassable, consider high dose palliative radiotherapy or alternative second line chemotherapy.

Radical radiotherapy

55Gy in 20 fractions over 4 weeks – to **start** 4 - 6 weeks after day 1 last cycle chemotherapy (max 6 weeks)

Radical radiotherapy alone

Indications

PS 0, 1, and selected PS 2

Small bulk localised disease encompassable in radical radiotherapy volume

Not considered fit for chemotherapy or refuses chemotherapy

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 5 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

Sufficient lung function with respect to overall volume to be irradiated (FEV1 = > 1.0 litres)

Dose

55Gy in 20 fractions over 4 weeks

5.4 Stage IIIA or IIIB not Suitable for radical radiotherapy; Stage IV

Systemic Treatment

Overall Rationale

Chemotherapy is superior to BSC in terms of median survival and is not detrimental to quality of life in fit patients ⁽¹⁾

Indications

PS 0, 1 and selected 2

Stage IIIA, IIIB or IV not amenable to radical treatment

Adequate cardiac and renal function to tolerate chemotherapy

Consider palliative radiotherapy first if troublesome focal symptoms from thoracic or distant metastatic disease

The chemotherapy regime depends on tumour histology, EGFR status, and line of treatment.

FIRST LINE

a) Adenocarcinoma, Bronchoalveolar or Large cell

i) If EGFR exon 19 and 21 mutation positive:

Chemotherapy

Erlotinib 150mg oral d1-28 q28d until disease progression.

Rationale

accepted by SMC for first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations. ^(2, 3, 4.)

In these patients erlotinib was associated with significantly improved progression-free survival compared with platinum-based doublet chemotherapy regimens. There are no mature overall survival data.

Toxicity and response monitoring

Monitored at each clinic visit – dose reduce if appropriate.

Dose reduction: Initially to 100mg daily and then to 50mg daily if necessary

Baseline clinical assessment: CXR and CT.

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 6 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

Clinical assessment and CXR at 4 weeks. If no clinical or radiological evidence of progression continue erlotinib, with further clinical assessment and CXR 4 weekly and CT at 2 and 6 months or sooner if suspicion of progression.

If still no evidence of progression at 6 months, reduce assessment to CXR every 2 months and repeat CT only if suspicion of progression.

Patients with clinical or radiological evidence of disease progression at any point will be withdrawn from erlotinib therapy

ii) In EGFR Mutation exon 19 and 21 negative

Chemotherapy

Day 1 Cisplatin 75mg/ m²

Day 1 Pemetrexed 500mg/ m² q 21 days with pre treatment with Vitamin B12 and folic acid

Rationale

Cisplatin and Pemetrexed superior to Cisplatin Gemcitabine for adenocarcinoma (12.6 vs 10.9 month median survival) and for large cell tumours (10.4 vs 6.7 month median survival) with reduced toxicity ⁽⁵⁾.

Toxicity and response monitoring

4 -6 cycles, with review after cycle 2 to assess response with CXR or CT scan, and toxicities.

N.B. Must give pre-medication:

Folic Acid 400 micrograms daily start 7-14 days prior to chemotherapy continue daily throughout treatment and for 3 weeks after last cycle of pemetrexed.

Vitamin B12 1000 micrograms IM 7-14 days prior to chemotherapy then every 9 nine weeks. Continue until 3 weeks after the last dose of Pemetrexed.

Dexamethasone 8 milligrams starting the day before chemotherapy, take in the morning for 4 days.

Consider Carboplatin AUC 6 if Cisplatin contraindicated.

b) Squamous cell carcinoma and not otherwise specified (NOS) ⁽⁶⁾

Chemotherapy

Day 1 Carboplatin IV AUC6 (Cockcroft Gault) or AUC5 if EDTA GFR

Day 1 and 8 Gemcitabine 1250mg/m²

Rationale

In this pathology group there is no evidence that one regime is superior to another

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 7 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

Toxicity and response monitoring

4 cycles, with review after cycle 2, to assess response with CXR or CT scan, and toxicities.

SECOND LINE

Treatment depends on pathology and first line treatment given.

N.B. If more than 12 months after response to first line therapy consider re-challenging with the same first-line agents. Toxicity and response monitoring all as previously described in first line treatment.

a) EGFRm positive exon 19 or 21 mutation and no previous Erlotinib

Chemotherapy

Erlotinib 150mg PO daily ⁽⁷⁾.

Rationale

SMC and NICE approved ⁽⁷⁾ as an alternative to i.v. docetaxel only in those who have not received erlotinib first line. In the Shepherd trial Erlotinib was compared to placebo, not other iv chemotherapy.

b) If EGFRm positive exon 19 or 21 and previously received Erlotinib

Chemotherapy

Day 1 Cisplatin 75mg/ m²

Day 1 Pemetrexed 500mg/ m² q 21 days with pre treatment with Vitamin B12 and folic acid
4 – 6 cycles

Rationale

No evidence but best extrapolation of data.

c) EGFR wild type Adenocarcinoma, Bronchoalveolar and Large cell

Chemotherapy

Docetaxel 75mg/m² i.v. d1 q21d for up to 6 cycles ⁽⁸⁾

OR

Docetaxel 25mg/m² i.v. d1, 8, 15q 28d for up to 6 cycles in patients who are borderline fit or troubled by pancytopenia at higher doses

OR

Erlotinib 150mg PO daily as per physician's discretion

Rationale

TAILOR study ASCO 2012 ⁽⁸⁾ showed superior PFS with docetaxel compared to Erlotinib in EGFR wt patients. However TITAN ⁽⁹⁾ showed no difference in survival between Erlotinib and chemotherapy in poor prognostic patients, and recommends that the side effect profile of the treatment chosen, be taken in to consideration.

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 8 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

Therefore Erlotinib can be used as an alternative if not previously used.

2nd line Chemotherapy provides a median survival 7.0 vs 4.6 months compared to BSC. ⁽⁹⁾

d) Squamous Cell and NOS

Chemotherapy

Docetaxel 75mg/m² ⁽¹⁰⁾ up to 6 cycles maximum

OR

Docetaxel 25mg/m² i.v. d1, 8, 15q 28d for up to 6 cycles in patients who are borderline fit or troubled by pancytopenia at higher doses.

Rationale

Median survival 7.0 vs 4.6 months compared to BSC in second line treatment ⁽¹⁰⁾

OR

Erlotinib 150mg PO daily as per physician's discretion

THIRD LINE

Evidence free zone. To be prescribed only at physician's discretion in patients PS 0 or 1 and who have previously responded well to treatments. All with monitoring as described above.

a) EGFR exon 19 and 21 Mutation positive

Chemotherapy

Docetaxel 75mg/m² i.v. d1 q21d for 2-4 cycles

OR

Docetaxel 25mg/m² i.v. d1, 8, 15q 28d for up to 6 cycles in patients who are borderline fit or troubled by pancytopenia at higher doses

Consider clinical trials

b) EGFR wild type Adenocarcinoma, Broncoalveolar and Large cell

Chemotherapy

Docetaxel 75mg/m² i.v. d1 q21d for 2-4 cycles after permission as one off request granted by drugs and therapeutics committee and if not previously received

OR

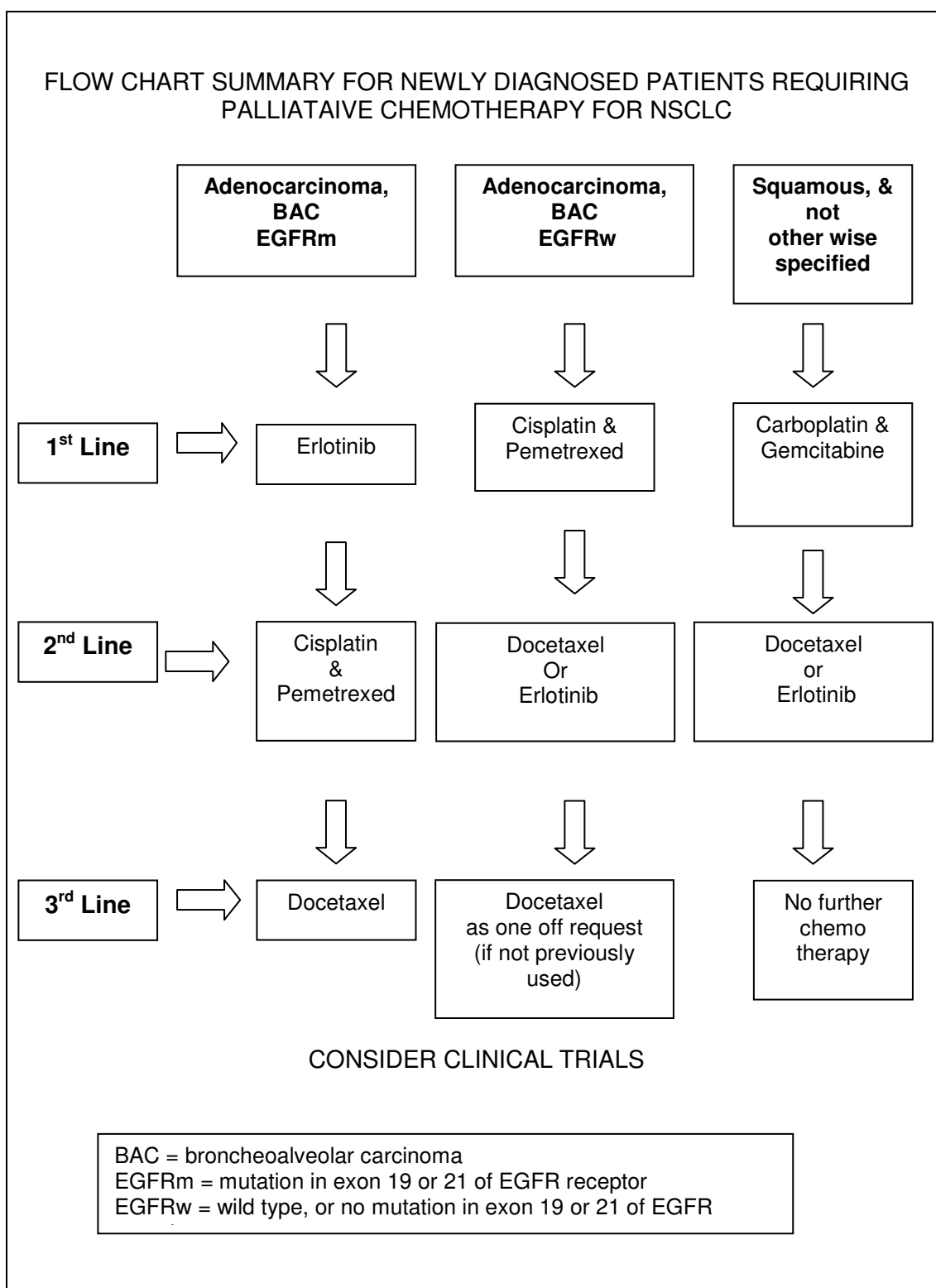
Docetaxel 25mg/m² i.v. d1, 8, 15q 28d for up to 6 cycles in patients who are borderline fit or troubled by pancytopenia at higher doses

Consider clinical trials

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 9 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer



This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 10 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

PALLIATIVE RADIOTHERAPY

High dose palliative thoracic radiotherapy

Rationale

13 fraction regime prolonged median survival from 7 to 9 months vs 17Gy in 2# ⁽¹¹⁾

Indications

PS 0, 1, or selected 2

Locally advanced NSCLC (Stage IIIA or IIIB with no effusion) not amenable to radical radiotherapy (volume too large even after attempt at down-staging chemotherapy or inadequate respiratory reserve)

Reasonable life expectancy

Consider chemotherapy first if no pressing need for radiotherapy e.g. haemoptysis, airway obstruction.

Dose

39Gy in 13 fractions over 2.5 weeks

Low dose palliative thoracic radiotherapy

Indications

Any stage

Poor performance status (2-4)

Anticipated survival > 1 month

Symptoms amenable to palliation with radiotherapy:

- Haemoptysis (80% response)
- Chest pain (60% response)
- Cough (40% response)
- Breathlessness (30% response)
- Fatigue (20% response)
- SVCO (if severe or recurrent after previous radiotherapy consider stenting)

Dose

8Gy single fraction, or 20Gy in 5 fractions over 5-7 days

Palliative radiotherapy to other sites

Bone metastases ^(12,13)

Indications

Painful bone metastasis

Malignant spinal cord compression

Post-surgical fixation of pathological fracture

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 11 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

Dose

8Gy single fraction or 20Gy in 5 fractions over 5-7 days

Rationale ^(12, 13,)

Cost efficient and effective

Whole brain radiotherapy

Indications

Radiologically proven brain metastases

Capable of at least limited self care (i.e. Karnofsky Performance status >70)

Anticipated survival >3 months

Dose

20Gy in 5 fractions over 5-7 days

Patients with a solitary brain metastasis on MRI with either:

previously radically treated and controlled thoracic disease (as confirmed on CT scanning)

OR

potentially curable thoracic disease (i.e. resectable or treatable with radical radiotherapy and who are fit for general anaesthetic should be considered for resection of brain metastasis or stereotactic radiosurgery followed by whole brain radiotherapy (30Gy in 10 fractions over 2 weeks). Then consider chemotherapy.

CONSIDER CLINICAL TRIALS

SUPPORTIVE THERAPIES

Bisphosphonates ⁽¹⁴⁾

Rationale

Reduces skeletal related events from 44% to 35% ⁽¹⁴⁾

Indications

Malignant hypercalcaemia

Bone metastases causing severe bone pain which is uncontrolled by analgesia or radiotherapy.

Dose

Pamidronate 90mg IV every 28 days

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 12 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

REFERENCES

Section 5.1: Adjuvant therapy

1. JP Pignon “Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative” Group *Journal of Clinical Oncology*, Vol 26, No 21 (July 20), 2008: pp. 3552-3559 <http://jco.ascopubs.org/cgi/reprint/26/21/3552>
2. “PORT metaanalysis. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group”. *Lancet* 1998; 352; 257-63 <http://www.ncbi.nlm.nih.gov/pubmed/9690404>
3. Burdett S, Stewart L; “PORT Meta-analysis Group. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis” .*Lung Cancer* 2005; 47, 81-83 <http://linkinghub.elsevier.com/retrieve/pii/S0169500204005215>
4. Dautzenberg et al, “A controlled study of postoperative radiotherapy for patients with completely resected non small cell lung carcinoma.” *Groupe d'Etude et de Traitement des Cancers Bronchiques. Cancer* 1999 ; 86; 265-273 <http://jco.ascopubs.org/cgi/reprint/19/19/3912>
5. B E. Lally et al “Postoperative Radiotherapy for Stage II or III Non–Small-Cell Lung Cancer Using the Surveillance, Epidemiology, and End Results Database” *Journal of Clinical Oncology*, Vol 24, No 19 (July 1), 2006: 2998-3006 <http://www.jco.ascopubs.org/cgi/reprint/24/19/2998>

Section 5.2: Stage 1-2

1. N P Rowell et al “Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review” *Thorax* 2001;56:628-638 <http://thorax.bmj.com/cgi/content/abstract/56/8/628>

Section 5.3: Stage 3

1. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non–small-cell lung cancer. *J Clin Oncol* 1999; 17:2692-9. <http://www.jcojournal.org/cgi/content/abstract/17/9/2692>
2. Curran D, Scott C, Langer C, et al. Long-term benefit is observed in a phase III comparison of sequential versus concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003; 22:621 (Abstract 2499).

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 13 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

3. Pierre F, Maurice P, Gilles R, et al. A randomized phase III trial of sequential chemo-radiotherapy versus concurrent chemo-radiotherapy in locally advanced non-small cell lung cancer (NSCLC) (GLOT-GFPC NPC 95-01 study). *Proc Am Soc Clin Oncol* 2001; 20:312 (Abstract 1246).

4. Kong F-M et al. (2006) "Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis." *Int J Radiat Oncol Biol Phys* 65: 1075–1086 [PubMed](#)

5. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991; 83:417-23. <http://jnci.oxfordjournals.org/cgi/content/abstract/83/6/417>

Section 5.4: Stage 3b and 4

1. S G Spiro "Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life" *Thorax* 2004;59:828-836 <http://thorax.bmj.com/cgi/content/abstract/59/10/828>

2. Rosell et al (2011). Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomised trial. *Abstract 7503. ASCO 2011 Annual Meeting. Chicago. USA*

3. Zhou C, Wu Y-L, Chen G et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncology* 2011;12:735-42.

4. Zhou et al (2011a). Updated efficacy and quality-of-life (QoL) analyses in OPTIMAL, a phase III, randomised, open-label study of first-line erlotinib versus gemcitabine / carboplatin in patients with EGFR-activating mutation-positive (EGFR Act Mut+) advanced non-small cell lung cancer (NSCLC). *Abstract 7520. ASCO Annual Meeting, Chicago. USA.*

5. Scagliotti et al "Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer" *Journal of Clinical Oncology*, Vol 26, No 21 (July 20) 2008: pp. 3543-3551 NICE approved Sept 2009 <http://www.jco.ascopubs.org/cgi/reprint/26/21/3543>

6. Joan H. Schiller et al "Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer" *New England Journal of Medicine* Volume 346:92-98 <http://content.nejm.org/cgi/content/abstract/346/2/92>

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 14 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG

Clinical Management Protocol – Non-surgical management of Non-small Cell Lung Cancer

7. Shepherd et al "Erlotinib in previously treated non small cell lung cancer" *New England Journal of Medicine* 2005 353 (2):123-32
8. Garassino MC et al "TAILOR: A PHASE III trial comparing erlotinib with docetaxel as the second line treatments of NSCLC patients with wild type (wt) EGFR" ASCO 2012
9. Ciuleano T "Efficacy and safety of erlotinib versus chemotherapy in second line treatment of patients with advanced, non small cell lung cancer with poor prognosis (TITAN) a randomised multi-centre, open label phase 3 study" *The Lancet Oncology* Vol 13, Issue 1 300-308 2012
10. Shepherd et al "Prospective Randomized Trial of Docetaxel Versus Best Supportive Care in Patients With Non-Small-Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy" *Journal of Clinical Oncology*, Vol 18, Issue 10 (May), 2000: 2095-2103 <http://jco.ascopubs.org/cgi/reprint/18/10/2095>
11. Macbeth et al "Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status" *JCO* Vol 8, Issue 3, 137-208 (1996)
<http://www.sciencedirect.com/science?ob=ArticlesURL&udi=B6WXW-4FYB11Y-7C&user=10&rdoc=1&fmt=&fmt=7 orig=search& sort=d& do anchor=&view=c&searchStrId=1107689510&rerunOrigin=scholar.google&acct=C000050221&version+1&urlVersion=0&userid=10&md5=d3dd31ceeb258e197a74cc6efd34ee23>
12. E. Steenland "The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone *Radiotherapy and Oncology*, Volume 52, Issue 2, 101-109
13. J. Yarnold et al "8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multi-fraction schedule over 12 months of patient follow-up on behalf of the Bone Pain Trial Working Party" *Radiotherapy and Oncology*, Volume 52, Issue 2, 111-121
14. Rosen et al "Zoledronic Acid Versus Placebo in the Treatment of Skeletal Metastases in Patients With Lung Cancer and Other Solid Tumors: A Phase III, Double-Blind, Randomized Trial—The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group" *Journal of Clinical Oncology*, Vol 21, Issue 16 (August), 2003: 3150-3157 <http://www.jco.ascopubs.org/cgi/reprint/21/16/3150>

This document is uncontrolled when printed

File Name: LU-01 NSCLC	Page 15 of 15	Date of Issue: July 2013 Review Date: July 2015
	Written by: Dr Hannah Lord	Authorised by: OHMMG