Avoiding Toxicity With Lung Radiation Therapy: An IASLC Perspective

Nicholas W. Bucknell, M.B.B.S. (Hons), FRANZCR, a,b,c,* José Belderbos, MD, PhD, d David A. Palma, MD, PhD,e Puneeth Iyengar, MD, PhD,f Pamela Samson, MD, MPHS,g Kevin Chua, M.B.B.S., FRCR,h,i Daniel Gomez, MD, MBA,j Fiona McDonald, MD, M.B.B.S., MRCP , FRCR,k Alexander V. Louie, MD, PhD, MSc, FRCP, FRCPC, l Corinne Faivre-Finn, FRCR, MD, PhD, m,n Gerard G. Hanna, MB, PhD, MRCP, FRCR, FRANZCR, o Shankar Siva, M.B.B.S., FRANZCR, PhD, b,c on behalf of the International Association for the Study of Lung Cancer Advanced Radiation Technology Committee

*Corresponding author.

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Address for correspondence: Nicholas W. Bucknell, M.B.B.S. (Hons), FRANZCR, Department of Radiation Oncology, Sir Charles Gardiner Hospital, Perth, Australia. E-mail: nicholas.bucknell@health.wa.gov.au

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ABSTRACT

Toxicity concerns from thoracic radiation therapy in the treatment of lung cancers have changed substantially over the past few decades. Survival in the treatment of lung cancer has markedly improved and the introduction of advanced radiation and imaging techniques to treatment planning and delivery has made reducing toxicity possible.
Phase 3 dose-escalation trials have revealed that excess dose to critical organs within the thorax can negatively impact overall survival. We summarize the existing literature on the known toxicities of thoracic radiation therapy, summarize the technological advances that have made toxicity reduction possible, and provide an overview of emerging technologies and biomarkers that are being evaluated to assess future toxicity reductions.

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Introduction

Lung cancer survival is continuously improving owing to improvements in screening, staging, delivery of radiation therapy (RT), surgical management, and systemic therapy. Surveillance, Epidemiology, and End Results analysis has revealed that, over the past four decades, the five-year relative survival rate of all patients with lung cancer diagnosis has improved from 10.7% in 1972 to 19.8% in 2010. Screening trials revealed reduced mortality in patients with smoking history. In early-stage lung cancer for patients not suitable for surgery, technical advances have improved overall survival in patients treated with stereotactic ablative body RT (SABR) compared with conventional RT. In locally advanced lung cancer, survival continues to increase through the improvement in patient selection by advanced imaging, improvement in RT technology, and the introduction of consolidation immunotherapy for locally advanced NSCLC. In oligometastatic disease, metastasis-directed therapy is the subject of intense investigation in the current phase 3 trials after promising data was reported in phase 2 studies.

As survival in lung cancer improves in both the metastatic and nonmetastatic settings, prevention of acute and late toxicities from RT becomes more clinically important. Acute toxicities (including radiation esophagitis) have been found to be associated with worse overall survival. In stage III lung cancer, acute nonhematologic and hematologic toxicities may delay the commencement or not permit the use of consolidation immunotherapy. In this disease, the timely introduction of consolidation immunotherapy may improve outcomes and, therefore, it is imperative that toxicities are minimized. Advances in RT planning, imaging, treatment techniques, and optimal sequencing with systemic therapy are allowing continued reductions in the rates of acute and late radiation toxicities.

Organ Specific Considerations

Modern RT aims to deliver a maximum radiation dose to the tumor while minimizing the dose to organs at risk. A number of clinical trials, particularly those using hypofractionation or dose-escalation strategies, have reported that intrathoracic structures may be at risk of severe and life-limiting toxicities. The common acute and late radiation-related toxicities of thoracic RT are summarized in Figure 1.

Radiation-Induced Lung Toxicity

Radiation-induced lung injury is a spectrum of disease that occurs in three phases: an early latent phase, an acute exudative phase, and a late fibrotic phase. The latent phase occurs in the first month after exposure to radiation; during this phase patients are asymptomatic. Over weeks, this then progresses to an acute symptomatic phase, and then, over months to years, post-RT fibrosis occurs. Clinically, both the acute and late phases manifest with a loss of perfusion and ventilation.

Radiation pneumonitis is a potentially fatal complication of thoracic RT, found to be associated with the following: (1) an increasing volume of lung receiving a mean lung dose of 20 Gy; (2) increasing age; (3) lower lobe tumor location; and (4) type of concurrent systemic therapy. An individual patient data meta-analysis reported that symptomatic pneumonitis occurs in a third of patients treated with curative-intent lung RT, with fatal pneumonitis occurring in 2%. However, there have been incremental improvements in modern RT trials, with modern trials exhibiting a risk of grade 3 or higher toxicity to be less than 5%. Recent phase 3 clinical trials have found that dose escalation is limited by intrathoracic organs at risk including the heart and lung. This is because of the acute and subacute effects of radiation pneumonitis and the late impact of radiation-induced lung injury. Severe toxicity including a high rate of mortality has also been reported in patients with known interstitial lung disease. Ongoing trials seek to establish the optimal dose, fractionation, and appropriateness of providing active treatment in patients with interstitial lung disease.

Cardiac Toxicity

In the previously mentioned phase 3 trials, the failure of dose escalation to improve outcomes has been
correlated with increased heart toxicity with higher RT doses.\textsuperscript{19,20} Increased cardiac dose has also been found to increase the risk of noncancer deaths in conventional chemoRT and SABR treatments.\textsuperscript{24,25} However, the relationship between dose and cardiac toxicity has not been consistently established in the literature.\textsuperscript{26} There are no consistent dose-volume limits to the entire cardiac contour or substructures that are well established and used in routine clinical practice.\textsuperscript{27} Cardiac toxicity from radiation is believed to arise from damage to functional cardiac subunits including the pericardium, myocardium, valves, conduction system, and coronary arteries through fibrotic processes.\textsuperscript{28–30} Studies are currently ongoing to identify the cardiac substructures that should be spared during the RT planning process.

**Esophageal Toxicity**

Acute radiation esophagitis is a common and potentially debilitating condition. The discomfort associated with eating typically results in patients not receiving adequate nutrition and, in some patients, this can necessitate hospital admission and enteral feeding. In the treatment of stage 3 lung cancer treated with 60 Gy in 30 fractions and concurrent chemotherapy, one-third of patients experience grade 2 esophagitis, and 5% experienced grade 3 esophagitis.\textsuperscript{18,31} These recent studies using modern planning and treatment techniques have revealed an incremental reduction of grade 3 toxicity. There is no accepted dose constraint in the routine setting; however, the esophagus is typically considered as both a serial and parallel organ for treatment planning purposes. Late esophageal toxicity occurs in approximately 5% of patients treated with standard RT techniques.\textsuperscript{19} This can manifest as stenosis of the esophagus, esophageal perforation, or the formation of a tracheoesophageal fistula.\textsuperscript{32} Although acute esophageal toxicity is rarely fatal, late toxicities in particular perforation and fistula formation can lead to death.

**Chest Wall Toxicity**

Chest wall pain is a common toxicity after SABR for thoracic tumors but uncommon in conventionally fractionated treatments. In a pooled analysis evaluating chest wall toxicity, the overall rate of long-term chest wall pain post-SABR was 11.0%, with lower rates of grade 3 or higher toxicity at 1.2%.\textsuperscript{33} Factors associated with the development of chest wall pain included tumor to chest wall distance, the patient’s body mass index, maximum dose of 0.5 to 5 cm\(^2\), and the volume of the chest wall or ribs receiving greater than 30 Gy.\textsuperscript{33,34}

**Spinal Cord and Brachial Plexus Toxicity**

Both the spinal cord and brachial plexus are critical structures at risk with strict tolerance doses that must
not be exceeded. Excess dose to these organs at risk results in considerable morbidities of brachial plexopathy, radiation myelopathy, or even spinal cord injury. In the setting of the first course of radical treatment for lung cancer rates using modern image-guided SABR and conventionally fractionated treatment techniques, the rates of the severe spinal cord or brachial plexus toxicities are low, and less than 1% in most cases requiring treatment.6,10 These structures may become critical and dose-limiting if reirradiation is being considered. Reirradiation to the spinal cord or brachial plexus must be carefully considered and treatment plans may require adaptation to achieve a safe RT plan.

Airway Toxicity

Damage to the proximal bronchial tree remains one of the most frequent causes of grade 4 and 5 toxicity in central SABR and other hypofractionated treatments. Several studies have revealed that dose escalation to central airway structures—in particular, the main bronchi and trachea—involves a high risk of bronchopulmonary hemorrhage, strictures, fistulas, or other bronchopulmonary complications such as necrosis and stricture. Early phase trials have revealed a risk of grade 5 toxicity to the proximal bronchial tree in the order of 5% to 10%.35–38 The Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Tumors Treated With Stereotactic Body Radiotherapy (Nordic HILUS trial) evaluated the risk of toxicity in central lung tumors after 8 by 7 Gy SBRT (biologically effective dose 90, α/β = 10 Gy) and reported a 34% grade 3 or higher toxicity.38 The definition used for ultracentral tumors was gross tumors approximately 1 cm from the proximal bronchial tree.38 This trial reported more grade 3 to 5 toxicity for tumors close to the main bronchus and with a tumor location within 1 cm of the main bronchi.38 Ongoing trials such as the SBRT for Ultra-central NSCLC— a Safety and Efficacy Trial (SUNSET) are evaluating the optimal safe dose fractionation in cases when the tumor is in close proximity to the proximal bronchial tree.39 Most cases of severe toxicity related to damage to the peribronchial structures in which the primary tumors encased or were abutting the main stem or proximal lobar bronchus.39

Circulating Lymphocytes and Bone Marrow Toxicity

The immune system and its interaction with RT are increasingly being recognized as playing an increasingly important in oncologic outcomes.40 Emerging evidence suggest that increased dose to circulating blood and bone marrow during radiation treatment planning may lead to worse outcomes.41 Because of the smaller field sizes, immunotherapy combined with SBRT may better preserve lymphocytes than traditional RT.42 In conventional RT, limiting the volume of lung, heart, great vessels, and vertebral body receiving radiation may reduce the risk of lymphopenia.41,42

Radiation-Induced Carcinogenesis

The risk of second malignancy after exposure to ionizing radiation varies markedly with risk factors, including young age at treatment, higher radiation dose, and exposure to sensitive organs such as breast and thyroid.43 In the pediatric and young adult population, the use of proton therapy does reduce the volume of tissue irradiated, and referral to proton therapy is considered in health systems with access to this technology.44 In patients with thymoma, the use of proton compared with photon therapy has been modeled to prevent five excess secondary malignancies per 100 patients.45 Radiation-induced malignancy is an important consideration in patients presenting with a lung mass with a history of RT and is well documented in patients with a history of treatment for lymphoma and breast cancer.46,47 This risk of second malignancy can be reduced by smoking cessation.48

Multimodality Therapies

The concurrent use of systemic therapies is the standard of care for patients with locoregionally advanced and metastatic lung cancer.49 Although this treatment improves disease outcomes, it is important to note both sequential and particularly concurrent therapies increase the risk of toxicity from thoracic RT. This increased risk may be synergistic, in which the risk of toxicity is increased to a level greater than the sum of the toxicity rate of the two treatments when given separately.

Concurrent chemotherapy typically causes a synergistic effect on toxicity. Therefore, the type and sequencing of chemotherapy have been found to influence a number of local thoracic toxicities. The use of concurrent taxane-based chemotherapy has been noted to increase the risk of radiation pneumonitis with a significantly increased risk revealed in the systematic analysis of toxicity after radical irradiation: pneumonitis and esophagitis (STRIPE meta-analysis), with an OR equal to 3.33.17,50 The risk of radiation esophagitis is increased with the use of concurrent chemotherapy—in particular, cisplatin-based regimens—with meta-analysis reporting the risk of acute esophageal toxicity of grade 3 or higher as increased from 4% to 19% when using a concurrent chemotherapy regimen.49,51 The addition of concurrent chemotherapy also increases the risk of radiation-induced myelopathy—although with
modern planning techniques and image guidance this risk can be minimized.\textsuperscript{52}

Immunotherapy does independently place patients at risk of a number of toxicities— in particular, lung, heart, and endocrine toxicity. Patients who received both immunotherapy and RT treatments have an increased incidence of these toxicities although the current evidence suggests that the toxicities occur in an additive rather than a synergistic fashion.\textsuperscript{53} It is important to recognize patients who develop these toxicities and manage them according to the likely cause. Radiation pneumonitis more often occurs in-field, within 6 to 12 weeks postradiation treatment radiographically has more sharply defined, nonanatomical borders, and is managed with steroids.\textsuperscript{54} Immunotherapy pneumonitis involves florid bilateral lung changes involving multiple lobes is managed with steroids, dose reduction, or cessation of treatment, and consideration of immunosuppressive monoclonal antibodies.\textsuperscript{53}

Other rare toxicities including the radiation recall phenomenon can occur in all patients receiving systemic therapies including immunotherapy.\textsuperscript{54} Typically the most common type of recall reaction after thoracic treatment is radiation pneumonitis, although rare conditions such as recall myelopathy may also occur.\textsuperscript{16}

The use of RT in patients who have received surgical management has recently been explored in the lung ART trial in which patients with resected stage III lung cancer were randomized to receive postoperative RT or observation.\textsuperscript{55} This technique involved a large field using a three-dimensional (3D) conformal technique covering the operative bed and elective nodal regions.\textsuperscript{55} Although local control improved in the investigational RT arm this treatment was associated with high rates of cardiopulmonary toxicity. Eleven patients died from cardiopulmonary causes in the RT arm compared with no deaths in the observation arm.\textsuperscript{55} In addition, rates of grade 3 to 4 cardiopulmonary toxicity in the RT arm were 11% compared with 5% in the control arm.\textsuperscript{55} This phase 3 trial suggests that RT does increase cardiopulmonary morbidity and mortality when added to surgery.

**Strategies to Minimize Risk of Radiation Toxicity**

**Patient Selection and Management**

**Early Diagnosis of Toxicity.** The most common strategy currently used in clinical practice is to identify and manage radiation-related toxicities. Clinicians often score the level and incidence of toxicity using the Common Toxicity Criteria for Adverse Events. Moreover, currently used prediction models of late toxicities such as radiation-induced esophagitis and radiation pneumonitis are using Common Toxicity Criteria for Adverse Events scores as one of the main indicators. The use of patient-reported outcomes has been established as a useful method to supplement routine clinician assessment and identity patients at increased risk of developing substantial toxicities.\textsuperscript{56}

**Management of Comorbidities.** A patient’s previous functional status and other comorbidities are known to be significantly associated with the risk of developing acute and late radiation toxicity.\textsuperscript{57} Older patients are known to be at risk of functional decline postrtreatment and selected patients may be better suited to a palliative treatment approach. A pretreatment comprehensive geriatric assessment has been found to improve decision-making for older patients in a retrospective series, with prospective trials being conducted.\textsuperscript{58} In patients identified to have comorbidities, pretreatment prehabilitation, and postrtreatment rehabilitation have been found to benefit patients. In a meta-analysis of 437 patients with NSCLC treated with a combination of RT, surgery, and systemic therapy, clinically relevant improved physical fitness with (pre)rehabilitation intervention was evident.\textsuperscript{58} Figure 2 describes the "prehab-rehab" and then survivorship patient journey.

**Shared Care Decision-Making and Decision Support Systems.** Oncology decisions are often complex and involve detailed conversations between the radiation oncologist and patients, taking into account individual preferences and acceptance of potential risks of morbidity. In those with comorbid conditions, patients also benefit from the involvement of their other specialists in treatment decision-making. Shared care decision-making is a tool used to formalize this process and to assist patients to formulate decisions around their health care.\textsuperscript{60} The shared care decision-making process provides evidence-based information about treatment options, expected outcomes, and uncertainties leading to appropriate counseling and recording of the patient’s informed preference.\textsuperscript{60} Infographics combined with simple hand written questions may assist patients in formulating this decision.\textsuperscript{61} In the future predictive models may be able to further tailor risk at the patient level, which may lead to decision support systems tailored to the individual rather than to a population.\textsuperscript{52}

**Biomarkers.** Patients with particularly rare medical conditions such as interstitial lung disease, connective tissue disease, or familial syndromes such as ataxiataelangiectasia are known to be sensitive to RT. However, the rarity of these genetic conditions and the cost of testing make screening all patients impractical. The ideal
biomarker would be cost-effective, can select patients who may develop severe toxicity, and be useful to guide treatment decisions. An initial study of single nucleotide polymorphisms and plasma inflammatory cytokines both reveal promise for models to predict the risk of toxicities; however, it needs further clinical validation. Another promising biomarker is the radiation-induced lymphocyte apoptosis (RILA) assay. In the RILA assay, lymphocytes extracted from peripheral blood are irradiated. Ex vivo apoptosis is then scored before and then after irradiation. Retrospective studies have suggested that patients with lower RILA scores (those with less radiation-induced apoptosis) are at increased risk of early and late radiation toxicity. Methods individualizing radiation dose may enable improved dose selection. Some patients may be able to be treated with reduced doses while maintaining equivalent tumor control. This strategy has the potential to reduce toxicity. The concept of Genomically Adjusted Radiation Dosing is a dose selection technique, with retrospective data supporting the concept may lead to improved dose selection and, therefore, reduced toxicity and improved tumor control. Genomically Adjusted Radiation Dosing involves testing a series of genes and then using mathematical modeling to tailor a patient’s physical prescription dose (in Gray) to their own individual likelihood of treatment response or risk of toxicity. Pathologic biomarkers have been proposed to individualize radiation doses. These include testing for common mutations within the tumor such as KRAS and TP53. Preclinical data suggest these mutations may indicate radiation resistance, which can be overcome using targeted therapies or increased radiation dose. Histopathologic subtype has also been associated with the risk of local failure in patients treated with SABR. Furthermore, imaging data has also been reported as a potential biomarker that may predict the radiation sensitivity of tumors. Quantitative forms of imaging analysis have been used to generate risk scores that predict local failure and it has been proposed that using this profiling, dose reductions could be safely achieved in 23% of patients. In summary, biologic and imaging biomarkers are novel methods of individualizing lung RT, which require prospective clinical validation.

**Technique and Technical Considerations**

**Dose Constraints.** The key to minimizing radiation toxicity is a detailed knowledge of dose-volume effects on normal tissues. Modern RT planning involves the use of Dose-Volume Histograms, which graphically summarize the distribution of radiation to the various organs at risk that is individualized to the patient’s tumor location and anatomy. Treatment plans are then selected to maximize the dose to the known tumor and minimize the dose to key organs at risk. Established dose-response...
constraints exist for normal tissues in patients being treated with both SABR or conventionally fractionated RT on the basis of published data on radiation effects on normal tissues.\textsuperscript{73,74} Adherence to defined protocols by avoiding overdosing of critical organs at risk, or delivering a dose as low as reasonably possible is vital in minimizing radiation-induced toxicity; patients treated in centers with a substantial number of major protocol violations were noted to have an increased risk of toxicity.\textsuperscript{75} In a feasibility study of isotoxic intensity-modulated RT (IMRT), which limited dose to the central structures on the basis of strict dose constraints, comparable toxicity rates were reported despite dose escalation and acceleration.\textsuperscript{76}

**Normal Tissue and Target Definition Uncertainties.** The accuracy of target volumes and normal tissues is also critical to avoid excessive doses to organs at risk.\textsuperscript{77} Considerable interobserver variability exists in defining lung cancer target volumes and normal tissues and the increased size of targets has increased the risk of increasing radiation-related normal tissue toxicity.\textsuperscript{78} Peer review is a fundamental tool that can be used to reduce contouring inaccuracy and detect errors in the treatment planning process.\textsuperscript{77}

**Individualized Margins and Motion Management.** A reduction in the size of the irradiated volume has been reported to reduce the normal tissue volume irradiated, which may reduce the dose to key organs at risk such as the lung.\textsuperscript{79} Two technical ways to reduce the irradiated volume are to reduce respiratory motion by breath-hold or avoid treating during certain stages of the respiratory cycle. In free-breathing treatments, individual margins are designed for the patient's movement and to encompass other uncertainties in treatment planning and delivery.\textsuperscript{80} These motion management strategies can achieve a reduction in dose to organs at risk.\textsuperscript{81,82} To further improve the geometric accuracy and plan quality, information on the patient-specific systematic and random variations in mean position and amplitude is required. A phase 3 randomized trial investigating 3D conformal RT (3D CRT), with, or without respiratory gating in patients with NSCLC, most of whom were stage III was conducted to assess the clinical impact of this treatment approach.\textsuperscript{83} This trial overall did not reveal a statistically significant difference in the primary end point of pneumonitis and the locoregional response rates were no different between the arms.\textsuperscript{84} However, the trial did not use advanced planning techniques such as IMRT or volumetric modulated arc therapy (VMAT), which have evolved only at the completion of the trial.\textsuperscript{84}

**Treatment Planning and Delivery.** Treatment planning has become substantially more conformal. Moving from 3D-RT to IMRT was an important step to reduce the dose to the surrounding normal tissues. The ability to perform image guidance using cone-beam computed tomography (CT) has been a major advance in modern RT. Advances in imaging during radiation and major advances with treatment planning have allowed the first clinical systems that can image and adapt radiation plans to account for day-to-day variations in tumor and organ position. This approach has been found to greatly reduce the dose to organs at risk.\textsuperscript{82,85,86} In a phase 3 trial with treatment adaptation on the basis of weekly CT scan images, 50 out of 217 patients with NSCLC were able to be replanned owing to disease response.\textsuperscript{87} This trial was successful in exhibiting reduced esophageal and pulmonary toxicity compared with historical controls and achieved a low rate of marginal failures of 6%.\textsuperscript{87} There are a number of CT and magnetic resonance imaging (MRI)-based systems available that allow online adaptation. The advantage of MRI-based imaging on linear accelerators is superior soft tissue imaging. This is seen in Figure 3D in which imaging with MRI allows more soft tissue structures to be clearly visible during treatment and a similar dose distribution as the standard linear accelerator-based IMRT or VMAT treatments are able to be achieved. The key disadvantage of these systems is the increased time required for replanning during treatment.

**Functional Adaptation.** Functional Tumor Imaging. A number of studies have investigated the ability to use modern RT techniques combined with functional imaging to increase the dose to the tumor. In the Radiation Therapy Oncology Group (RTOG) 1106 study, adaptive RT was delivered using a midtreatment fluorodeoxyglucose–positron emission tomography (PET)/CT to escalate the dose to as high as 80.4 Gy in 30 fractions.\textsuperscript{88} In another functional adaptation trial, PET Boost patients were treated to 66 Gy in number 24 with randomization between a simultaneous integrated boost on the basis of a pretreatment fluorodeoxyglucose–PET/CT to the whole tumor and a simultaneous integrated boost to the 50% maximum standardized uptake value area within the tumor, leading to high local control rates, but also increased toxicity.\textsuperscript{89} Generally, the outcomes of these dose-escalation trials have highlighted that increasing dose results in increasing acute and late normal tissue toxicity in particular radiation esophagitis.

**Functional Organ Imaging.** A number of methods exist to image functional regions of the lung using imaging, including CT, MRI, single-photon emission CT, and PET.
Depending on the techniques, ventilation, perfusion, or gas exchange can be imaged. A meta-analysis of planning studies has reported that this information, integrated into treatment optimization, can reduce the functional volume receiving 20 Gy by 4.2% and the mean dose to the functional lung by 2.2 Gy. Prospective assessment is currently underway with trials including CT, single-photon emission CT, MRI, and PET used to identify and spare functional lung.

**Photons With Modulation.** Traditional RT in the CT era involved a number of fields used to deliver RT beams to the involved primary tumor and nodes delineated on the planning CT scan. These radiation beams were able to be shaped using tools such as multileaf collimators or wedges with radiation dosimetrists planning to maximize the dose to the primary tumor and minimizing the dose to organs at risk in a technique known as 3D CRT. IMRT, and later VMAT, techniques have since been introduced, changing the practice and improving the therapeutic ratio for a number of disease sites. In the delivery of these techniques, the machines make use of multileaf collimator leaves to conform to the dose to treat the tumor but avoid adjacent organs at risk. The key differences in dose distribution between 3DCRT and VMAT techniques are illustrated in the cartoon depiction of dose distribution in Figures 3A and B. In thoracic tumors, modulated techniques such as IMRT and VMAT have been reported to decrease heart dose likely resulting in less cardiac toxicity and reduced dose to lung, resulting in reduced rates of pneumonitis. Posthoc analysis of the RTOG 0617 trial revealed that patients treated with IMRT, despite having larger treatment volumes experienced less grade 3 pneumonitis (7.9% versus 3.5%), reduced risk of any pneumonitis (OR = 0.41), and lower heart doses. A higher dose to cardiac substructures, including the left anterior descending artery and left ventricle, have been associated with an increased risk of major coronary adverse events. Dose to these structures can be reduced using modulated techniques. An additional important oncologic consideration in the treatment of locally advanced NSCLC is that these techniques can reduce acute toxicities, such as radiation esophagitis, and improve quality of life. These reduced risks result in fewer delays in the commencement of consolidation immunotherapy and the number of patients completing the prescribed treatment. Significant reductions in esophagitis have been reported when RT plans are optimized to reduce esophagus toxicity in patients.
treated with both palliative and radical intent. Figure 4 illustrates the potential advantages of IMRT or VMAT over 3D CRT techniques.

**Particle Therapy.** Protons and other particles have distinct advantages over photons of a steep dose drop off beyond the target and the delivery of a lower integral dose, which can assist in reducing the dose to critical organs at risk. Recent technical advances, including the development of pencil beam scanning and efficient in-room imaging, make particle therapy a potential avenue for patients with thoracic tumors. In particular, young patients who require treatment are likely to receive substantial clinical benefits owing to a reduction of dose to heart, lung, and normal tissues with proton-based techniques. A number of clinical trials are currently underway to assess the potential benefits of this technology for patients with NSCLC. Previous negative studies using proton therapy used older passive scattering techniques and faced methodologic issues owing to a significant number of patients assigned to the proton therapy arm being treated with photons because of issues with insurance coverage. FLASH RT. Ultra-high dose rate (FLASH) RT is a new technique not currently clinically available to treat thoracic tumors. This composes of a high dose rate of over 40 Gy per second, which has been found, in laboratory models, to improve the therapeutic ratio owing to impressive responses that have been reported in tumor cells, with significant sparing of normal tissues. Using these high-dose rates would mean that tumor motion is no longer an issue. In the thorax, single doses to rodents up to 17 Gy in a single fraction have been given to the whole thorax with no pneumonitis or resulting pulmonary fibrosis. At conventional dose rates, this dose would be lethal. This technique exhibits great promise; however, the technical challenge of creating a linear accelerator that can deliver these dose rates to deep tumors needs to be achieved before clinical trials can commence.

**Survivorship**

Longer-term survivors of advanced and metastatic lung cancer are increasing in number owing to the improvement in treatments. These patients have been found to experience considerable physical, psychological, and functional concerns from their cancer journey, and many of the needs for support are not currently met in traditional cancer services. These patients need a more
Conclusions

Over the past decade, we have gained important knowledge and insights regarding the toxicities that may arise from thoracic RT. Technical developments including image-guided RT treatment techniques have markedly reduced toxicity. Other developments including multimodality treatments, especially systemic treatments with chemotherapy or immunotherapy have altered the timing and rate of toxicities observed. More research is required on methods to further reduce toxicity. Immediately, the task of validating dose-volume constraints to the heart, its substructures, and the esophagus remains a priority. Technical advances—including particle therapy, MRI, and functional imaging—are already in clinical use with evolving evidence to support the use of these technologies. Treatment adaptation with CT or MRI-based image guidance has the potential to further reduce treatment-related toxicity. Proton therapy, FLASH RT, and integrating biomarkers to treatment paradigms are promising treatments on the horizon.

CRediT Authorship Contribution

Nicholas W. Bucknell: Conceptualization, Writing - original draft, Writing - review & editing.
José Belderbos, David Palma, Puneeth Iyengar, Pamela Samson, Kevin Chua, Daniel Gomez, Fiona McDonald, Alexander V. Louie, Corinne Faivre-Finn, Gerard G. Hanna: Writing - review & editing.
Shankar Siva: Conceptualization, Supervision, Writing - review & editing.

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