Original Article

Singapore Cancer Network (SCAN) Guidelines for Adjuvant Chemotherapy in Resected Non-Small Cell Lung Cancer

The Singapore Cancer Network (SCAN) Lung Cancer Workgroup

Abstract

Introduction: The SCAN lung cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the use of adjuvant systemic therapy for non-small cell lung cancer in Singapore. Materials and Methods: The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. Results: Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), European Society of Medical Oncology (2014), National Institute of Clinical Excellence (2012), Scottish Intercollegiate Guidelines Network (2014), and the Cancer Care Council Australia (2012). Recommendations on the selection of patients, chemotherapy regimen, treatment for stage I disease, treatment for positive margins and treatment options for pN2 disease with negative margins were produced. Conclusion: These adapted guidelines form the SCAN Guidelines 2015 for adjuvant systemic therapy of non-small cell lung cancer.

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Key words: Decision-making, Postoperative therapy

Introduction

In Singapore and also worldwide, lung cancer is one of the most common cancers and is also a leading cause of cancer-related deaths. In Singapore, there were 6558 cases of newly diagnosed lung cancer and 5628 deaths from 2009 to 2013. Lung cancer is the leading cause of cancer mortality among males and second highest among females in Singapore.[1] Approximately 15% of patients with non-small cell lung cancer (NSCLC) present in the early stage (stage I-II) where surgery is the mainstay of curative treatment.[2] Long-term survival however remains poor with distant failure being a major cause of relapse.

The role of adjuvant chemotherapy has been examined in multiple randomised controlled studies and several meta-analyses. Based on studies showing an improvement in 5-year overall survival of 4% to 15%,[3-6] international guidelines have recommended adjuvant chemotherapy as the standard of care in patients with resected stage II-III NSCLC. However there are no local guidelines on treatment recommendations for local patients with resected stage II-III NSCLC.

The development and updating of high quality clinical practice guidelines requires extensive resources. As pre-existing guidelines are available and to reduce duplication of effort, guideline adaption has been formulated as an alternative to guideline development.[7]

Our objective is to produce local guidelines for adjuvant chemotherapy in patients with resected NSCLC by adapting pre-existing international guidelines.

The SCAN Guidelines for Adjuvant Systemic Therapy of NSCLC

The SCAN Guidelines are clinical practice guidelines for adjuvant chemotherapy in patients with resected NSCLC.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of NSCLC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

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Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients with NSCLC.

Guideline Recommendations/Development

The SCAN Lung Cancer Workgroup comprises a panel of 12 oncologists and 1 pharmacist from Singapore with special interests in the management of lung cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework 7 was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to answer the following questions pertaining to the use of adjuvant chemotherapy in patients with NSCLC (Table 1):

1. Which patients are suitable?
2. What regimen should be used?
3. What is the role of adjuvant chemotherapy in stage I?
4. What treatment options are available for positive margins?
5. What are the treatment options for pN2 disease with negative margins?

Five international guidelines were selected for review (Supplementary Table 1):

- "NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer" (version 5.2015) by the National Cancer Comprehensive Network (NCCN, USA)[8]
- "Early and Locally Advanced Non-Small-Cell Lung Cancer (NSCLC): ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up" by the European Society for Medical Oncology (ESMO), 2013[9]
- "NICE Pathways – Treatment for Non-Small-Cell Lung Cancer" by the National Institute for Health and Care Excellence (NICE, 2014)[10]
- "Management of Lung Cancer" by the Scottish Intercollegiate Guidelines Network (SIGN), 2014[11]
- "Cancer Council Australia Lung Cancer Guidelines Working Party (CCCALCGWP) Clinical Practice Guidelines for the Treatment of Lung Cancer" by the Cancer Council Australia Lung Cancer Guidelines Working Party, 2014[12]

For each recommendation, the grade of recommendation as defined by the original guideline is given. The definition of the levels of evidence and grades of recommendation for each guideline are provided in the supplementary material. The level of evidence or grades of strength of their recommendation were not stated in the NICE guidelines.

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of NSCLC, it will be reviewed earlier.

1. Which Patients are Suitable?

The majority of randomised adjuvant trials studied patients with resected stage II-III NSCLC.[6] The role of adjuvant chemotherapy in resected stage I NSCLC will be addressed in a later section. In a recent meta-analysis of individual patient data from 34 trial comparisons and 8447 patients, an absolute survival benefit of 4% (from 60% to 64%) at 5 years was seen with the addition of adjuvant chemotherapy with a hazard ratio [HR] of 0.86 (95% CI, 0.81 to 0.92; P <0.0001).[6] There is no local data available on the benefits of adjuvant chemotherapy in patients with NSCLC.

In the recent meta-analysis, it appeared there was an increasing relative effect of adjuvant chemotherapy on the

Table 1. Singapore Cancer Network (SCAN) Guidelines for the Use of Adjuvant Systemic Therapy for Non-Small Cell Lung Cancer

	Guideline Recommendations
1. Which Patients are Suitable?	SIGN Guidelines: 1. The risks and benefits of postoperative systemic anticancer therapy should be discussed with each patient (GPP). 2. Patients with good performance status (PS 0-1) and completely resected pathological stage II-III NSCLC with negative margins should be offered platinum-based postoperative systemic anticancer therapy (A).
2. What Regimen Should be Used?	CCCALCGWP Guidelines: Patients with completely resected stage II NSCLC should be offered 3-4 cycles of adjuvant cisplatin-based chemotherapy (A). Patients who have a good performance status (WHO 1, 2) and completely resected stage III non-small cell lung cancer should be offered adjuvant cisplatin-based chemotherapy (A).
3. What is the Role of Adjuvant Chemotherapy in Stage I?	NCCN Guidelines: 1. Observation is recommended for patients with T1ab, N0 tumours with negative surgical margins (Category 2A). 2. Patients with T2ab, N0 tumours with negative surgical margins are usually observed (Category 2A). 3. Chemotherapy for high risk features (include poorly differentiated tumours, vascular invasion, wedge resection, >4 cm, visceral pleural involvement, and incomplete LN sampling) (Category 2A).
4. What Treatment Options are Available for Positive Margins?	NCCN Guidelines: 1. Stage IA with R1 or R2: (1) re-resection (Category 2A) or (2) RT (Category 2B). 2. T2abN0: (1) re-resection +/- chemotherapy, (2) RT +/- chemotherapy (Category 2A). 3. Stage II positive margins with R1: (1) re-resection and chemotherapy, (2) chemo-radiation (either sequential or concurrent), with R2: (1) re-resection and chemotherapy or (2) concurrent chemo-radiation (Category 2A). 4. T1-3, N2 or T3N1 with R1: Chemo-radiation (either sequential or concurrent), with R2: concurrent chemo-radiation (Category 2A).
5. What are the Treatment Options for pN2 Disease with Negative Margins?	CCCALCGWP Guidelines: 1. Patients who have a good performance status and completely resected stage III NSCLC should be offered adjuvant platinum-based chemotherapy (A). 2. PORT in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. PORT could be considered in selected patients with pN2 disease (C).

CCCALCGWP: Cancer Care Council Australia Lung Cancer Guidelines Working Party; ESMO: European Society for Medical Oncology; GPP: Good practice point; LN: Lymph node; NCCN: National Cancer Comprehensive Network; NICE: National Institute for Health and Care Excellence; NSCLC: Non-small cell lung cancer; PORT: Postoperative radiotherapy; SIGN: Scottish Intercollegiate Guidelines Network; WHO: World Health Organisation

improvement of performance status but it was noted very few patients with a performance status of ≥2 were included in the studies.[6] Although age itself was not a contra-indication for adjuvant chemotherapy,[13] in a larger analysis, no other subgroups defined by age, gender or histology benefited from adjuvant chemotherapy.[6]

Recommendations on Patient Inclusion

Following discussion, the workgroup has unanimously expressed support for the adoption of SIGN guidelines.

Recommendations are as follows:

1. The risks and benefits of postoperative systemic anticancer therapy should be discussed with each patient (Grade of recommendation: Good practice point).
2. Patients with good performance status (PS 0-1) and completely resected pathological stage II-III NSCLC with negative margins should be offered platinum based postoperative systemic anticancer therapy (A).

2. What Regimen Should be Used?

Most studies used a platinum based 2-drug combination administered in 3 to 4 cycles.[6] No trials have compared different adjuvant chemotherapy regimens but based on the meta-analysis, it appears there are no significant differences between regimens. The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, which included only modern cisplatin-based regimens, confirmed the survival benefits of adjuvant cisplatin (HR = 0.89; 95% CI, 0.82 to 0.96; $P = 0.005$) with 5-year absolute benefit of 5.4% from chemotherapy.[14] All 5 guidelines have addressed the issue on what adjuvant chemotherapy regimen should be used (Supplementary Table 1).

Recommendations on Adjuvant Chemotherapy Regimen

Following discussion and consensus, the workgroup is in favour of adopting the CCCALCGWP Guidelines (Table 1).

Recommendations are as follows:

1. Patients with completely resected stage II NSCLC should

be offered 3 to 4 cycles of adjuvant cisplatin based chemotherapy (A).

2. Patients who have a good performance status (WHO 1, 2) and completely resected stage III NSCLC should be offered adjuvant cisplatin-based chemotherapy (A).

3. What is the Role of Adjuvant Chemotherapy in Stage I?

Most guidelines have recommended observation for T1ab, N0 NSCLC with negative margins (Supplementary Table 1). There is no evidence of a clear survival benefit for postoperative adjuvant chemotherapy for stage IA disease. The role of adjuvant chemotherapy in stage IB NSCLC remains controversial. There appears to be no benefit in patients with stage IA disease but there may be benefit in those with tumours >4 cm.[15,16] In a phase III study of patients with resected stage IB NSCLC randomised to carboplatin/paclitaxel or observation (CALGB 9633), survival was similar in both arms (HR = 0.83; 95% CI, 0.64 to 1.08; P = 0.12). Posthoc exploratory analysis demonstrated a significant survival difference in favour of adjuvant chemotherapy for patients who had tumours ≥4 cm in size (HR = 0.69; 95% CI, 0.48 to 0.99; P = .043). In a retrospective analysis of an adjuvant study JBR.10,[4] patients with tumours 4 cm or larger benefited from adjuvant chemotherapy (HR = 0.66; 95% CI, 0.39 to 1.14; P = 0.13).[16] However, these analyses are posthoc and caution should be exercised in interpreting their significance.

Recommendations on the Role of Adjuvant Chemotherapy in Stage I

After review of the guidelines and by consensus, the workgroup is in favour of adopting the NCCN guidelines.

Recommendations are as follows:

1. Observation is recommended for patients with T1ab, N0 tumours with negative surgical margins (Category 2A).
2. Patients with T2ab, N0 tumours with negative surgical margins are usually observed (Category 2A).
3. Chemotherapy is recommended for high risk features (include poorly differentiated tumours, vascular invasion, wedge resection, >4 cm, visceral pleural involvement, and incomplete LN sampling) (Category 2A).

4. What Treatment Options are Available for Positive Margins?

Several guidelines have reviewed treatment options for positive margins and are summarised in Supplementary Table 1.

Recommendations on the Treatment Options Available for Positive Margins

By consensus, the workgroup has agreed to adopt the NCCN guidelines.

Recommendations are as follows:

1. Stage IA with R1 or R2: 1) re-resection (Category 2A) or 2) RT (Category 2B).
2. T2abN0: 1) re-resection +/- chemotherapy, 2) RT +/- chemotherapy (Category 2A).
3. Stage II positive margins with R1: 1) re-resection and chemotherapy, 2) chemo-radiation (either sequential or concurrent), with R2: 1) re-resection and chemotherapy or 2) concurrent chemo-radiation (Category 2A).
4. T1-3, N2 or T3N1 with R1: Chemo-radiation (either sequential or concurrent), with R2: concurrent chemo-radiation (Category 2A).

5. What are the Treatment Options for pN2 Disease with Negative Margins?

Postoperative radiotherapy (PORT) has been reported in a meta-analysis to have an adverse effect in patients after complete resection of clinical early stage NSCLC with pathological N0 or N1 disease whereas for patients with stage III, N2 disease there was no clear evidence of an adverse effect.[17] However the results were limited by the inclusion of small randomised studies using older radiotherapy techniques and dosing regimens. In a population base analysis within the Surveillance, Epidemiology, and End Results database, patients with N2 nodal disease (HR = 0.855; 95% CI, 0.762 to 0.959; P = 0.0077).[18] The Adjuvant Navelbine International Trialist Association (ANITA) study also reported postoperative radiotherapy improved survival in patients with N2 disease following adjuvant chemotherapy.[19] Guidelines on treatment options for pN2 disease with negative margins are summarised in Supplementary Table 1.

Recommendations on the Treatment Options for pN2 Disease with Negative Margins

By consensus, the workgroup has adopted the CCCALCGWP guidelines.

Recommendations are as follows:

1. Patients who have a good performance status and completely resected stage III NSCLC should be offered adjuvant platinum-based chemotherapy (A).
2. PORT in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. PORT could be considered in selected patients with pN2 disease (C).

Cost-effectiveness

The cost-effectiveness of adjuvant chemotherapy has been addressed in one study of patients.[20] In this study, a cost-effectiveness analysis of adjuvant chemotherapy from the perspective of Canada's public healthcare system was performed based on the study population derived from the landmark National Cancer Institute of Canada Clinical Trials Group JBR.10 adjuvant cisplatin-vinorelbine study.[4] Ng and colleagues found the mean costs of treatment per patient in the observation and adjuvant chemotherapy arms were USD $19,149 and $25,110, respectively, with an incremental cost effectiveness ratio of USD $5754 per life-year gained. The authors concluded adjuvant cisplatin and vinorelbine was a highly cost-effective treatment that compared favourably with other standard healthcare interventions.[20] No cost-benefit/cost-effectiveness analyses have been published locally.

Conclusion

Guidelines have recommended adjuvant chemotherapy as the standard of care in patients with resected stage II-III NSCLC. Clinical questions related to adjuvant therapy for patients with resected NSCLC were identified. Local data on adjuvant therapy in patients with resected NSCLC is lacking. The development of local guidelines from international treatment recommendations using the ADAPTE methodology was feasible. Future work to implement, review and revise the guidelines is warranted.

Conflicts of Interest

Dr Chang reports receiving advisory board fees from Pfizer, Celegene and BMS and lecture fees from MSD, Pfizer and BMS; Dr Tan, receiving research funding from Novartis and advisory board fees from Novartis, Boerhinger Ingelheim and Pfizer; Dr Yeo, serving on advisory boards of Roche and Bayer; Ms Chew, Dr Chin, Dr Goh, Dr Leong, Dr Lim, Dr Lim, Dr Soo, Dr Tan and Dr Toh have nothing to disclose.

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Reviewers

Invited reviewers were Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fergus Macbeth, MA, DM, FRCP, Wales Cancer Trials Unit, Cardiff University, UK.

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Supplementary Table 1. International Guidelines for Adjuvant Systemic Therapy of NSCLC

Guideline Title	Evidence Summary (Level of Evidence)	Recommendation (Grade of Recommendation)	Member Votes
1. Which Patients are Suitable?			
NCCN	NA	Stage II-III with negative surgical margins (Category 1)	
SIGN	• Postoperative SACT in patients with completely resected stage II to IIIa NSCLC confers an overall survival advantage of around 4% at 5 years (HR = 0.86; 95% CI, 0.8 to 0.92). The benefit appears to diminish with longer follow-up, possibly due to an increase in non-cancer deaths in those treated with SACT (Level I+). • There appears to be a correlation between an effect from SACT and better performance status, but very few patients with PS ≥2 were included in the trials (Level I++). • No other subgroup defined by sex, age or histology benefits more or less from adjuvant SACT (Level I++).	• Patients with good performance status (PS 0-1) who have completely resected NSCLC (stage II to IIIa) (A). • The risks and benefits of postoperative systemic anticancer therapy should be discussed with each patient (GPP).	13 of 13 votes.
NICE	NA	• Offer postoperative chemotherapy to patients with good performance status (WHO 0 or 1) and T1-3 N1-2 M0 NSCLC. • Ensure eligible patients have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy.	
ESMO	NA	• Adjuvant chemotherapy should be offered to patients with resected stage II or III NSCLC (I,A).	
CCCALCGWP	NA	• For stage III NSCLC, caution is advised in recommending adjuvant cisplatin-based chemotherapy to good performance status patients who are 70 years of age or older and/or who have clinically significant cardio-respiratory or renal comorbidities (PP).	
2. What Regimen Should be Used?			
NCCN	NA	• Cisplatin combined with vinorelbine, etoposide, vinblastine, gemcitabine, docetaxel or pemetrexed (Category IIA). For patients with comorbidities or unable to tolerate cisplatin, carboplatin combined with paclitaxel (Category IIA).	
SIGN	• Different SACT regimens were used in the trials but most contained platinum. • No particular SACT regimen appears better than any other (Level II+).	• Platinum-based postoperative systemic anticancer therapy (A).	
NICE	NA	• Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy.	
ESMO	NA	• A 2-drug combination with cisplatin is preferable (I, A).	
CCCALCGWP	• In patients with operable stage II NSCLC, the evidence supports the use of 3 to 4 cycles of adjuvant cisplatin-based chemotherapy (I, II). • In patients with completely resected stage III NSCLC, adjuvant cisplatin-based chemotherapy increases survival compared with observation. Further research is required to identify which stage III patients have the most favourable risk-benefit profile for adjuvant chemotherapy (I).	• Patients with completely resected stage II NSCLC should be offered 3 to 4 cycles of adjuvant cisplatin based chemotherapy (A). • Patients who have a good performance status (WHO 1, 2) and completely resected stage III non-small cell lung cancer should be offered adjuvant cisplatin-based chemotherapy (A).	13 of 13 votes.

CCCALCGWP: Cancer Care Council Australia Lung Cancer Guidelines Working Party; ESMO: European Society for Medical Oncology; GPP: Good practice point; LN: Lymph node; NA: Not applicable; NCCN: National Cancer Comprehensive Network; NICE: National Institute for Health and Care Excellence; NSCLC: Non-small cell lung cancer; PORT: Postoperative radiotherapy; PS: Performance status; PP: Practice point; RCT: Randomised controlled trial; SACT: Systemic anticancer therapy; SIGN: Scottish Intercollegiate Guidelines Network; WHO: World Health Organisation

Supplementary Table 1. International Guidelines for Adjuvant Systemic Therapy of NSCLC (Con't)

Guideline Title	Evidence Summary (Level of Evidence)	Recommendation (Grade of Recommendation)	Member Votes
3. What is the Role of Adjuvant Chemotherapy in Stage I?			
NCCN	NA	• Observation is recommended for patients with T1ab, N0 tumours with negative surgical margins (Category 2A). • Patients with T2ab, N0 tumours with negative surgical margins are usually observed (Category 2A). • Chemotherapy for high risk features (include poorly differentiated tumours, vascular invasion, wedge resection, >4 cm, visceral pleural involvement, and incomplete LN sampling) (Category 2A).	13 of 13 votes.
SIGN	• The benefit of adjuvant SACT in patients with stage I disease is less certain. There appears to be no benefit in patients with stage Ia disease but there may be benefit in those with tumours >4 cm. Further trials are required in this group (Level 1+).	NA	
NICE	NA	• Consider postoperative chemotherapy in patients with good performance status (WHO 0 or 1) and T2-3 N0 M0 NSCLC with tumours greater than 4 cm in diameter.	
ESMO	NA	• Consider in patients with resected stage IB disease and a primary tumour >4 cm [II, B].	
CCCALCGWP	• In studies of adjuvant chemotherapy for stage I NSCLC, stage IA patients were either excluded or represent a small percentage of the total number of included patients. There is no evidence of a clear survival benefit for postoperative adjuvant chemotherapy for stage IA disease (II). • Platinum-based adjuvant chemotherapy for patients with stage IB NSCLC has not been consistently demonstrated to provide a survival benefit. Meta-analyses reveal a small absolute survival benefit, in the order of 2% to 3%. A subgroup analysis from one randomised trial suggested that there may be a benefit for tumours greater than 4 cm in maximal diameter (II).	• Postoperative adjuvant chemotherapy is not recommended for stage IA NSCLC (B). • Platinum-based adjuvant chemotherapy is not recommended for all patients with stage IB NSCLC (B). • Based on the 7th edition of TNM classification, tumour size of >5 cm would fall under stage IIA. These patients may be considered for adjuvant chemotherapy (PP).	
4. What Treatment Options are Available for Positive Margins?			
NCCN	NA	• Stage IA with R1 or R2: 1) re-resection or 2) RT. • T2abN0: 1) re-resection +/- chemotherapy, 2) RT +/- chemotherapy (Category2B). • Stage II positive margins with R1: 1) re-resection and chemotherapy, 2) chemo-radiation (either sequential or concurrent), with R2: 1) re-resection and chemotherapy or 2) concurrent chemo-radiation (Category 2A). • T1-3, N2 or T3N1 with R1: Chemo-radiation (either sequential or concurrent), with R2: concurrent chemo-radiation (Category 2A).	13 of 13 votes.
SIGN	• Postoperative radiotherapy (PORT) has been shown to reduce local recurrence in the radiotherapy arm. • The PORT meta-analysis suggests an adverse effect of radiotherapy on survival with a hazard ratio of 1.21 (95% CI, 1.08 to 1.34), favouring surgery; 2-year survival with adjuvant RT was 48% versus 50% in the surgery alone group. A subsequent RCT examined the effect of PORT in pathological stage I patients and demonstrated a significant survival advantage in favour of RT (5-year survival 67% vs 58%, $P = 0.048$). It is not clear whether the adverse effect of PORT on survival applies to PORT using modern planning techniques and treatment technology (Level I++).	• Patients with NSCLC who have had complete tumour resection should not receive postoperative radiotherapy, except as part of a randomised trial (Grade A).	

CCCALCGWP: Cancer Care Council Australia Lung Cancer Guidelines Working Party; ESMO: European Society for Medical Oncology; GPP: Good practice point; LN: Lymph node; NA: Not applicable; NCCN: National Cancer Comprehensive Network; NICE: National Institute for Health and Care Excellence; NSCLC: Non-small cell lung cancer; PORT: Postoperative radiotherapy; PS: Performance status; PP: Practice point; RCT: Randomised controlled trial; SACT: Systemic anticancer therapy; SIGN: Scottish Intercollegiate Guidelines Network; WHO: World Health Organisation

Supplementary Table 1. International Guidelines for Adjuvant Systemic Therapy of NSCLC (Con't)

Guideline Title	Evidence Summary (Level of Evidence)	Recommendation (Grade of Recommendation)	Member Votes
NICE	NA	NA	
ESMO	NA	• Postoperative radiotherapy in completely resected early-stage NSCLC is not recommended [I, A].	
CCCALCGWP	• A meta-analysis demonstrates no clear evidence of an adverse or beneficial effect of PORT on survival in patients with pN2 disease. The applicability of this finding to current day practice is questionable (Level I). • Data from 3 more recent but non-randomised studies suggest a survival benefit for PORT in pN2 disease (Level II, III-C).	• Postoperative radiation therapy in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. The use of PORT could be considered in selected patients with pN2 disease (C).	
5. What are the Treatment Options for pN2 Disease with Negative Margins?			
NCCN	NA	• Sequential chemotherapy and radiotherapy (Category 1).	
SIGN	• Postoperative radiotherapy (PORT) has been shown to reduce local recurrence in the radiotherapy arm. • The PORT meta-analysis suggests an adverse effect of radiotherapy on survival with a hazard ratio of 1.21 (95% CI, 1.08 to 1.34), favouring surgery; 2- year survival with adjuvant RT was 48% versus 50% in the surgery-alone group. A subsequent RCT examined the effect of PORT in pathological stage I patients and demonstrated a significant survival advantage in favour of RT (5-year survival 67% vs 58%, $P = 0.048$). It is not clear whether the adverse effect of PORT on survival applies to PORT using modern planning techniques and treatment technology (Level I++).	• Patients with NSCLC who have had complete tumour resection should not receive postoperative radiotherapy, except as part of a randomised trial (Grade A).	
NICE	NA	NA	
ESMO	NA	• Postoperative radiotherapy in completely resected early-stage NSCLC is not recommended [I, A].	
CCCALCGWP	• A meta-analysis demonstrates no clear evidence of an adverse or beneficial effect of PORT on survival in patients with pN2 disease. The applicability of this finding to current day practice is questionable (Level I). • Data from 3 more recent but non-randomised studies suggest a survival benefit for PORT in pN2 disease (Level II, III-C).	• Postoperative radiation therapy in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. The use of PORT could be considered in selected patients with pN2 disease (C).	13 of 13 votes.

CCCALCGWP: Cancer Care Council Australia Lung Cancer Guidelines Working Party; ESMO: European Society for Medical Oncology; GPP: Good practice point; LN: Lymph node; NA: Not applicable; NCCN: National Cancer Comprehensive Network; NICE: National Institute for Health and Care Excellence; NSCLC: Non-small cell lung cancer; PORT: Postoperative radiotherapy; PS: Performance status; PP: Practice point; RCT: Randomised controlled trial; SACT: Systemic anticancer therapy; SIGN: Scottish Intercollegiate Guidelines Network; WHO: World Health Organisation