

# RADIO THERAPY IN LUNG CANCER

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## Abstract

Radiotherapy is an important modality in the treatment of lung cancer. In Australia, up to 76% of patients have an indication for radiotherapy at diagnosis. This includes curative radiotherapy for patients with inoperable stage I and II non-small cell lung cancer, and in combination with chemotherapy, for patients with stage III non-small cell lung cancer and limited stage small cell lung cancer. There are challenges in delivering curative radiotherapy to this group of patients, many of whom have smoking-related comorbidities. However, newer technologies allow selection of appropriate patients for treatment, improve identification of the tumour, individualise radiotherapy treatment according to patient specific motion and reduce normal tissue toxicities. Image guided radiotherapy is increasingly becoming the standard of care, whereby the tumour position is confirmed on cone-beam CT performed on the linear accelerator prior to treatment. Intensity modulated radiotherapy is improving dose conformity and avoidance of normal tissue structures. Stereotactic ablative radiotherapy is currently being evaluated as a treatment option for patients with inoperable stage I non-small cell lung cancer. Radiotherapy is also an important palliative treatment for lung cancer, with well-established indications for palliation of thoracic symptoms such as airway obstruction, chest pain, cough and haemoptysis. Bone and brain metastases are common in lung cancer and radiotherapy remains the prime modality for alleviating symptoms from these. Multidisciplinary discussion of lung cancer patients is essential to ensure that appropriate patients receive the evidence-based benefits of radiotherapy.

Radiotherapy is an important modality in the treatment of lung cancer. According to evidence-based guidelines, 76% of patients diagnosed with lung cancer in Australia have an indication for radiotherapy.<sup>1</sup> Thoracic radiotherapy is a potentially curative treatment option for stage I-III non-small cell lung cancer (NSCLC) and limited stage small cell lung cancer (SCLC). It is also important in palliating symptoms for those unfit for curative treatment or those who present with metastatic disease. Despite this, it remains underutilised for lung cancer patients in Australia.<sup>2,3</sup> This review will discuss important advances in radiotherapy for lung cancer in order to update referring clinicians.

## Patient selection

Patient selection for radiotherapy is ideally discussed at a multidisciplinary meeting where all specialists who treat lung cancer are present. Discussion at such a forum has been shown to increase the utilisation of both radiotherapy and chemotherapy.<sup>4</sup> There are many factors to consider when discussing the option of curative radiotherapy in patients. Generally, patients suitable for curative radiotherapy will have good performance status (ECOG 0-1), and locoregional disease extent (stage I-III). Despite the frequency of underlying chronic obstructive pulmonary disease in lung cancer patients, there are no cut-offs in terms of pulmonary function which determine suitability for curative radiotherapy.<sup>5</sup> Similarly, there is no upper limit to tumour size beyond which curative radiotherapy is not possible. In an observational study of 509 patients treated

with curative radiotherapy, tumour volume was not an independent predictor of survival beyond 18 months.<sup>6</sup> In many cases, the ability to deliver a curative dose of radiotherapy may not be known until a radiotherapy plan is generated and evaluated according to dose volume metrics known to be predictive of lung toxicity. Hence assessment by a radiation oncologist is essential to ensure that patients do not miss out on potentially curative radiotherapy.

## Radiotherapy treatment

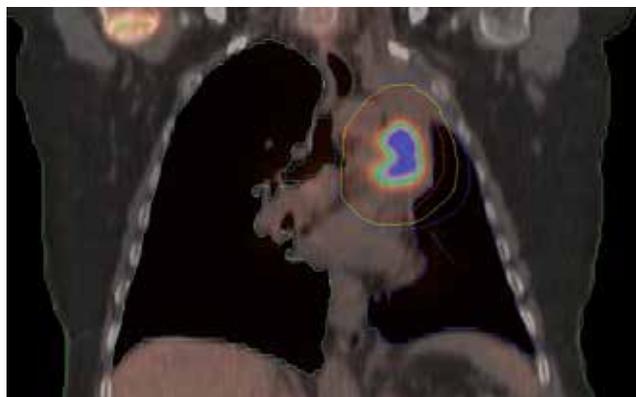
Once a recommendation for radiotherapy is made, there are several factors to consider in optimising the radiotherapy plan and treatment delivery. Accurate radiotherapy treatment of lung cancer is reliant on 18F-deoxyglucose position emission tomography (FDG-PET) scans both for patient selection for curative treatment and for tumour delineation. A contemporaneous PET scan, performed within the past month, is essential to ensure that the cancer has not progressed beyond a curable stage.<sup>7-9</sup> The registration of FDG-PET scans to the CT simulation scans for radiotherapy planning also improves delineation of lung cancer by reducing uncertainties, especially when there is adjacent atelectasis or consolidation (figure 1).<sup>10,11</sup>

Accounting for tumour motion with respiration is crucial to ensure that the whole tumour is encompassed by the radiotherapy fields. Commonly, this motion is measured at simulation on a 4D CT scan, where image acquisition is linked to phase of respiratory motion (figure 2). This allows individual tailoring of radiotherapy margins to a

patient's specific tumour motion and minimises the risk of a geographic miss, where the tumour moves outside the radiotherapy field during treatment. A retrospective analysis of outcomes of 496 lung cancer patients treated with conventional 3D simulation and conformal radiotherapy, or 4D simulation and intensity modulated radiotherapy (IMRT), showed improved survival and reduced lung toxicity with the latter approach, although it is difficult to assess the impact of 4D CT alone.<sup>12</sup> Newer linear accelerators come with either kilovoltage or megavoltage CT scanning capability, allowing the possibility of image guided radiotherapy (IGRT), where the position of the tumour is verified at the time of treatment.

While the imaging options discussed above aim to ensure that the tumour is encompassed during all phases of respiration, other technologies aim to treat the tumour at a specific phase in the respiratory cycle to minimise radiation of surrounding lung and hence toxicity. Respiratory motion can be reduced with abdominal compression devices or breathhold techniques.<sup>13</sup> However, patients with lung cancer who have underlying respiratory comorbidity are not always able to tolerate these. Respiratory gating is an alternative, whereby the radiotherapy beam is only turned on, in response to detection of an internal or external fiducial marker.<sup>13</sup>

**Figure 1:** Coronal CT with registered PET scan of patient with left upper lobe collapse from a centrally located FDG avid tumour. Tumour is encircled by lines of equal radiotherapy dose.



**Figure 2a:** Diagnostic coronal CT scan of a right lower lobe tumour.



Dose conformity to the tumour can be improved through IMRT. With this technique, a greater number of non-uniform radiotherapy beams are used to converge on the tumour. While this can limit dose to adjacent critical structures such as the spinal cord, it can sometimes also result in a greater volume of tissue receiving a lower dose, potentially increasing some toxicities. As stated above, a combination of IMRT and 4D CT planning has shown improved survival and reduced lung toxicity compared to conventional techniques.<sup>12</sup> This technique may increase patient suitability for curative radiotherapy by overcoming problems associated with tumour location adjacent to

**Figure 2b:** 4D CT scan of the same patient. The position of the tumour is imaged at all phases of the respiratory cycle, requiring a large increase in the volume to be targeted to avoid a 'geographic miss'.

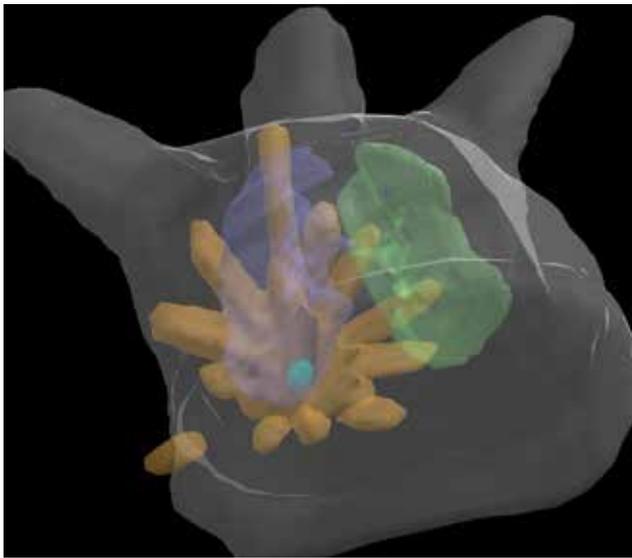


critical normal tissues.

## Stage I NSCLC

Although surgery is the preferred treatment for stage I and II NSCLC, many patients are not fit for an operation because of smoking-related comorbidities. These patients can be considered for treatment with curative radiotherapy. As with other forms of high dose radiotherapy, treatment is given as a number of fractions over a period of four to six weeks, since this minimises risk of damage to normal tissues. Recently, technical innovations have allowed treatment to be given more precisely with multiple or moving beams, minimising dose to normal tissues and so reducing the need for fractionation. The method of giving precise treatment, in one to five very large doses, is known as stereotactic ablative radiotherapy (SABR) (figure 3). In a phase 2 North American trial of SABR in stage I NSCLC, the estimated control rate at the primary site was 97% at three years.<sup>14</sup> However, the treatment appears to be safe only for peripheral smaller tumours, as fatalities have been reported with centrally located or larger cancers.<sup>15</sup> An Australasian randomised trial (TROG 09.02 'CHISEL') is currently evaluating SABR against conventional radiotherapy.<sup>16</sup>

**Figure 3:** Multibeam (yellow) SABR treatment plan for a right lower lobe tumour (light blue). Right lung is violet and left lung green.



### Stage III NSCLC

For patients who have had complete resection of NSCLC, and who are found to have involvement of mediastinal lymph nodes, the effect of postoperative radiotherapy on survival is uncertain, and it cannot be recommended outside the trial setting.<sup>17</sup> For more advanced disease, which is unresectable for technical reasons or because of mediastinal lymph node involvement, fractionated radiotherapy in combination with concomitant chemotherapy is the standard of care.<sup>18</sup> The addition of surgery in this setting does not increase survival.<sup>19</sup> One exception where surgery does appear important for local control is the superior sulcus or 'pancoast' tumour, located in the apex of the lung.<sup>20</sup> The optimal chemotherapy regimen is not clearly settled, but one small randomised study suggested that cisplatin/etoposide is superior to carboplatin/paclitaxel.<sup>21</sup> The addition of chemotherapy before or after concomitant chemoradiotherapy increases treatment toxicity but not survival.<sup>22,23</sup> There does not appear to be any advantage in increasing total radiotherapy dose from 60 to 74 Gy.<sup>24</sup> With five year survivals in excess of 20% being reported with chemoradiation,<sup>19</sup> and 18% at 10 years,<sup>25</sup> 'cure' is now a realistic goal for a significant minority of patients with inoperable NSCLC. For patients with T3-4 N0-1 superior sulcus NSCLC treated on a prospective phase II trial with a combination of radiotherapy, chemotherapy and surgical resection, survival was 44% at five years.<sup>20</sup>

It is now recognised that many cancers repopulate at an accelerated rate during treatment, and that this can be countered by shortening overall treatment time. A method for achieving this is continuous hyperfractionated accelerated radiotherapy (CHART), consisting of three treatments a day, seven days per week, so that treatment is completed in 12 days instead of 42. In a randomised trial in NSCLC, CHART improved local control and survival compared with conventional fractionation.<sup>26</sup> This benefit of shortening overall treatment time has since been confirmed by meta-analysis.<sup>27</sup> Accelerated radiotherapy has never

been compared head-to-head with chemoradiation, but the challenges of delivering treatment three times per day, seven days per week, has limited the widespread adoption of CHART in comparison with chemoradiation. Both the addition of concomitant chemotherapy and accelerated fractionation increase oesophagitis, but there is less evidence of an effect on other toxicities.

Prophylactic cranial irradiation (PCI) is now well established in the treatment of SCLC. Brain metastasis is also common in NSCLC. In one prematurely terminated randomised trial, the actuarial risk at one year was 18% in patients with stage III disease.<sup>28</sup> This was reduced to 7.7% by PCI ( $P=0.004$ ), but there was no associated survival advantage, so it cannot be recommended for NSCLC outside the trial setting.

### Small cell lung cancer

The combination of chemotherapy and thoracic radiotherapy for locoregional (limited) SCLC is well established.<sup>29</sup> As with NSCLC, a shorter radiotherapy treatment time appears to be more effective, but the evidence is not as strong.<sup>27</sup> For practical reasons, chemotherapy is often started before combined chemoradiation, and one review demonstrated that the shorter the time between the start of chemotherapy and the end of thoracic radiotherapy, the better the survival.<sup>30</sup> This suggests that the phenomenon of accelerated repopulation may also occur in response to chemotherapy. The optimal radiotherapy dose is not clearly established, and is under investigation in two separate collaborative group trials.<sup>31</sup> Prophylactic cranial irradiation is a standard of care for patients who have achieved a complete response to initial treatment;<sup>32</sup> 25 Gy in 10 fractions appears to be as effective as higher doses.<sup>33</sup> Prophylactic cranial irradiation also produces a survival benefit in patients with extensive SCLC, provided they have had a response to chemotherapy.<sup>34</sup>

### Palliative radiotherapy

Symptom palliation is a common indication for radiotherapy, both for intrathoracic disease (haemoptysis, cough, dyspnoea and superior vena caval obstruction) and for metastatic sites such as bone and brain. The palliative benefit of thoracic radiotherapy is the same regardless of the radiotherapy fractionation scheme used, however longer fractionation schemes result in increased toxicity, especially oesophagitis.<sup>35</sup> Patients with NSCLC who have good performance status and thoracic dominant disease may get a survival advantage, as well as longer duration of symptom relief if higher doses (30-36Gy) are used.<sup>36</sup> The fractionation of palliative thoracic radiotherapy should be tailored to the performance status of the patient and disease burden.

Patients with brain metastases are usually treated with external beam radiotherapy for palliation. There is no advantage in prolonging radiotherapy beyond a week. In patients with 1-3 brain metastases and stable extra-thoracic disease, the addition of a stereotactic boost reduces steroid use and improves patient performance status at six months.<sup>37</sup> In those with a single metastasis, there is a modest improvement in survival with stereotactic boost. Following surgical resection of brain metastases,

whole brain radiotherapy reduces intracranial progression and neurological deaths, but does not improve survival.<sup>38</sup> Many patients with brain metastases have poor performance status and corticosteroids alone may be just as effective as radiotherapy in terms of quality adjusted survival.<sup>39</sup> For bone metastases, single doses are as effective in relieving pain compared with fractionated courses, although there is more likelihood of causing a pain 'flare' with a single dose of 8Gy if there is an associated neuropathic component.<sup>40</sup>

### Treatment toxicity

With conventional radiotherapy, oesophagitis during treatment and radiation pneumonitis following treatment are the toxicities of concern. Whilst oesophagitis is usually only seen during radiotherapy and resolves shortly after completion, it can have a considerable impact on a patient's quality of life and lead to poor nutrition. Factors predictive of oesophagitis include mean radiation dose to the oesophagus, twice daily treatment, chemotherapy and neutropaenia.<sup>41</sup> Early dietitian and/or feeding intervention should be considered under these circumstances.

Radiation pneumonitis occurs post-treatment to up to six months later. Factors predictive of this include increasing age, radiation dose to the lung and the volume of lung irradiated. The use of combined dose-volume metrics (such as the volume of lung receiving 5 Gy (V5) or 20 Gy (V20), or the mean lung dose) to evaluate plan safety is now standard practice.<sup>42</sup> Although the meta-analysis comparing sequential with concomitant chemoradiation did not demonstrate an increased risk of pneumonitis with concomitant chemotherapy,<sup>18</sup> the type of chemotherapy, in particular the taxanes, may be important in increasing risk.<sup>43</sup> Palma et al performed a meta-analysis and found that patients older than 65 years who were treated with concurrent carboplatin and paclitaxel had up a 57% incidence of grade 2 or higher pneumonitis (requiring medical intervention), regardless of lung radiation dose.<sup>43</sup> The choice of chemotherapy should be carefully considered in older patients, many of whom have pre-existing renal or auditory comorbidities, precluding the standard cisplatin and etoposide combination chemotherapy.

The toxicity profile of radiotherapy in lung cancer is changing with implementation of newer techniques. Chest wall pain and rib fractures are potential toxicities following SABR, although this risk can be minimised using risk-adapted fractionation according to the location of the tumour.<sup>44</sup> Toxicity from SABR is more common in central tumours with grade 3-4 toxicities occurring in up to 9% of patients.<sup>45</sup>

### Conclusion

Radiotherapy is an important modality for the treatment of lung cancer. Technological advances have improved patient selection for treatment, identification of tumour and treatment accuracy, while reducing treatment toxicities. Future opportunities for 'personalising radiotherapy' include the identification of genetic determinants of radiation response, and countering causes of radioresistance in the tumour environment such as hypoxia. A number of trials currently underway will guide future radiotherapy. These include the Trans-Tasman Radiation Oncology Group (TROG) trials, CHISEL (randomising patients

with inoperable stage I-IIA NSCLC to conventional radiotherapy or SABR), PLUNG (randomising patients with stage III NSCLC unsuitable for curative radiotherapy to palliative radiotherapy alone, or with chemotherapy). In addition to the international trials mentioned above, ongoing randomised trials are also investigating the role of postoperative radiotherapy in completely resected NSCLC using modern techniques (LungART), and the combination of chemoradiation with cetuximab, a monoclonal antibody against the epidermal growth factor receptor, which may be implicated in repopulation (RTOG 0617).

For now, it is important that multidisciplinary discussion of patients takes place to ensure that appropriate lung cancer patients receive the existing, evidence-based benefits of radiotherapy.

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