Expert Opinion

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Strategies for enhanced radiation delivery in patients with lung cancer

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Since the 1970s primary management for regionally advanced non-small cell lung cancer has shifted from radiotherapy alone to sequential chemoradiation to concurrent chemoradiation. The increase in survival with these approaches has been small; an ~ 3 – 4 month per decade increase in median survival. Future avenues to improve on these outcomes could involve: i) dose-intense radiotherapy; ii) better target delineation; and iii) combining molecularly targeted agents with optimised radiation therapy. However, to accomplish this, techniques to control tumour motion and decrease toxicity must be developed.

Keywords: dose intensification, image guidance, lung cancer, motion control, radiotherapy

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1. Introduction

With an incidence of 160,000 and median survival of < 12 months, lung cancer represents a major oncologic challenge [1]. Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, referred to as non-small cell lung cancer (NSCLC) account for ~ 75 – 80% of cases of carcinoma of the lung [1,2]. Although surgery offers the best chance for long-term survival in patients with early-stage NSCLC, > 50% of patients are inoperable at presentation. A third (> 50,000) of all patients will have locally advanced disease that is unresectable, without evidence of spread outside of the thorax. For these patients, radiation therapy represents one of the primary treatment modalities. However, the 5-year survival rate for locally advanced lesions treated with conventional radiation generally ranges from 3 to 9% [3-8], which may be up to 22% in patients with a Karnofsky Performance Status (KPS) > 80 in whom local control is achieved [9].

2. The evolution to sequential chemoradiotherapy

The Radiation Therapy Oncology Group (RTOG) established what was felt to be the 'standard of care' in terms of radiation dose, volume, and beam arrangement for locally advanced, unresectable NSCLC in their dose-escalation trial 7301 [7]. This trial evaluated split-course radiation totalling 40 Gy versus continuous radiation to 40, 50 and 60 Gy. The split course was clearly inferior to the continuous arms. As a result of this trial 60 Gy continuous radiation therapy was adopted as a common US standard. However, the median survival with this approach was ~ 10 months, whereas the 3 and 6 year overall survival was 20 and 5%, respectively. In the years following RTOG 7301, strategies explored in the US and Europe involved sequential chemotherapy and radiation, and altered fractionation. The Cancer and Leukaemia Group B (CALGB) launched a trial in 1984, which randomised 155 patients to sequential cisplatin-based chemotherapy and radiation (60 Gy in 6 weeks) versus the same dose of radiation alone [10]. The median survival was 13.8 versus 9.6 months, whereas the 5-year survival was 17 versus 6% for the combined modality and

radiation alone arms, respectively [10]. The patients who received combined modality therapy had a 5-year survival probability that was 2.8-times greater than those who received radiation alone. Following the CALGB trial the Eastern Cooperative Oncology Group (ECOG) and the RTOG opened a study in 1989 evaluating both of the arms of the CALGB study plus a hyperfractionated radiation alone arm (69.6 Gy in 1.2 Gy twice-daily fractions). This trial accrued 455 patients over 3 years, and with greater power it redemonstrated a survival benefit in the combined modality arm compared with both radiation alone arms [11]. The median survival in the intergroup study was 13.8 versus 11.4 months, whereas the 3 year survival was 15 versus 6% in the combined modality and standard radiation (60 Gy) arms, respectively. At the same time similar questions were being asked in Europe, and in 1983 Le Chavelier *et al.* randomised 351 patients with locally advanced NSCLC to radiation alone (65 Gy over 45 days) or combination chemotherapy followed by radiation [12]. The distant metastases rate was significantly lower in the combined modality arm. Local control was low in both arms (17 versus 15%, respectively). Although at first analysis this study demonstrated no statistically significant difference in overall survival, at 3 years there was a statistically significant survival benefit for the combined modality therapy arm (12 versus 4%, $p < 0.02$). This study demonstrated the impact of chemotherapy not only on survival, but also on systemic control.

3. Concurrent chemoradiotherapy

The next paradigm shift was towards the concurrent administration of low-dose chemotherapy as a radiation sensitiser. A number of trials have combined radiation-sensitising doses of chemotherapy with thoracic radiation. A large three-arm study published by Schaake-Koning *et al.* compared split-course radiation (55 Gy) alone with the same radiation with weekly or daily cisplatin in a large number of patients with inoperable NSCLC [13]. There was a significant survival advantage in the daily cisplatin group when compared with the radiation alone arm (16 versus 2%, 3-year survival). Four randomised trials evaluating this concept followed: reported by Trovo *et al.*, Ansari *et al.*, Soresi *et al.* and Blanke *et al.* [14]. These trials were all negative; however, none of these trials duplicated the exact design of the positive study [14]. The effect in the positive study was mediated by increased local and regional control, with no documented effect of single-agent cisplatin on systemic control [15].

Recently, concurrent versus sequential chemoradiotherapy approaches have been tested in two major randomised trials [16,17]. Furuse *et al.* reported results from a Phase III trial comparing sequential versus concurrent chemoradiotherapy in unresectable stage III NSCLC patients. In the concurrent arm, a split course of radiation therapy (28 Gy in 3 weeks, followed by a 10-day break, then an additional 28 Gy in 3 weeks) was started on day 2 of chemotherapy (cisplatin, vindesine, mitomycin). In the sequential arm, radiation therapy (56 Gy in 28 fractions delivered sequentially) was initiated after completion of chemotherapy. An improved response rate, as well as improved 2-, 3-, 4- and 5-year survival rates (34.6 versus 27.4%, 22.3 versus 14.7%, 16.9 versus 10.1%, and 15.8 versus 8.9%, respectively), were noted for the concurrent arm [16]. Similarly, Curran *et al.* have reported results from RTOG 94-10: a Phase III study comparing sequential cisplatin-based chemo-radiation (60 Gy) to two concurrent arms: i) a standard 60 Gy arm; and ii) a 69.6 hyperfractionated arm. The standard concurrent chemoradiation arm demonstrated improved median and 4-year survival when compared with the sequential arm (17.0 versus 14.0 months, and 21 versus 12%, respectively) [17].

In summary, over the last three decades primary management concepts for locoregionally advanced unresectable lung cancer have shifted from so-called 'high-dose radiotherapy (60 Gy)' to sequential chemoradiotherapy to concurrent chemoradiation, with a shift in the median survival from 10 to 14 to 17 months, respectively. This dismal increase in survival has led to the investigation of several strategies. To this end, two concepts will be in this review: i) 'dose-intense' radiotherapy; and ii) the prospect of combining systemic targeted agents with optimised radiation therapy.

4. Dose-intense radiotherapy

Early strategies exploring this concept focused on hyperfractionation. The intent was to deliver higher doses of radiotherapy by delivering more than one treatment per day; keeping the overall treatment duration of ~ 6 – 8 weeks relatively constant. RTOG protocol 83-11, a Phase I/II trial of hyperfractionated radiation therapy, evaluated total doses up to 79.2 Gy (fractions of 1.2 Gy b.i.d.) with acceptable acute and subacute toxicities [18]. Results in the 69.6 Gy arm (median and 2-year survival of 13.0 months and 29%) were significantly better than the two lower dose arms (60 and 64.8 Gy) and prior RTOG studies using 60 Gy in 30 fractions with standard fractionation (2-year survival of 19%). However, there was no further improvement in survival with the higher total doses (74.4 and 79.2 Gy), and subsequent randomised evaluation of the 69.6 Gy arm failed to confirm a survival advantage. Similarly, RTOG 94-10 demonstrated a non-statistically significant benefit in survival for the concurrent hyperfractionated arm (69.6 Gy) when compared with the standard fractionation (60 Gy) sequential arm ($p = 0.069$) [17]; however, there was a statistically significant improvement in time to infield progression ($p = 0.007$). These studies suggest that indiscriminate dose escalation without knowledge of dose volume and time (overall treatment duration) effects may have a deleterious effect on outcome. Part of the problem with these hyperfractionation approaches is that overall treatment duration is lengthened. The ability of tumours to proliferate and of some clonogens to 'accelerate' their growth rate during this long time course has given rise to the concept of 'accelerated repopulation', which is a radiation-resistance phenomenon expressed by the tumour.

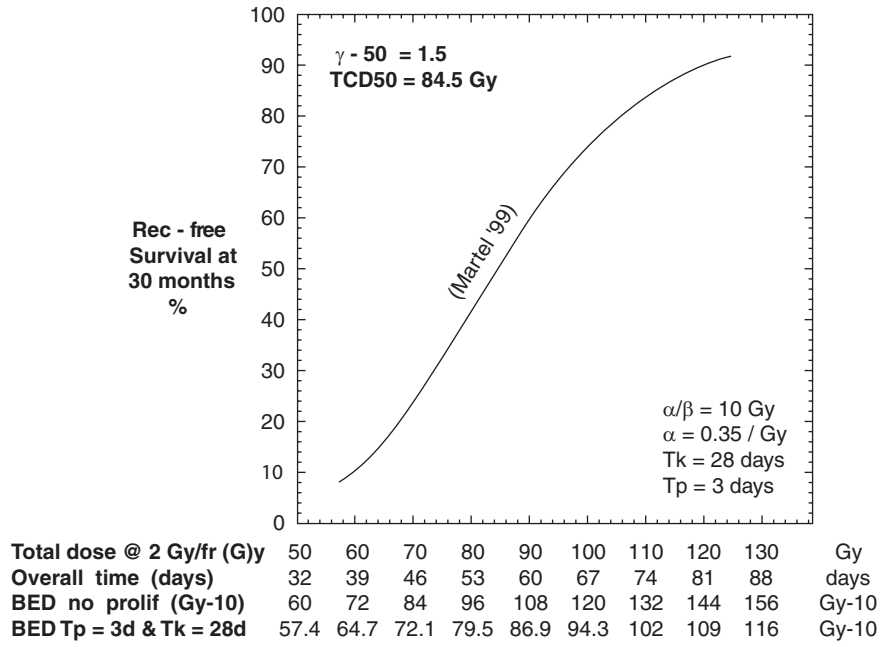

Figure 1. Response–dose curve calculated from clinical parameters. Analysed by Martel *et al. Lung Cancer* (1999) **24**:31-37. Demonstrates local progression free survival as a function of dose. According to this data doses of ~ 84 Gy would be needed for a 50% local progression free survival in 30 months.
BED: Biologically equivalent dose.

5. Conventional dose intensification improves local control

The typical radiotherapy schedule delivers 2 Gy per fraction per day, or 10 Gy per week. Conventional escalation approaches add more dose at the 'tail-end', at ~ 10 Gy per week. One such example is the report from the University of Michigan group, which explored dose-escalation techniques using CT-based three-dimensional planning [19]. They successfully tested the three-dimensional conformal dose delivery paradigm targeting only grossly involved sites of disease and excluding potential sites of micrometastatic disease [20]. Such work has led to the understanding that high doses (> 60 Gy) can relatively safely be delivered to limited volumes, and that there is, in-fact, a dose-to-local control relationship. **Figure 1**, which is based on modelling studies founded on these data, illustrates this concept. The figure suggests that with 'standard' (60 Gy) radiation, local control rates are ~ 20% at 30 months; doses of about 84 Gy are needed to improve this value to 50%.

6. Prolonged treatment schedules retard the gain in local control

In this context, the hypothesis that dose escalation (i.e., increasing total dose by increasing the number of fractions and total treatment time) has some limitations will be presented. One major radiobiological limitation to this strategy is accelerated repopulation, which tends to limit gains in tumour control probability achieved by increasing total dose [21,22]. Broadly, there are two lines of clinical evidence that provide proof of the premise that decreasing total treatment time (i.e., before accelerated repopulation becomes a significant factor) can improve local control and survival. The first comes from posthoc analysis of survival as a function of actual treatment duration in clinical trials in which the planned duration was fixed, but subsets of patients ended up requiring treatment interruptions; thereby lengthening the delivery duration. One such analysis demonstrated a survival loss of 1.6% per day of treatment prolongation beyond the planned 6.5 weeks [21].

7. Shortened treatment schedules improve local control and survival

Another line of evidence supporting the negative consequences of accelerated repopulation comes from clinical trials in which deliberate schedule shortening is attempted. The European continuous hyperfractionated accelerated radiation therapy (CHART) study is one example. This study tested the concept of 'dose-dense radiotherapy' using an accelerated hyperfractionated regimen, so delivering all treatment within 2 weeks. It provided level-1 evidence demonstrating a 24% reduction in the relative risk of death and a 23% reduction in the relative risk of local progression (with the accelerated

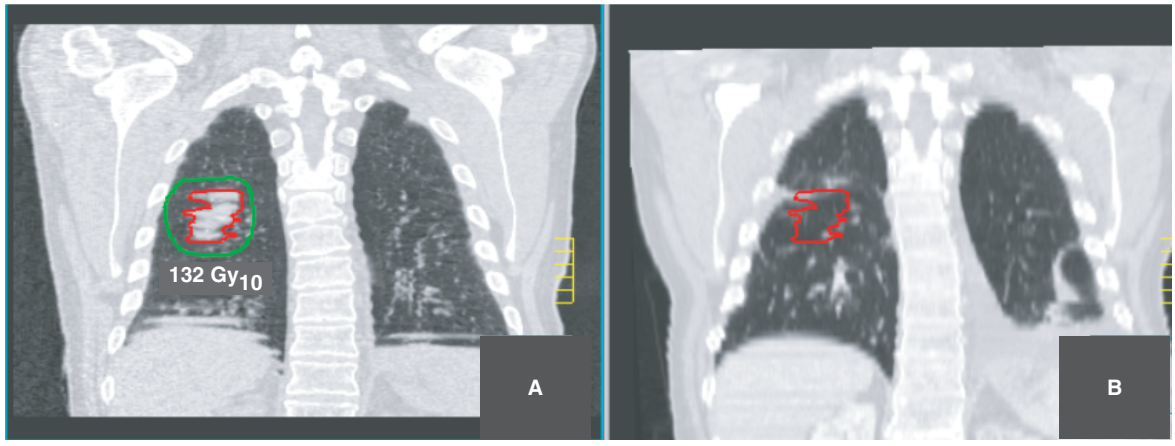

Figure 2. Tumour response to extreme dose-per-fraction escalation. Coronal, in-plane CT reconstructions **A**) before and **B**) after (6 months), 5 fractions of 12 Gy each (biologically equivalent dose of 132 Gy), demonstrate a complete response.

hyperfractionation arm [23]); however, there was a higher incidence of dysphagia associated with this arm. The hyperfractionated accelerated radiation therapy (HART) study, which closed early due to lack of accrual, is a second example. The HART study also demonstrated a large benefit in survival with dose-dense radiotherapy, which did not reach statistical significance due to lack of power [24]. These two trials provide clinical proof for the concept of accelerated repopulation and suggest that schedule shortening may be an effective strategy to minimise the impact of this phenomenon.

8. Schedule shortening with extreme dose escalation is curative

A third line of evidence supporting the negative consequences of accelerated repopulation comes from the work that has been done with extracranial stereotactic radioblation (ESRA) or stereotactic-body irradiation (SBI). This technique is an extension of the long-established practice of intracranial stereotactic radiosurgery to sites outside the brain. Like radiosurgery, it involves the use of image localisation to deliver high doses of radiation to small targets with few fractions using multiple radiation beams. ESRA incorporates a variety of systems that allow the adequate visualisation of targets (ultrasound, CT, fiducials) and systems that decrease tumour motion to give large doses of radiation to the target while avoiding high doses to normal structures. These systems allow for the reduction in treatment volumes, facilitating hypofractionation with increased daily doses and decreased overall treatment times. Several experiences with this technique have been reported. Timmerman *et al.* reported on the results of their ESRA dose-escalation protocol at the University of Indiana. Patients with inoperable T1 or T2 lesions (< 7 cm) were treated with escalating dose levels starting at 8 Gy x 3 fractions [25]. Doses up to 24 Gy x 3 fractions were evaluated and doses up to 22 Gy x 3 were delivered safely. After a median follow-up of 18 months, of the 44 patients enrolled 6 failed locally; all local failures occurred below the 18 Gy x 3 dose level. Onishi *et al.* have also reported the results of a Japanese multi-institutional retrospective experience on 241 patients [26]. In their experience maximum tumour diameters in the range of 0.7 – 5.8 cm (median 2.8 cm) were treated with doses of 18 – 75 Gy in 1 – 22 fractions. With a median follow-up of 18 months radiation-induced pulmonary toxicity greater than NCI-CTC grade II was noted in five patients (2.1%). Higher local recurrence rates were noted when the biologically equivalent dose (BED) was < 100 Gy versus > 100 Gy (20 versus 6.5%, p = 0.04). These experiences demonstrate that small-volume lesions can be treated safely to very high doses, in a very short time, with excellent local control rates (**Figure 2**).

There are certain limitations with accelerated hyperfractionation and ESRA techniques. The former poses significant obstacles in terms of resource consumption. Treating patients three times a day requires significant amount of machine and staff time, and may be inconvenient for patients. Proof of this principle is the early closure of the Eastern Cooperative Group study due to slow accrual [24]. ESRA on the other hand requires only a few treatments (typically 3 – 10, usually over 2 weeks). However, this technique is limited to small peripheral lesions [24]. Large volumes cannot be treated in this manner due to toxicity constraints of the lungs. In addition, lesions that are in close proximity to large bronchi (i.e., trachea or main stem bronchi) must be avoided due to concern for damaging airway passages and lung tissues functionally distal to airway passages. For those patients who are not candidates for ESRA, the concept of dose-per-fraction escalation to increase the effective dose to non-small cell lung tumours [21] will be presented. This strategy involves increasing the dose per fraction, but maintaining the number of fractions

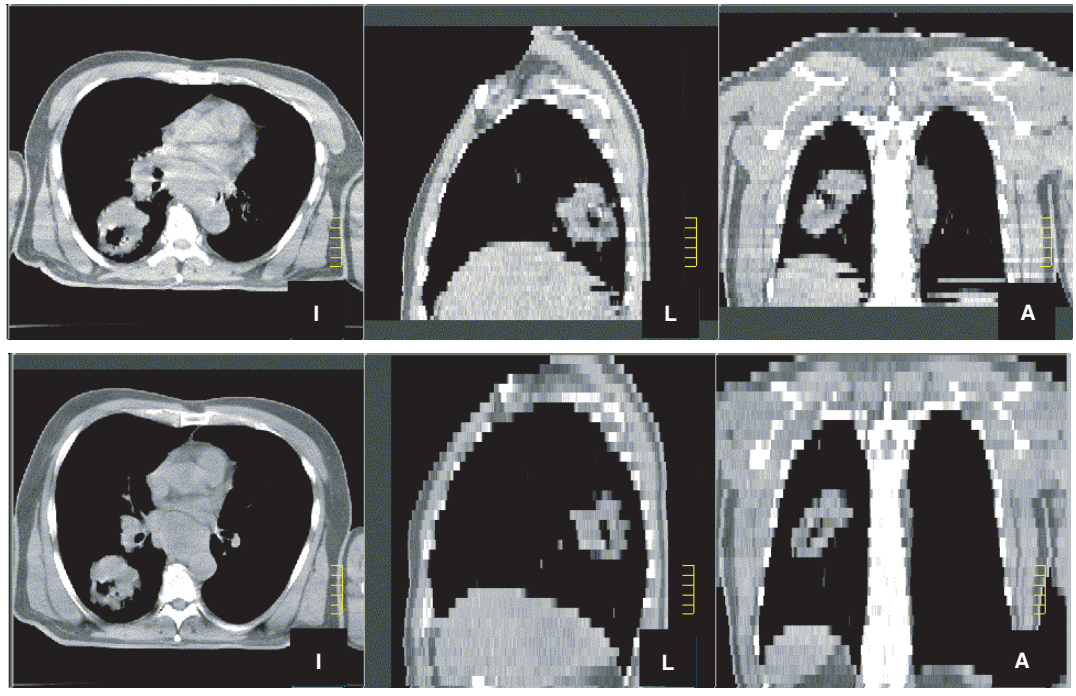

Figure 3. Tumour motion during respiration. CT images in maximum inspiration and expiration illustrate the magnitude of lung volume change and tumour motion during a respiratory cycle. The upper panel is obtained during maximum expiration, and the lower panel during maximum inspiration.

constant, which avoids the usual prolongation in overall treatment time. Modelling has shown that increased BED to tumours can be achieved by shortening the radiation delivery schedule and increasing the dose per fraction [21]. This requires decreasing the total dose to hold lung toxicity constant at each dose per fraction level. Such a technique overcomes the pitfalls of accelerated repopulation by completing treatment before the onset of accelerated repopulation (Tk), which has been estimated to be 28 days for lung cancer [22]. At the same time this technique avoids the inconvenience and resource consumption of hyperfractionation. This is a major paradigm shift in the treatment in this disease, and is projected to result in significant improvements in patient outcome as well as a substantial cost savings.

9. Technical advances permitting dose-per-fraction escalation

9.1 Positron emission tomography

To implement a dose-per-fraction escalation strategy, certain technological innovations and philosophical shifts are needed in order to limit toxicities from more intensive treatment approaches. Recent efforts have focused on improvements in staging (i.e., with the introduction of positron emission tomography; PET), managing respiratory motion, and improving delivery techniques and target definition [27-31]. One major philosophical shift involves avoiding prophylactic nodal irradiation. Recent studies have demonstrated a low incidence of failure in clinically uninvolved regions that are excluded from the radiotherapy field, and treatment of clinically uninvolved regions outside the ipsilateral hilum has demonstrated no obvious impact on outcome [32,33]. In the context, PET scanning may allow more accurate definition of both the primary tumour and involved nodal regions. For example, PET imaging may distinguish tumour from atelectasis, and also has a high negative predictive value for mediastinal nodes [30,34]. With the use of CT-PET to define tumour volumes adequately, and with the avoidance of prophylactic nodal irradiation, treatment volumes can be reduced. This decreases the volume of normal lung irradiated and, therefore, allows dose escalation.

9.2 Motion compensation

Because patients with lung cancer are treated while the lung is moving (**Figure 3**), adequate radiotherapy coverage requires that the treatment margins be expanded to include the motion envelope; thus resulting in additional normal lung being irradiated to high doses. This problem of lung and tumour motion is a major limiting factor for dose-intensification, and several approaches to overcome the problem have been proposed and tested. One such technique that has been described is deep or maximum inspiration breath hold

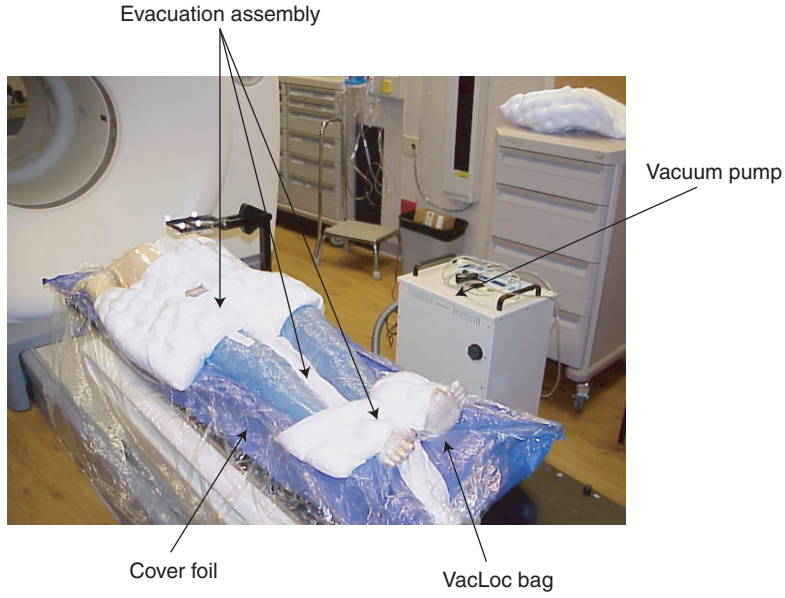

Figure 4. Depicts the Body-Fix system, which consists of a VacLoc bag, cover foil, and abdominal pressure pillow.

(MIBH) [27,35]. MIBH involves the gating of radiation therapy during periods of near-maximum inspiratory capacity [35]; the radiation beam comes on when the patient reaches this point in the breath cycle and holds his or her breath. The treatment of patients with this technique has two advantages over standard treatment in free breathing. First, treatment during MIBH restricts tumour motion, thereby allowing for the implementation of smaller margins during treatment planning. Second, because the lungs are optimally inflated during MIBH, the alveoli are recruited out of the path of the radiation beam; therefore, effectively reducing lung density and the functional volume irradiated. Decreasing the effective volume of lung irradiated leads to lower normal tissue complications probabilities, which facilitates dose escalation [27,31,35]. Rosenzweig *et al.* have used breath-hold and intensity-modulated radiotherapy (IMRT) to treat lung cancer patients safely to doses of 84 Gy, when treatment with free breathing at an intended dose was not deemed safe [31]. They are currently evaluating this dose level in a cohort of patients to establish its efficacy in inoperable NSCLC [31].

A major disadvantage of the MIBH technique is patient compliance. The procedure, when performed repeatedly, can exhaust a patient, and compromise reproducibility. In our experience at the University of Wisconsin patients tolerated repeated MIBH manoeuvres well; on average they were able to hold breath for 20 – 25 s repeatedly [27]. However, these patients were screened thoroughly for compliance prior to being enrolled in the study; therefore, this technique may not be as well tolerated by all patients with lung cancer. Hence, other techniques to account for target motion have been explored. The aim of these techniques is to decrease treatment volumes by allowing smaller planning treatment volumes to be generated by managing tumour motion. One technique that has been explored involves breath minimisation by the use of the Body-Fix system. This is an FDA-approved system, which consists of a VacLoc bag assembly, cover foil, and abdominal pressure pillow (**Figure 4**). A vacuum pump is connected to an evacuation assembly, and negative pressure is applied to the chest and abdomen [36]. This has two effects: i) reduction of chest wall and abdominal excursion during breathing; and ii) more rhythmic breathing [36]. In a pilot study conducted at the University of Wisconsin the extent of chest wall motion in the anteroposterior direction was decreased to ~ 2 mm with the application of the Body-Fix system [36]. This allows for a reduction in treatment volumes and consequently spares more normal lung.

Another technique that is currently being evaluated is synchronised delivery, which involves the delivery of radiation while the target is undergoing repetitive motion by 'synchronising' beam delivery to a given point in the target's repetitive motion cycle. One example of this is breathing synchronised delivery (BSD) [28], which is currently being developed for use with helical tomotherapy. Helical tomotherapy is a modality that combines rotational IMRT delivery with the ability to provide accurate verification of radiation delivery by using tomographic imaging [37]. With BSD, lung and tumour motion, as defined by a four-dimensional CT scan (a CT scan that allows accurate assessment of motion over time), are directly incorporated into the treatment plan [38,39]. This technique relies on a reproducible breathing pattern. To accomplish this, the respiratory cycle of the patient is monitored and analysed with a

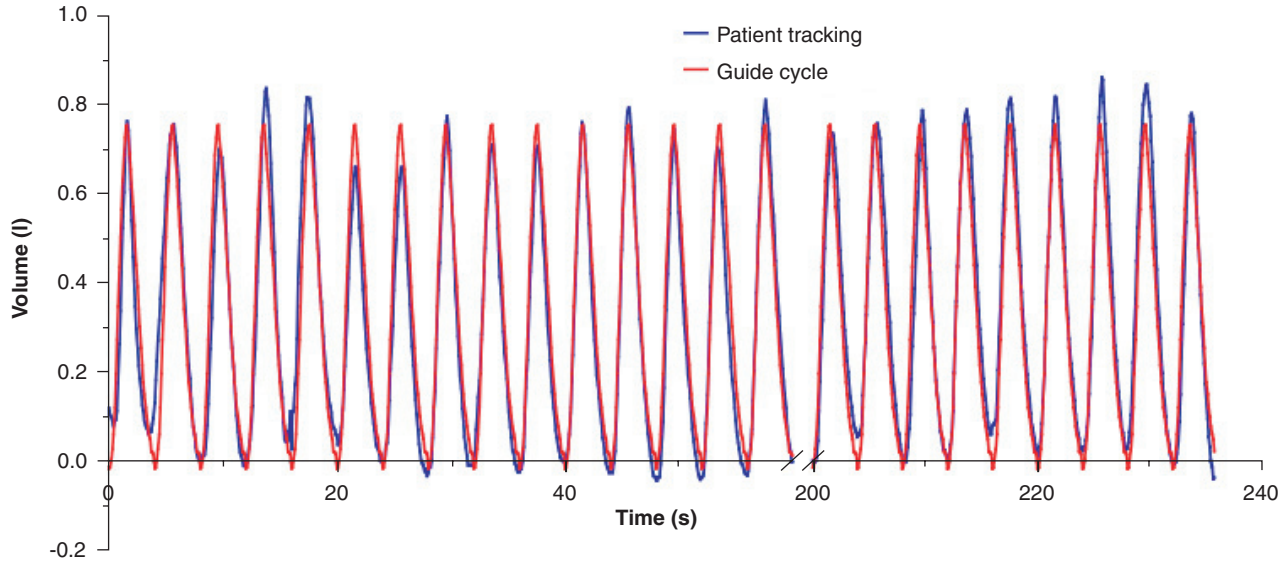

Figure 5. The guiding cycle and curve generated by healthy volunteer tracking the guiding cycle.

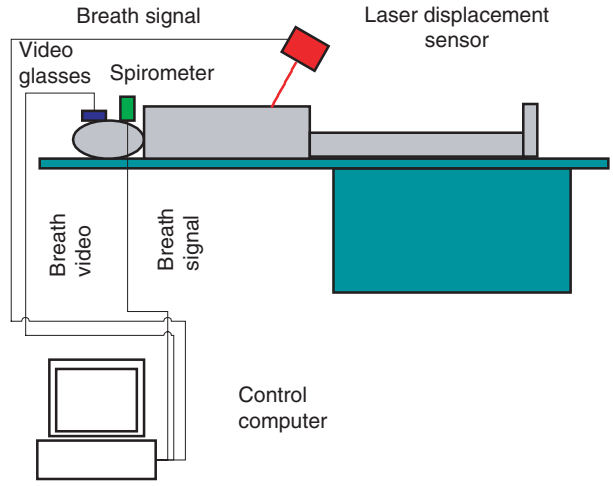

Figure 6. A laser/spirometer combined respiratory motion tracking system. The displacement measurements by the laser are scaled by spirometer reading to eliminate setup uncertainties.

laser-spirometer system, and a patient-specific average breathing cycle (guiding cycle) is derived. Prior to treatment, images are obtained at different breathing phases using a four-dimensional CT scan. During each treatment, the guiding cycle is projected onto video goggles worn by the patient who follows this guiding cycle (**Figures 5** and **6**). A fixed point in the respiratory cycle is chosen as the primary phase; contouring and dose delivery is mapped to the primary phase, and target motion and deformation are included into the treatment optimisation [28]. Beam delivery is synchronised to patient breathing, which results in conformal radiation therapy delivery to a moving target (**Figure 7**).

9.3 Intensity-modulated radiotherapy

Conventional conformal radiotherapy using beam's eye view planning techniques allows better shaping of radiation fields and more accurate custom shielding of normal structures [40]. IMRT is another technological advance that has shown promise in several sites by producing more conformal radiation fields and reducing doses to normal structures. The advantage of IMRT is that it allows for conformal avoidance of critical organs while making it possible to deliver a tumoricidal dose to the target [41]. The potential downside of IMRT is that there are fewer regions of normal lung that receive zero dose compared with traditional beam arrangements. However,

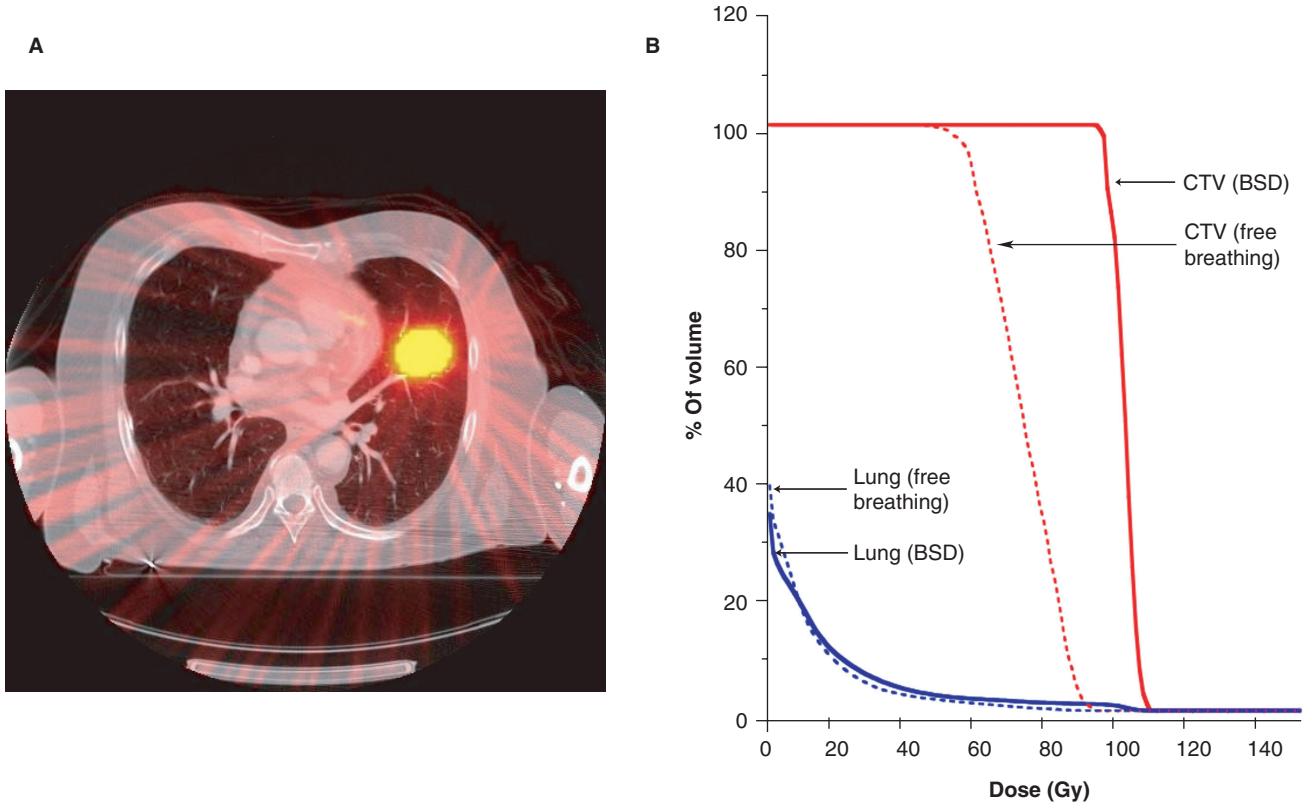

Figure 7. A) Demonstrates the conformal dose-distribution accomplished with BSD on a lung undergoing breathing motion.
B) The dose–volume histogram of a CTV with and without BSD.
BSD: Breathing synchronised delivery.

studies have shown that, on average, lower mean lung doses can be achieved with IMRT techniques compared with conventional conformal radiotherapy using beam's eye view planning [42]. The problem with implementing IMRT in the treatment of lung cancer lies in the fact that poor dose distributions are achieved when treating a moving target [28]. Thus, techniques to account for or diminish tumour motion are vital to the implementation of IMRT. Many techniques, such as active breathing control and tumour tracking, have been described in the literature [43,44]. The techniques that the authors have the most experience with have been described.

10. Dose-intense radiotherapy combined with cytotoxics or targeted agents

The second major theme that will be discussed is the prospect of combining systemic agents with dose-intense radiation therapy. Several randomised trials have shown a small survival advantage to concurrent chemoradiation (using standard dose radiotherapy) therapy as opposed to sequential approaches [16,17]. It is important to mention that although research has focused on which agents to use, nationally accepted radiation doses remain near the same level as prescribed > 30 years ago. However, with the advent of three-dimensional treatment planning our ability to deliver radiation has improved. This provides a basis for exploring dose escalation/intensification with systemic therapy as a step to improving local control.

One approach that has been used is combining full-strength induction systemic chemotherapy with lower dose chemotherapy as a radiation sensitiser. Recently, Vokes *et al.* reported on a Phase III study evaluating induction chemotherapy (carboplatin/paclitaxel) followed by chemoradiation (carboplatin/paclitaxel + 66 Gy) [45]. In their report, there was a trend towards improved survival with the induction chemotherapy arm (14 versus 11.4 months), which at the time of analysis did not reach statistical significance ($p = 0.151$). In a Phase I study, investigators from the University of North Carolina treated unresectable stage III NSCLC patients with two cycles of induction carboplatin (AUC 6) and paclitaxel (225 mg/m^2) followed by thoracic radiation with lower (sensitising) doses of carboplatin and paclitaxel [46]. They have examined escalating radiation doses in the range of 60 – 74 Gy. The median survival rate with this technique was 26 months, which is higher than

conventional radiation dose concomitant approaches reported by Furuse *et al.* and RTOG 9410 (16.5 and 17.1 months, respectively) [16,17].

In recent years, the field of molecularly targeted therapy has resulted in the development of agents such as cetuximab, erlotinib and gefinitinib, which have been evaluated as monotherapy and combination therapy in several solid malignancies. When EGFR inhibitors are used as single agents in advanced/refractory NSCLC (the IDEAL-1 trial), they demonstrate a 20% response rate and 40% improvement in tumour-related symptoms [47]. Unfortunately, the largest clinical trials evaluating the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors erlotinib and gefitinib with chemotherapy failed to demonstrate a survival advantage [48-50]. More recently, a randomised multicentre Phase II trial evaluating the EGFR antibody cetuximab in combination with cisplatin and vinorelbine first-line chemotherapy demonstrated an improved response rate as well as a survival advantage (1- and 2-year survival of 32 and 14% for the cetuximab combination arm versus 26 and 0% for the chemotherapy alone arm) [51]. The EGFR pathway is believed to play a major role in lung cancer growth and progression, and preclinical experiments suggest that irradiating these tumours after EGFR inhibition results in cell-cycle arrest, reduced tumour growth, reduced tumour vasularisation, and enhanced apoptosis. These preclinical observations were recently confirmed in a Phase III study by Bonner *et al.*, which compared radiation plus cetuximab (C-225) with radiation alone in locoregionally advanced head and neck cancer patients. A survival benefit was found in the cetuximab plus radiation arm (median survival of 54 versus 28 months), with minimal enhancement of overall toxicity [52]. Most NSCLC tumours overexpress EGFR [53,54]; thus, applying such molecular targeted therapies to NSCLC patients is a logical direction for clinical exploration. One strategy that has shown promise in preclinical studies is the combination of cetuximab and tyrosine kinase inhibitors (erlotinib and gefininib). This strategy blocks the intracellular and extracellular domains of the receptor resulting in amplified apoptosis, inhibition of downstream effector molecules (MAPK and AKT), and profound tumour regression and regrowth delay in human lung cancer xenograft models, compared with single-agent therapy [55]. The use of these agents with radiation therapy is just beginning to be explored. The South West Onocology Group is evaluating erlotinib as maintenance therapy, together with docetaxel, following concurrent chemoradiotherapy, in a randomised Phase III trial. The ECOG is currently developing a trial that will evaluate two cycles of carboplatin-based chemotherapy followed by hyperfractionated accelerated radiation therapy plus cetuximab in NSCLC.

11. Expert opinion and conclusion

NSCLC continues to be a major oncologic problem. Progress in this disease has been limited, with about a 3 – 4 month increase in median survival per decade since the 1970s. Thus, newer strategies are needed to improve outcomes in NSCLC. These strategies may come from two fronts: i) optimising and intensifying radiation therapy delivery; and ii) improving systemic therapy with targeted agents. Three-dimensional treatment planning is a key step in optimising radiation therapy delivery. Improvements in radiation therapy could involve better target delineation (i.e., PET guidance) and dose-intense radiation therapy. However, to accomplish this, techniques to control tumour motion and decrease toxicity (IMRT) are necessary. In addition, the optimal sequencing between radiation and systemic agents, including both chemotherapy and targeted agents, has not yet been established. With new less toxic modalities such as EGFR inhibitors, both modalities may be optimised in the concurrent setting, perhaps reserving more cytotoxic regimens either for the induction or maintenance settings.

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