

Title: Australia and New Zealand Faculty of Radiation Oncology Lung Interest Cooperative (FROLIC): 2015 consensus guidelines for the use of advanced technologies in the radiation therapy treatment of locally advanced non-small cell lung cancer

Running Head: FROLIC guidelines for lung cancer radiation therapy

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8 Australia and New Zealand Faculty of Radiation Oncology Lung Interest Cooperative (FROLIC): 2015
9 consensus guidelines for the use of advanced technologies in the radiation therapy treatment of
10 locally advanced non-small cell lung cancer

11 **Abstract**

12 There have been significant advances in technologies in recent years that apply to lung cancer
13 radiation therapy. Currently many radiation oncology departments in Australia and New Zealand are
14 implementing these techniques. The Royal Australian and New Zealand College of Radiologists
15 (RANZCR) Faculty of Radiation Oncology Lung Interest Cooperative (FROLIC) identified appreciable
16 variation in methods of simulation, planning and image verification techniques across departments.
17 Therefore the FROLIC executive committee identified the need to develop guidelines for the use of
18 advanced RT technologies in the treatment of LA-NSCLC. In August 2015, the inaugural FROLIC
19 workshop was conducted with the aims of sharing knowledge and experience regarding the optimal
20 use of the advanced techniques in LA-NSCLC with a view to developing consensus guidelines. These
21 guidelines may assist in departments accelerating their implementation and reduce variations in
22 practice. They will help to ensure high quality utilisation of these technologies and best practice
23 radiation therapy for patients with lung cancer.

24 **Introduction**

25 Definitive radiation therapy (RT), generally combined with chemotherapy, is the standard of care for
26 patients with unresectable locally advanced (stage II-III) non-small cell lung cancer (LA-NSCLC). With
27 the advent of newer technologies, RT for LA-NSCLC has changed significantly in recent years. Some
28 of these advances include PET/CT in treatment planning, 4DCT simulation, 3D/4D cone beam CT
29 image guidance and IMRT/VMAT. Many of these techniques were used in the most recent RTOG

1 randomised controlled trial of chemo-RT for Stage III NSCLC, which reported a median overall
2 survival of 28.7 months in patients randomised to the standard therapy arm, much higher than
3 previously documented (1). Currently, many radiation oncology departments in Australia and New
4 Zealand are in the process of implementing these techniques.

5 In 2015, the Royal Australian and New Zealand College of Radiologists (RANZCR) Faculty of Radiation
6 Oncology Lung Interest Cooperative (FROLIC) conducted a patterns-of-practice survey amongst
7 radiation oncologists to investigate the range of radiation therapy management of lung cancer in
8 Australia and New Zealand and to define the gaps in optimal patient care. Results of this survey are
9 published in this issue of the journal. There was appreciable variation in methods of simulation,
10 planning and image verification techniques noted from the survey. With this in mind, the FROLIC
11 executive committee identified the need to develop guidelines for the use of advanced RT
12 technologies in the treatment of LA-NSCLC. In August 2015, the inaugural FROLIC workshop was
13 conducted with the aims of sharing knowledge and experience regarding the optimal use of the
14 advanced techniques in LA-NSCLC with a view to developing consensus guidelines. We felt there is a
15 need to develop local guidelines relevant to the Australian and New Zealand context for the
16 implementation of new technologies. These guidelines may assist in departments accelerating their
17 implementation and reduce variations in practice. They will help to ensure high quality utilisation of
18 these technologies and best practice radiation therapy for patients with lung cancer.

19 **Methods**

20 Draft guidelines were formed prior to the FROLIC workshop by members of the executive
21 committee. These were based on expert opinion and review of the pertinent literature, including
22 published guidelines from other geographical regions (2-5). Literature review did not follow any
23 stringently defined methodology. The FROLIC workshop convenors selected local expert speakers
24 from radiation oncology, medical physics and radiation therapy to present data covering topics from
25 simulation, target delineation, treatment planning, verification and delivery relevant to LA-NSCLC. In
26 particular, areas where there were gaps or controversies in the literature were incorporated into the
27 agenda to ensure discussion at the FROLIC workshop. During the workshop, proposed guidelines
28 were discussed and debated by all expert speakers and the workshop participants. Further literature
29 was provided by members of the FROLIC executive and workshop speakers and a consensus was
30 reached and documented to produce these guidelines.

31

32 **Results**

1 The FROLIC workshop was convened on August 7, 2015 in Sydney, New South Wales. The workshop
2 was attended by 95 registrants comprising radiation oncologists and radiation oncology trainees,
3 medical physicists and radiation therapists. It was the intention of the FROLIC executive and authors
4 to provide a consensus guideline based on review of the literature and open discussion among
5 experts and workshop participants - thus a grading system for these guidelines has not been
6 adopted. The consensus guidelines developed from the workshop and by the FROLIC executive are
7 discussed below. Key recommendations are highlighted in Table 1.

8 **Patient selection for Curative RT for LA-NSCLC**

9 All patients with LA-NSCLC should have their management discussed in a multi-disciplinary team
10 meeting. This enhances adherence to evidence based practice and may improve patient quality of
11 life and even survival (6, 7).

12 It was acknowledged that patients in lung cancer RT trials are highly selected and not necessarily
13 representative of patients seen in the clinic who often have an ECOG performance status of more
14 than one, multiple co-morbidities and compromised respiratory function. Patients who are ECOG 0-1
15 should be considered for curative RT. ECOG 2 patients, especially due to co-morbidities other than
16 lung cancer, should not necessarily be excluded from curative RT. Whilst most co-morbidity indices
17 such as the 'Charlson comorbidity index' have not been validated in lung cancer, it is recommended
18 the risk of morbidity and mortality from lung cancer be weighed against the risk from co-morbid
19 conditions when deciding whether to treat patients curatively (8). Input from clinicians treating
20 these comorbid conditions may be helpful in making the decision. Patients with ECOG more than 2
21 are usually not suitable for curative RT.

22 Interstitial lung disease is a specific comorbidity where radiation therapy must be approached with
23 caution, even in patients with normal lung function. Both clinical and radiological interstitial lung
24 disease is associated with significant risks of radiation pneumonitis which may be fatal, and the
25 decision to proceed with RT requires careful discussion with the patient (9).

26 With regards to respiratory function required for curative thoracic RT, no safe lower limits have been
27 defined (10). The consensus reached was that the functional impact on the patient of baseline
28 pulmonary physiology was a better determinant of the consequence of radiation pneumonitis or
29 radiation pulmonary fibrosis. Although tumour volume is a determinant of outcome after RT within
30 the first 18 months after RT, there is no upper tumour volume limit that should exclude patients
31 from curative RT provided that dose constraints for organs-at-risk can be achieved (11).

32 **RT Simulation**

1 Patients who are to undergo curative thoracic RT should be immobilized supine in a stable and
2 reproducible position. In most cases, arms above the head will allow a greater freedom of beam
3 arrangement. Intravenous contrast should be considered and protocols developed for incorporation
4 with the type of simulation scan performed. For 4DCT, IV contrast can be used based on a manual
5 timing calculation. For all curative cases, simulation should take into account tumour motion.

6 For free breathing patients, 4DCT simulation is recommended. The exception to this is Pancoast
7 tumours, where tumour motion is negligible. If patients need to be given coaching during simulation,
8 this needs to be consistent between both simulation and treatment so the breathing amplitude is
9 reproducible. Various methods of acquiring the 4D data and image processing techniques were
10 discussed and none recommended over others. Departments are advised to refer to vendor's
11 manuals for their individual 4D CT simulators to ensure optimal scan acquisition. Careful attention
12 should be paid to the reconstructed 4DCTs to detect artefacts and ensure the scan is an accurate
13 representation of motion. This is particularly a concern when tumours abut other soft tissues such as
14 the diaphragm or if respiration is irregular or there are large pauses in breathing. Discussion in real-
15 time between the multi-disciplinary team (Radiation Oncologist/Radiation Therapist/Medical
16 Physicist) should direct whether images can be used for planning or whether re-acquisition is
17 necessary. It was noted also that some vendors might have limitations on cranial-caudal span of
18 4DCTs. This may be due to time limits related to tube heating or reconstruction computation
19 requirements. 4DCT scan time is a function of pitch (thus breathing period) and collimation
20 thickness. In practice this may limit the ability to acquire the full lung volume in the scan. In these
21 cases, it is recommended that the region of the tumour be contained in a 4DCT for motion
22 management and a separate free-breathing 3DCT covering the full span of the lungs is acquired for
23 treatment planning purposes.

24 As accurate target volume definition is crucial to accurate delivery, rigorous quality assurance
25 processes should be applied to the simulation process.

26 If 4DCT is not available, other methods should be employed such as breath hold 3DCTs acquired at
27 inhale and exhale for motion management purposes. The use of 3D PET alone for motion estimation
28 has been shown to underestimate tumour motion and PTV margin reduction below 1.5cm in this
29 situation is discouraged (12). Unless the respiratory motion is otherwise managed, the use of a single
30 fast 3D CT simulation scan is usually inappropriate for curative RT. The entire lung volume should be
31 scanned at 2-3mm slices for the purposes of calculating dose-volume histograms.

32 **Target Volume Delineation**

1 It is recommended departments establish their own contouring protocols for lung cancer or use
2 external protocols such as eviQ (13). These should include details of standardised CT and PET
3 window levels for contouring the primary and nodal disease. It is advisable to consult with diagnostic
4 radiologists or nuclear medicine physicians for this. EORTC suggest using $W = 1600$ and $L = -600$ for
5 lung windows and $W = 400$ and $L = 20$ for mediastinal windows (14). Manual rather than automatic
6 target volume delineation is recommended until further validated by research. Peer review of
7 contouring is recommended to minimise inter-observer variability and ensure adherence to
8 departmental guidelines. This has been shown to be of benefit in the case of lung stereotactic
9 ablative RT and the authors' feel this can be reasonably applied to conventionally fractionated RT for
10 locally advanced lung cancer too (15).

11 The use of PET/CT is strongly recommended to aid target delineation and limit contouring variability
12 and the reader is referred to a recent IAEA consensus report (16). It is advised the time between
13 PET/CT and RT be no more than 4 weeks as disease progression and contouring inaccuracies can
14 occur when the PET/CT used for target delineation is not contemporaneous (17).

15 The co-registration of the PET and CT scans from PET/CT should be initially validated when used for
16 patient delineation in radiotherapy, especially if the scanner is not under quality control processes of
17 the radiotherapy department (18).

18 Where a PET/CT has not been acquired in the RT planning position, such as a diagnostic PET/CT, it
19 should be used only as a guide to locate the tissues containing tumour. The accurate definition of
20 the tumour/soft tissue interface must be evaluated on the RT simulation CT, ideally a 4DCT.

21 When 4D CT simulation is used, the PET/CT (ideally in the RT position) remains useful at
22 discriminating tumour from non-malignant consolidation such as collapse, as well as identifying
23 involved lymph nodes.

24 After co-registering the simulation CT and PET/CT as per one of the above situations, the gross
25 tumour volume should be delineated to include the primary tumour and involved nodes as defined
26 by FDG avidity on the PET or positive histology. Nodes with short-axis diameter of $\geq 1\text{cm}$ on CT or
27 that are centrally necrotic are usually pathologic and should be included. Additionally, clinician
28 discretion may be used to include PET negative nodes adjacent to involved regions or nodes that
29 have progressed over serial imaging. However, routine elective nodal RT is not recommended.

30 Once the simulation scan has been processed, target volume delineation begins with the
31 determination of the internal target volume (ITV). It was recommended the ITV concept be followed.
32 The ITV is the envelope of moving tissue containing gross tumour and microscopic disease. The

1 creation of the maximum intensity projection (MIP) image should theoretically show the combined
2 contour of the tumour in all phases of the breathing cycle. The GTV contoured throughout the
3 breathing cycle can be called the GTV MIP or reGTV (respiratory expanded GTV). It may be
4 contoured on the MIP, but should be checked against all phases of motion. It should also be checked
5 on all 3 reconstructed planes. Particular care should be taken when contouring nodal disease or at
6 the interface of tumour with solid tissue, as distinction between tumour and surrounding normal
7 tissue can be limited when using the MIP technique. To form the final ITV it is recommended 5 –
8 8mm be added to the GTV MIP or reGTV to account for microscopic extension (3, 19). This may then
9 be trimmed to anatomical barriers. Alternatively, the GTV may be contoured on the maximum inhale
10 and exhale phases of the 4DCT, both for the primary tumour and involved nodes, and 5 – 8mm
11 added for microscopic extension. Then all are combined to form the ITV. Again, the GTVs should be
12 checked on all phases of the 4DCT in case there is motion in the left-right or anterior-posterior
13 directions not seen on the two extreme phases of respiration.

14 Organ-at-risk contouring and radiation treatment planning is performed on the average intensity
15 projection (AIP) reconstructed dataset of a 4DCT. This provides a suitable approximation for dose
16 calculation and a reference image set for verification prior to treatment. Use of a planning organ-at-
17 risk (PRV) margin for critical serial organs should be considered especially for modulated high dose
18 gradient techniques.

19 The planning target volume (PTV) margin is determined by the immobilisation method, image
20 guidance method and other factors and it is recommended departments determine the required
21 margins individually. If tumour motion has not already been accounted for by using one of the above
22 methods, it must be when applying a margin for PTV.

23 **Dose Prescription**

24 The consensus from the workshop was to prescribe 60 – 66Gy in 30-33 fractions, once daily, when
25 chemotherapy is administered concurrently. This is in agreement with consensus statements from
26 other groups (20-22). When RT is used alone, the workshop acknowledged the wide range of
27 acceptable doses including 50 – 55Gy in 20 fractions, once daily; 60 – 66Gy in 30 – 33 fractions, once
28 daily; and continuous accelerated hyper-fractionated regimens. RT dose escalation or intensification
29 beyond these recommendations can only be recommended as part of a clinical trial.

30 It was noted that recent randomised trials did not mandate compliance with protocol normal tissue
31 dose constraints (1). Regarding lung constraints, there is no absolute safe threshold dose below
32 which there is no risk of radiation pneumonitis (RP). As well as lung dose volumetrics, other factors

1 such as advanced age and taxane chemotherapy can contribute to the risk of RP (23). There was
2 general agreement in the workshop that suggested OAR constraints from eviQ (Table 2) are
3 reasonable (13). It was suggested the GTV be subtracted from the combined lung volume when
4 assessing the lungs DVHs to be conservative. Individual departments are advised to develop their
5 own planning aims and constraints document.

6 **Radiation therapy planning**

7 Due to the poor long-term survival of patients with LA-NSCLC and the potential toxicity of lung RT,
8 groups continue to explore modern treatment planning techniques, such as intensity-modulated RT
9 (IMRT) or volumetric-modulated arc therapy (VMAT), to improve the therapeutic ratio. The
10 consensus from the workshop was that 3D conformal and modulated RT techniques both have their
11 place in the treatment of LA-NSCLC. The pros and cons of each were discussed.

12 IMRT and VMAT give highly conformal dose distributions around planning targets and steep dose
13 gradients. Whilst there are no published prospective randomised trials directly comparing 3D
14 conformal and IMRT techniques, there are retrospective studies and secondary analyses showing
15 more normal tissue sparing and potentially reduced rates of RP (24-26). Conversely, there is a SEER
16 data population-based analysis showing similar survival and toxicity of IMRT and 3D conformal
17 techniques (27). The debate between the two techniques continues in the literature (28, 29).

18 IMRT/VMAT probably has most clinical benefit when the target volume is in close proximity to a
19 critical organ-at-risk (eg spinal cord, brachial plexus), or when the target volume is very large or
20 comprises multiple non-contiguous targets where 3D conformal techniques would deliver
21 prohibitive doses of radiation to the normal lungs. To embark on a modulated technique, a
22 department must first consider the pre-requisites. IMRT/VMAT efficacy relies critically on accurate
23 target and normal tissue delineation, as there is a higher risk of geographic miss. Due to the steep
24 dose gradients, target motion must be accurately accounted for. A strict image guidance protocol
25 must also be adopted and will be discussed later. It was also acknowledged that despite the
26 theoretical risk of the interplay effect in the treatment of lung malignancies, when using a
27 fractionated course of radiotherapy, the literature does not demonstrate any significant impact on
28 dosimetry or outcomes in a fractionated course of RT (30). Nonetheless, steps can be taken in the
29 planning process to minimize any potential interplay effect issues. These include the use of minimum
30 segments size and segment monitor units. There was also concern expressed by some about the
31 integral dose delivered with modulated techniques and the low dose bath of radiation potentially
32 received by a large volume of lung tissue. Planners need be mindful of the number and arrangement

1 of beams when balancing the decision between target coverage conformity by high doses and
2 minimising the low dose bath. Departments are advised to aim for the lowest V5 and V10 possible
3 (see Table 2). As above, departments are strongly advised to develop their own planning protocol
4 including planning aims for target coverage and organ-at-risk constraints. Whilst VMAT often has
5 shorter treatment times, beyond this no recommendation can be made as to the optimal modulated
6 technique.

7 It was acknowledged a great proportion of patients are treated satisfactorily with 3D conformal
8 techniques. The benefit of reduced low dose bath may come at the expense of less target
9 conformity. 3D conformal RT may not be as sensitive to target motion although it must still be
10 accounted for in target delineation. Acceptable lung doses may be achieved dependant on target
11 volume and location. There was general agreement that higher-level evidence is needed to compare
12 the efficacy and safety of IMRT and conformal techniques in lung cancer RT.

13 “Type B” convolution/superposition beam modelling or Monte Carlo algorithms that account for
14 effects of heterogeneity on primary and scattered radiation should be used for dose calculations in
15 lung RT planning (31).

16 The potential benefits of inverse planned modulated treatments may be further realised in the
17 future as functional lung avoidance strategies are employed. Additionally, as biomarkers develop (eg
18 novel PET tracers), we may be able to specifically target regions of hypoxia or
19 repopulation/proliferation within target volumes and this may allow biologically guided dose
20 intensification.

21 **Treatment verification**

22 Improvements in outcomes rely on the aforementioned technological advances delivering the dose
23 to the desired location. A robust image guidance strategy is needed to ensure this. In general, the
24 IGRT method and frequency should reflect the complexity of the overall treatment plan and the level
25 of treatment accuracy required. It should take into consideration factors such as treatment intent,
26 dose prescription, ability to accurately define the target, PTV margins used, location and nature of
27 adjacent critical OAR, motion management method, degree of uncertainty when a surrogate is used
28 for matching and accuracy of treatment delivery. For IMRT/VMAT in particular or where normal
29 tissues are close to/at tolerance, or when the PTV margin is tight, daily cone-beam CT (CBCT)
30 substantially reduces setup error and may permit margin reduction compared to less than daily CBCT
31 (32). Each department should consider their own processes and uncertainties when deciding on IGRT
32 frequency. Where the ITV concept is used, four-dimensional CBCT can be useful to verify that the

1 tumour motion remains within the ITV and to assess baseline shift. This should be considered for
2 highly mobile tumours or for IMRT/VMAT at least on day 1. Then it should be decided if ongoing 4D
3 imaging is necessary throughout treatment which depends on the magnitude of tumour breathing
4 motion present during treatment and how safely it is encompassed by the PTV. If RT planning is
5 undertaken on the average intensity projection of the 4DCT, this is the most appropriate dataset to
6 use as a reference to match a CBCT. Ideally if the target is readily identifiable on imaging, treatment
7 verification should be matched there. Other regions such as bone or carina may not be reliable
8 surrogates of tumour location due to tumour baseline shift and instability of the surrogate itself. If
9 these are used for matching, the degree of uncertainty should be taken into account when applying
10 PTV margins. In situations where the target has two components (the primary and nodes), it may be
11 necessary to compromise between tumour and carina matching. Frequent and volumetric IGRT also
12 allows monitoring of anatomic changes and tumour regression/progression during the course of RT.
13 This may allow for adaptive RT strategies although higher-level evidence is required before any
14 recommendation regarding implementation of adaptive RT can be made.

15 Whichever IGRT method is used, it is important to have a multi-disciplinary team responsible for
16 overseeing the IGRT program and ensuring staff education and regular quality assurance following
17 international guidelines (33).

18 **Special techniques: Gating and breath hold**

19 At the workshop both spirometric breath hold and respiratory gating techniques were discussed.
20 The potential advantages of these techniques are to limit tumour motion while the beam is on and
21 therefore reduce the normal tissue volume receiving radiation and potentially reduce toxicity. They
22 may also reduce the artefacts seen with mobile tumours and aid in more accurate target delineation.
23 These techniques may be part of future dose escalation strategies. Whilst it was acknowledged that
24 accounting for respiratory motion in some way is vital, the specific benefits of respiratory gating are
25 modest and implementing a program is associated with great cost and complexity and the risks of
26 poorly conducted gating may negate its potential benefit. They may only have significant benefits in
27 selected patients with large tumour amplitudes and small tumour sizes (34). Breath hold techniques
28 such as Active Breathing Control (ABC) show more promise at reducing the lung V20 and mean
29 doses, however these techniques may be associated with significant inter-fraction variation and
30 poor tolerability by some patients (35). Whilst further detailing these techniques is beyond the scope
31 of this paper, the expert presenters at the FROLIC workshop warned against their routine use for the
32 reasons aforementioned.

1 **Conclusions**

2 Whilst the clinical judgement of the treating team remains vital, the FROLIC executive has developed
3 these guidelines through literature review and an expert led workshop to inform patient selection
4 and RT management of patients with LA-NSCLC. With the development of technological advances in
5 lung cancer these guidelines can assist individual departments in the adoption of these techniques
6 and allow some consistency in practice between departments. As with other RANZCR special interest
7 group consensus documents, we hope these guidelines will be adopted widely by radiation
8 oncologists treating lung cancer in Australia and New Zealand. This will contribute to delivery of
9 quality radiation therapy for lung cancer and possibly allow for pooling of outcome data if patients
10 are more uniformly managed. With likely further technological advances and evolution in the future
11 these guidelines will be updated to retain currency. The FROLIC executive and members will
12 continue to look for areas to share knowledge and experience and pursue research to try to improve
13 quality practice and outcomes in lung cancer patients.

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17 **References**

18 1. Bradley JD, Paulus R, Komaki R et al. Standard-dose versus high-dose conformal
19 radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or
20 without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer
21 (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol.*
22 2015;16:187-199.

23 2. Ettinger DS, Wood DE, Akerley W et al. Non-Small Cell Lung Cancer, Version 6.2015.
24 *J Natl Compr Canc Netw.* 2015;13:515-524.

25 3. De Ruyscher D, Faivre-Finn C, Nestle U et al. European Organisation for Research
26 and Treatment of Cancer recommendations for planning and delivery of high-dose,
27 high-precision radiotherapy for lung cancer. *J Clin Oncol.* 2010;28:5301-5310.

28 4. Chang JY, Kestin LL, Barriger RB et al. ACR Appropriateness Criteria® nonsurgical
29 treatment for locally advanced non-small-cell lung cancer: good performance
30 status/definitive intent. *Oncology (Williston Park).* 2014;28:706-10, 712, 714 passim.

31 5. Lim E, Baldwin D, Beckles M et al. Guidelines on the radical management of patients
32 with lung cancer. *Thorax.* 2010;65 Suppl 3:iii1-27.

- 1 6. Mitchell PL, Thursfield VJ, Ball DL et al. Lung cancer in Victoria: are we making
2 progress. *Med J Aust.* 2013;199:674-679.
- 3 7. Boxer MM, Vinod SK, Shafiq J, Duggan KJ. Do multidisciplinary team meetings make
4 a difference in the management of lung cancer. *Cancer.* 2011;117:5112-5120.
- 5 8. Ball D, Thursfield V, Irving L et al. Evaluation of the Simplified Comorbidity Score
6 (Colinet) as a prognostic indicator for patients with lung cancer: a cancer registry study.
7 *Lung Cancer.* 2013;82:358-361.
- 8 9. Yamaguchi S, Ohguri T, Matsuki Y et al. Radiotherapy for thoracic tumors: association
9 between subclinical interstitial lung disease and fatal radiation pneumonitis. *Int J Clin*
10 *Oncol.* 2015;20:45-52.
- 11 10. Brunelli A, Charloux A, Bolliger CT et al. ERS/ESTS clinical guidelines on fitness for
12 radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J.*
13 2009;34:17-41.
- 14 11. Ball DL, Fisher RJ, Burmeister BH et al. The complex relationship between lung tumor
15 volume and survival in patients with non-small cell lung cancer treated by definitive
16 radiotherapy: a prospective, observational prognostic factor study of the Trans-Tasman
17 Radiation Oncology Group (TROG 99.05). *Radiother Oncol.* 2013;106:305-311.
- 18 12. Callahan J, Kron T, Siva S et al. Geographic miss of lung tumours due to respiratory
19 motion: a comparison of 3D vs 4D PET/CT defined target volumes. *Radiat Oncol.*
20 2014;9:291.
- 21 13. eviQ Cancer Treatments Online 2015. [<https://www.eviq.org.au>] Cancer Institute NSW,
22 [Updated November 2015, cited 2015 November 29]. Available from:
23 <https://www.eviq.org.au/>
- 24 14. Giraud P. Influence of CT images visualization parameters for target volume
25 delineation in lung cancer. *Proceedings of the 19th ESTRO Istanbul. Int J Radiat Oncol*
26 *Biol Phys.* 2000;56:S39.
- 27 15. Lo AC, Liu M, Chan E et al. The impact of peer review of volume delineation in
28 stereotactic body radiation therapy planning for primary lung cancer: a multicenter
29 quality assurance study. *J Thorac Oncol.* 2014;9:527-533.
- 30 16. Konert T, Vogel W, MacManus MP et al. PET/CT imaging for target volume
31 delineation in curative intent radiotherapy of non-small cell lung cancer: IAEA
32 consensus report 2014. *Radiother Oncol.* 2015;116:27-34.
- 33 17. Everitt S, Plumridge N, Herschtal A et al. The impact of time between staging PET/CT
34 and definitive chemo-radiation on target volumes and survival in patients with non-

- 1 small cell lung cancer. *Radiother Oncol.* 2013;106:288-291.
- 2 18. Xing L. Quality assurance of positron emission tomography/computed tomography for
3 radiation therapy. *Int J Radiat Oncol Biol Phys.* 2008;71:S38-42.
- 4 19. Giraud P, Antoine M, Larrouy A et al. Evaluation of microscopic tumor extension in
5 non-small-cell lung cancer for three-dimensional conformal radiotherapy planning. *Int J*
6 *Radiat Oncol Biol Phys.* 2000;48:1015-1024.
- 7 20. Eberhardt WE, De Ruyscher D, Weder W et al. 2nd ESMO Consensus Conference in
8 Lung Cancer: locally advanced stage III non-small-cell lung cancer. *Ann Oncol.*
9 2015;26:1573-1588.
- 10 21. Rodrigues G, Choy H, Bradley J et al. Definitive radiation therapy in locally advanced
11 non-small cell lung cancer: Executive summary of an American Society for Radiation
12 Oncology (ASTRO) evidence-based clinical practice guideline. *Pract Radiat Oncol.*
13 2015;5:141-148.
- 14 22. Lehman, M, Cancer Council Australia Lung Cancer Guidelines Working Party. What is
15 the recommended treatment approach for the definitive management of patients with
16 good performance status and inoperable stage III disease? [Version URL:
17 <http://wiki.cancer.org.au/australiawiki/index.php?oldid=118586>, cited 2015 Dec 10].
18 Available from
19 http://wiki.cancer.org.au/australia/Clinical_question:What_is_the_recommended_treatm
20 [ent_approach_for_the_definitive_management_of_patients_with_good_performance_st](http://wiki.cancer.org.au/australia/Clinical_question:What_is_the_recommended_treatm)
21 [atus_and_inoperable_stage_III_disease%3F](http://wiki.cancer.org.au/australia/Clinical_question:What_is_the_recommended_treatm). In: Cancer Council Australia Lung Cancer
22 Guidelines Working Party. Clinical practice guidelines for the treatment of lung cancer.
23 Sydney: Cancer Council Australia. Available from:
24 http://wiki.cancer.org.au/australia/Guidelines:Lung_cancer
- 25 23. Palma DA, Senan S, Tsujino K et al. Predicting radiation pneumonitis after
26 chemoradiation therapy for lung cancer: an international individual patient data meta-
27 analysis. *Int J Radiat Oncol Biol Phys.* 2013;85:444-450.
- 28 24. Chun SG, Hu C, Choy H et al. Comparison of 3-D conformal and intensity modulated
29 radiation therapy outcomes for locally advanced non-small cell lung cancer in NRG
30 Oncology/RTOG 0617. *Int J Radiat Oncol Biol Phys.* 2015;93:S1-2.
- 31 25. Liao ZX, Komaki RR, Thames HD et al. Influence of technologic advances on
32 outcomes in patients with unresectable, locally advanced non-small-cell lung cancer
33 receiving concomitant chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;76:775-
34 781.

- 1 26. Yom SS, Liao Z, Liu HH et al. Initial evaluation of treatment-related pneumonitis in
2 advanced-stage non-small-cell lung cancer patients treated with concurrent
3 chemotherapy and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys.*
4 2007;68:94-102.
- 5 27. Harris JP, Murphy JD, Hanlon AL, Le QT, Loo BW, Diehn M. A population-based
6 comparative effectiveness study of radiation therapy techniques in stage III non-small
7 cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2014;88:872-884.
- 8 28. Price A. Intensity-modulated radiotherapy, not 3 dimensional conformal, is the
9 preferred technique for treating locally advanced disease with high-dose radiotherapy:
10 the argument against. *Semin Radiat Oncol.* 2015;25:117-121.
- 11 29. Chang JY. Intensity-modulated radiotherapy, not 3 dimensional conformal, is the
12 preferred technique for treating locally advanced lung cancer. *Semin Radiat Oncol.*
13 2015;25:110-116.
- 14 30. Berbeco RI, Pope CJ, Jiang SB. Measurement of the interplay effect in lung IMRT
15 treatment using EDR2 films. *J Appl Clin Med Phys.* 2006;7:33-42.
- 16 31. Aarup LR, Nahum AE, Zacharitou C et al. The effect of different lung densities on the
17 accuracy of various radiotherapy dose calculation methods: implications for tumour
18 coverage. *Radiother Oncol.* 2009;91:405-414.
- 19 32. Higgins J, Bezjak A, Hope A et al. Effect of image-guidance frequency on geometric
20 accuracy and setup margins in radiotherapy for locally advanced lung cancer. *Int J*
21 *Radiat Oncol Biol Phys.* 2011;80:1330-1337.
- 22 33. Jaffray DA, Langen KM, Mageras G et al. Safety considerations for IGRT: Executive
23 summary. *Pract Radiat Oncol.* 2013;3:167-170.
- 24 34. Hau E, Rains M, Browne L, Muirhead R, Yeghiaian-Alvandi R. Minimal benefit of
25 respiratory-gated radiation therapy in the management of thoracic malignancy. *J Med*
26 *Imaging Radiat Oncol.* 2013;57:704-712.
- 27 35. Brock J, McNair HA, Panakis N, Symonds-Taylor R, Evans PM, Brada M. The use of
28 the Active Breathing Coordinator throughout radical non-small-cell lung cancer
29 (NSCLC) radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;81:369-375.
- 30

Table 1. Key recommendations for radiation therapy simulation and treatment for LA-NSCLC

Simulation and target delineation

Respiratory motion must be accounted for. 4DCT is the recommended method in most cases.

In the absence of 4DCT, a 3D PET/CT may underestimate tumour motion and therefore larger PTV margins are recommended.

PET fusion, ideally in the RT treatment position, is recommended to aid target delineation.

Departments should use contouring protocols and assess setup margins individually

Peer review of target volumes is recommended

Prescription and treatment technique

For chemo-radiation 60 – 66 Gy in 30 – 33 fractions, once daily

Whether employing 3D conformal or intensity-modulated techniques, departmental planning protocols should be developed to guide planning aims and specify normal tissue constraints

Treatment Verification

The method and frequency needs to reflect accuracy required for delivery.

Daily volumetric imaging is recommended when using modulated techniques with narrow PTV margins or when critical OARs are close to tolerance

Table 2. Suggested OAR dose constraints for conventionally fractionated RT for LA-NSCLC adapted from eviQ (10)

Organ	Constraint	Additional information
Lung	<p>Mean lung dose <20Gy</p> <p>V20Gy ≤ 35%</p> <p>V5Gy ≤ 60%</p>	<p>To keep risk of ≥ Grade 2 radiation pneumonitis ≤ 20%</p> <p>Volume both lungs and subtract GTV</p>
Spinal Cord	< 50Gy	To keep risk of myelopathy < 1%
Oesophagus	<p>V60 ≤ 17%</p> <p>Mean dose ≤ 28Gy</p>	<p>To keep risk of ≥ Grade 3 oesophagitis ≤ 10%</p> <p>Contour external wall from cricoid cartilage to gastro-oesophageal junction</p>
Heart	<p>V60 ≤ 33%</p> <p>Mean heart dose ≤ 20Gy</p> <p>V30 ≤ 46%</p>	There are no good DVH criteria for the heart in lung cancer context
Brachial plexus	≤ 60 Gy	To keep risk of brachial plexopathy < 1 – 2%. Up to 66Gy may be acceptable for Pancoast tumours