Published text:

Improvement in tumour control probability with active breathing control and dose escalation: a modelling study

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Type of paper: Full length original paper
Short Title: “Modelling dose escalation with ABC”
Total number of pages: 12
Number of figures: 0
Number of tables: 2
Keywords: Lung cancer
Radiotherapy
Active breathing control
Tumour control probability
Radiobiological Modelling

Conflict of Interest Statement:

The authors have no conflicts of interest to report.
Improvement in tumour control probability with active breathing control and dose escalation: a modelling study

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Abstract

Introduction

The prognosis from non-small cell lung cancer remains poor, even in those patients suitable for radical radiotherapy. The ability of radiotherapy to achieve local control is hampered by the sensitivity of normal structures to irradiation at the high tumour doses needed. This study aimed to look at the potential gain in tumour control probability from dose escalation facilitated by moderate deep inspiration breath hold.

Method

The data from 28 patients, recruited into two separate studies was used. These patients underwent planning with and without the use of moderate deep inspiration breath hold with an active breathing control (ABC) device. Whilst maintaining the mean lung dose (MLD) at the level of the conventional plan, the ABC plan dose was theoretically escalated to a maximum of 84 Gy, constrained by usual normal tissue tolerances. Calculations were performed using data for both lungs and for the ipsilateral lung only. Resulting local progression-free survival at 30 months was calculated using a standard logistic model.

Results

The prescription dose could be escalated from 64 Gy to a mean of 73.7±6.5 Gy without margin reduction, which represents a statistically significant increase in tumour control probability from 0.15±0.01 to 0.29±0.11 (p < 0.0001). The results were not statistically different whether both lungs or just the ipsilateral lung were used for calculations.

Conclusion

A near-doubling of tumour control probability is possible with modest dose escalation, which can be achieved with no extra increase in lung dose if deep inspiration breath hold techniques are used.
Introduction

Lung cancer is the second most common cancer diagnosed in the UK and accounts for more than 1 in 5 cancer deaths\(^1\). Radical radiotherapy is an important therapeutic modality in patients with non-small cell lung cancer which is either localised and medically inoperable locally advanced and inoperable. Nevertheless the prognosis for patients who can be treated radically remains poor.

One reason for the failure of radical radiotherapy is that very high doses of radiotherapy are needed to locally control the tumour. Historically it has not been possible to safely escalate the dose due to the sensitivity of surrounding lung tissue to radiotherapy.

Various strategies have been employed to facilitate dose escalation though improved target volume definition. Selective irradiation of FDG-PET-positive mediastinal areas has been shown to yield smaller target volumes in some patient [1] thus allowing dose escalation. Another highly promising technique involves the construction of respiratory motion artefact free mid-ventilation CT scans from 4DCT data, allowing significant reduction of PTV volumes [2]. An alternative use of 4D data, which is currently being actively researched, is dynamic tracking of respiratory-induced motion with an MLC [3].

Patient-specific dose escalation using isotoxic (or iso-NTCP) prescriptions have been demonstrated using field size reduction and allowing greater inhomogeneity within the PTV [4], or by treating all patients to the same normalised mean lung dose [5] with either standard fractionation schemes, or with hypofractionation or accelerated fractionation schemes.

We have previously shown that, with breath holding using an active breathing control (ABC) device in a real clinical situation, taking into account all treatment uncertainties, planning target volume (PTV) margins can be reduced whilst still adequately treating the tumour [6]. This reduction in PTV volume could theoretically reduce normal tissue complication probability (NTCP) and therefore enable dose escalation to the same toxicity level, hence increasing tumour control probability (TCP). However, the potential to reduce margins has been shown to be small, since systematic set-up errors still dominate setup accuracy [7].

In this study we investigate the potential magnitude of benefit which can be gained primarily using the increased lung volume (and hence reduced mean lung dose and consequent toxicity) achievable with moderate deep inspiration breath-hold facilitated by ABC. The reduction in normal lung irradiated when using the ABC device is exploited to escalate prescription dose to iso-NTCP levels, subject to standard dose-volume constraints for the oesophagus, heart and spinal cord and restricting the tumour dose to 84 Gy. The results of the potential dose escalation are expressed in terms of increased tumour control probability (TCP).

Patients and Methods

Patients

Two separate cohorts of patients were available for this study. The first patient group, described by Panakis et al [6], were recruited into institutional review board (IRB) approved planning studies to assess interfraction and intrafraction tumour and oesophageal motion with ABC. All patients had histologically verified NSCLC and were eligible for radical radiotherapy. A 10 patient subset of the above group (mean age 69, range 53–80) was used for this study for whom three complete sets of cone-beam CT data were available to allow patient-specific margins calculation. Three conformal treatment plans were produced for each patient, the first using a standard free-breathing CT scan and standard institutional margins (1.5 cm superiorly and inferiorly and 1.0 cm axially), the second using a breath-hold CT scan acquired using the active breathing control (ABC) device and the standard institutional margins listed above and the third using the breath-hold CT scan and reduced, patient-specific margins calculated from CT-derived tumour motion studies [6].

The second group of patients, also with histologically verified NSCLC and eligible for radical radiotherapy, were recruited into a separate IRB approved pilot study to assess the clinical feasibility of routine use of ABC during radiotherapy. 18 patients (mean age 68, range 44–85) had three treatment plans each: i) free-breathing CT scan with standard conformal planning techniques and standard institutional margins of 1.5 cm superiorly and inferiorly and 1.0 cm axially, ii) breath-hold CT acquired using the ABC device, standard conformal planning techniques and standard institutional margins, and iii) breath-hold CT, standard conformal planning and reduced margins of 0.8 cm superiorly and inferiorly, 0.7 cm right-left and 0.6 cm anterior-posterior. These reduced margins were calculated from the population average of the patient-specific reduced margins applied to the first cohort [6] and account for random interfraction and intrafraction error only. These represent an estimate of the theoretical minimum margin size that could be used, assuming that systematic error can be reduced to zero by image guidance.

The same beam arrangements were used for each set of three plans. A dose prescription of 64 Gy in 32 fractions was initially used for all treatment plans ensuring that the GTV was covered by the 95% isodose. We aimed to cover as much of the PTV as possible, but given the lack of electron equilibrium in the lungs, 95% coverage of the PTV is not typically achievable. The PTV dose-volume histograms for each of the three plans were matched as closely as possible to make the plans comparable. All outlines were drawn by the same person for each cohort in an effort of reduce inter-observer variation. A collapsed-cone dose calculation algorithm was used for all plans [8]. Patient details are listed in table I. Informed consent was obtained from all participating patients in accordance with national legislation and local guidelines.

ABC device

The ABC device consists of a mouthpiece connected to a spirometer air-flow meter and is coupled to a balloon valve [9]. A nose clip was used to ensure that breathing was only through the mouthpiece. The valve was closed at moderate
deep inspiration breath hold (mDIBH), which was set at 75% of the maximum inspiration volume for each patient. The tidal volume resets to zero at the end of each exhalation. Patients were trained using this device prior to treatment and received audio prompting during therapy. The device was found to be well tolerated with only one out of the 18 patients in the second cohort failing to complete their course of treatment successfully with ABC. The average breath-hold time for this group was 21 s (range 15 – 30 s).

**Normal tissue toxicity calculation**

The principal dose-limiting toxicity in lung radiotherapy in this study is assumed to be radiation pneumonitis. Models presented for describing radiation pneumonitis have included the logistic model [10], with a near-linear dose effect at 3–4 months post irradiation, the linear-quadratic model [11], which derived a low $\alpha/\beta$ of 3.3 for pneumonitis reflecting the late-responding nature of lung tissue, and the Lyman model [12-15]. Analysis of outcome data by Seppenwoolde yielded values of $n$ for the Lyman model very close to 1.0, indicating that lung tissue can be modelled as having purely parallel architecture and reducing the equation predicting pneumonitis to being directly proportional to mean lung dose [14]. Some controversy remains as to whether the mean dose to both lungs together or just the ipsilateral lung provide the best predictor [16-18]. Therefore, for this study, mean lung dose was taken to be the best available predictor of pneumonitis, but was scored separately for ipsilateral lung and both lungs together.

**Dose escalation calculation**

The potential for dose escalation was calculated for each patient by escalating the prescription dose in the ABC plans until the mean lung dose was equal to that of the free-breathing plan, thus producing iso-lung-toxic plans. This was done separately using the MLD to both lungs and to the ipsilateral lung. Dose escalation was stopped if any of the following constraints were met: maximum cord dose $>$45 Gy, 33% of the heart $>$40 Gy, 66% of the heart $>$45 Gy, 32% of the oesophagus $>$50 Gy [19] or a target dose of $>$84 Gy.

**Tumour control probability calculation**

In order to express the potential dose escalation in terms of increased tumour local control, TCP for a given uniform dose $D$ was calculated using the logistic model [20]

$$TCP(D) = \frac{1}{1 + \left(\frac{D_{50}}{D}\right)^{4\gamma}}$$

where $D_{50}$ is the dose resulting in 50% local progression-free survival at a given time following treatment and $\gamma$ is the normalised slope of the sigmoidal dose-response curve at $D_{50}$. This expression was extended to non-uniform dose distributions using the standard method of considering the sum of uniform dose sub-volumes $D_i$ with fractional volume $V_i$, thus
Revised 1.0

\[ TCP_{\text{total}} = \prod_i [TCP(D_i, t)]^{\gamma}. \]  

Repopulation was not taken into account in this analysis and all calculations assume 2 Gy fractions. Parameters for the logistic model for local progression-free survival at 30 months of \( \gamma = 1.5 \) and \( D_{50} = 84.5 \) Gy were taken from the work of Martel et al [20].

Results

The data from 28 patients were analysed. Table 2 shows the individual patient data. For the free breathing plans the GTV, PTV and lung volumes are given together with the mean lung dose for a 64 Gy prescription and resulting TCP. For the ABC plans, the GTV and lung volumes are given together with PTV volumes using standard and reduced margins. The mean lung dose is listed for a 64 Gy prescription dose and the potential iso-NTCP escalated dose (giving the same MLD as the free-breathing case, subject to normal tissue toxicity limits). Finally, the TCP and dose-limiting normal tissue (where relevant) are listed for each case.

Considering both patient cohorts together, the prescription dose can be escalated to 73.7±6.5 Gy (±1 standard deviation) using ABC, without increasing margins and without increasing the mean lung dose (considering the mean dose to both lungs together). When considering the mean dose to just the ipsilateral lung, this value changes to 73.0±6.9 Gy, which is not statistically significantly different (\( p = 0.8 \), data not shown). For the remainder of this work, we will consider the MLD as the mean dose to both lungs. For 3 patients (patient numbers 6, 10 and 16) no dose escalation was possible without breaching normal tissue tolerance, (cord tolerance has already been reached in 6 and 10 and oesophagus tolerance in 16 in the free-breathing plans). For one patient (patient 18) the tumour appeared to be larger on the ABC CT scan than on the free-breathing scan, and the total lung volume smaller with ABC than for free breathing (caused by significant motion artefacts on the free-breathing CT). This would have led to a dose reduction to maintain iso-NTCP. Dose escalation was limited by normal tissue constraints in a further 5 cases: patient 1, oesophagus; patients 19 and 25 cord and in patients 12 and 17 the 84 Gy target dose constraint was reached.

When using patient-specific reduced margins in the first cohort, the prescription dose can be escalated to 76.6±8.4 Gy and to 77.1±7.1 Gy for population-based reduced margins in the second cohort. Further dose escalation was limited by the 84 Gy target dose constraint in 3 cases (patients 4, 7 and 9) and the oesophagus in one case (patient 14).

Using the TCP model, the average local progression-free survival at 30 months would be expected to rise from 15%±1% to 29%±11% using deep inspiration breath hold and no margin reduction. Using a 2-tailed t-test for 2 samples with unequal variance, this result is statistically significant (\( p < 0.0001 \)). The use of reduced margins further increases TCP to 31%±12% for patient-specific margins and 36%±12% for population-based margins, although these TCP
values are not statistically significantly larger than those obtained in the standard margin cases (p = 0.09).

Dose could also be escalated to a theoretical ‘maximum tolerated dose’ [21], producing a higher risk of lung toxicity. Using our 28 patient cohort, prescribing to an MLD of 18 Gy (both lungs) and subject to the normal tissue toxicity constraints listed above would result in a further theoretical increase in TCP to 58% ± 29% with a mean escalated dose of 79.1 Gy (TCP of 67% ± 36% for the first cohort and 53% ± 24% for the second cohort). It is interesting to note that MLD was the dose-limiting factor for just 2/28 patients; the majority (18/28) reached the maximum prescription dose of 84 Gy, 4/28 were restricted by spinal cord dose and 4/28 limited by oesophageal toxicity.

**Discussion**

The outcome for patients with NSCLC remains poor. The margins needed to adequately treat a discrete tumour need to be large enough to accommodate respiratory movement and its effect on imaging and treatment delivery, as well as set-up uncertainties. Consequently a relatively large volume of normal tissue is irradiated. The risk of pneumonitis correlates with dose to the lung and the volume of normal lung irradiated represented by MLD and other lung volume parameters [22].

By using the ABC device for moderate deep inspiration breath hold, the lung volume is larger and hence the dose to lung, per unit volume, is reduced. The use of modelling here has shown that these volume changes can lead to a dramatic effect on tumour control, virtually doubling TCP. Reducing respiratory movement of the tumour also means that the treated volume can potentially be reduced. In addition, scanning in breath-hold reduces the blurring of the tumour usually seen with respiratory motion, and so the gross tumour volume on the scan may also be smaller. The potential for margin reduction however is small, since random set-up errors still dominate. Although a trend towards higher doses was seen using ABC and margin reduction, this failed to give a statistically significant TCP gain for the small number of patients in this study. In terms of planning tumour volume (PTV) coverage it is accepted that, because of the slower dose build-up through lung tissue, it is often not possible to cover the PTV with the 95% isodose. This is accepted as unavoidable, particularly as the margins used ensure that the 95% isodose adequately covers the GTV.

One limitation of this study is GTV delineation accuracy, although a single observer was used for each cohort to minimise interobserver variation. Caution should also be exercised over the choice of dose calculation algorithm. The collapsed cone algorithm used here is expected to perform reasonable well within the lung, but result may differ slightly if other algorithms were to be used [8]. It should be noted that conventional 2 Gy fractions have been assumed in all modelling to permit easy comparison with published work. For clinical implementation dose escalation by increasing fraction size may be preferable to prolonging total treatment time so that the effects of repopulation (which are not modelled) are reduced. We note that the choice of TCP model and parameters will affect predictions. Using the range of published D50 for local progression-free survival at 30 months [20] of 84.5 ± 8.0 Gy, the calculated TCP gain for a lower
bound $D_{50}$ of 76.5 Gy is from 0.09±0.01 (free breathing) to 0.21±0.09 (deep inspiration) using standard margins. An upper bound estimate of $D_{50}$ of 92.5 Gy yields predictions of 0.25±0.02 (free breathing) to 0.43±0.13 (deep inspiration). Although the absolute value of TCP clearly changes with $D_{50}$ the relative increase is still roughly twofold.

The advantage of individualised dose escalation, as described here, is that the theoretical risk of lung toxicity is no higher with the dose escalated plan and ABC, than it is with a standard conformal plan and free-breathing. Therefore the patient stands to gain an increase in tumour control, with no additional risk of pneumonitis. It should be noted that ABC is not the only method of breathing control, reproducible voluntary breath hold has also been demonstrated [23] and would be expected to yield similar benefits.

We have chosen in this work to compare moderate deep inspiration breath hold with a standard free-breathing treatment technique. Comparison of our work with 4D CT treatment planning techniques, which have shown large changes in both GTV and lung volumes [24], or improved GTV definition using mid-ventilation scans [2] or reductions in mean lung dose using adaptive image guided techniques [25] would also be interesting, but are outside of the scope of this paper. Such techniques may also improve tumour control simply by reducing the chance of a geographical miss, which can occur even with the relatively large margins used in conventional radiotherapy treatments.

While many studies have investigated augmentation of radiotherapy planning accuracy, few have modelled the potential TCP gain from improved radiotherapy planning techniques. Van Der Wel et al planned 21 patients both conventionally and using only PET-CT data, which reduced the median GTV volume [26]. The potential for increasing dose was modelled, and in doing so the TCP increased from 14.3% to 22.8%. Although using a very different approach, this strengthens the assertion that by modestly reducing the PTV, large gains in TCP can be achieved at no cost to the patient’s risk of lung toxicity.

Evidence suggests that dose escalation improves TCP as predicted by radiobiological modelling. Kong et al describes a trial where the radiotherapy dose was escalated depending on the risk of lung toxicity (pneumonitis) in each patient. They analysed data from 106 patients and allocated doses between 63–103 Gy depending on NTCP using the Lyman model, as used here. They found a statistically significant correlation between higher doses and overall survival with an overall survival at 5 years of 4% in the conventional dose arm (63–69 Gy), 22% in the 74–84 Gy dose arm, and 28% in the 92–103 Gy dose range ($p = 0.0002$). A dose increase of 1 Gy was estimated to improve long term locoregional control by 1% [27]. Interestingly stage and GTV size, previously thought to be prognostic factors, were not so in the above group of patients. Zhao et al have noted that higher doses nullify the prognostic impact of a larger GTV. Patients receiving a BED of less than 79.2 Gy with a GTV of more than 51.8 cm$^3$ predicted a poorer survival. However for patients treated to a BED of more than 79.2 Gy, the size of the GTV (greater than or less than 51.8 cm$^3$) did not predict for survival [28].

Lung tolerance is conventionally thought to be dose-limiting for lung cancer radiotherapy. Clinically significant pneumonitis develops in 13–37% of patients
undergoing radical radiotherapy for lung cancer [29]. Mean lung dose has been shown to be the best parameter for modelling pneumonitis risk [14] although there are many other factors which may alter risk including performance status, pre-morbid pulmonary function, location of primary tumour and use of concurrent chemotherapy [29].

We performed the dose escalation calculations both considering the ipsilateral lung alone and for both lungs together. Some previous studies have indicated that modelling NTCP in lungs is more robust if only the ipsilateral lung is taken into consideration [18, 30]. Other studies have found that both ipsilateral lung mean lung dose (MLD) and total lung MLD are significantly associated with radiation pneumonitis risk [13] and some have correlated total lung MLD with pneumonitis risk [31]. In our calculations the dose escalations achievable considering unilateral or total lung volume were not significantly different (p = 0.8). As total lung MLD, and $V_{20}$ are the parameters most commonly assessed in clinical practice, this study supports the view that the additional assessment of ipsilateral lung dose is not necessary.

Although lung is the most common dose limiting structure, for a minority of patients in this study we could not escalate the dose to an isotoxic lung dose due to breaching dose constraints for other organs. In 4 patients the dose could not be escalated, or only be escalated by a small amount, due to breaching spinal cord tolerance, which we set at 45 Gy. None of the patients breached our constraints for heart, the oesophagus was a dose constraint in 3 patients and a maximum allowed target dose of 84 Gy was reached in 2 cases.

This study models the potential benefit of improved radiotherapy delivery using active breathing control. We have shown that an increase in overall lung volume (and modest reduction in PTV), results in a large reduction in mean lung dose, and hence capacity for the dose to be escalated with no additional toxicity to the normal structures, particularly the lungs, and no reduction of margins. With a mean dose escalation to 74 Gy, the tumour control probability almost doubles to 29%, potentially resulting in a large increase in survival for these patients. This warrants further investigation with a dose escalation trial using these techniques.
Acknowledgements

The authors wish to thank Richard Symonds-Taylor and Phil Evans for their work with the ABC device, John Fenwick for helpful conversations and to Cancer Research UK (CR UK) for supporting this work under in the Section of Radiotherapy Grant under number C46/A2131. We acknowledge NHS funding to the NIHR Biomedical Research Centre.

References


Table 1

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| overall mean | 0.15 | 73.73 | 0.29 |
| overall stdev| 0.01 | 6.49  | 0.11 |

Note: TCP (Tumor Control Probability) and Dose are given for the lung and PTV (Planning Target Volume) margins.
Table Captions

Table 1
Characteristics of patients used in this study giving disease stage, primary tumour location and performance status. (LUL = left upper lobe, RUL = right upper lobe, RML = right middle lobe, LLL = left lower lobe, RLL = right lower lobe, RMZ = right mid-zone. PS = ECOG performance status).

Table 2
Individual patient data showing tumour and lung volumes determined from free breathing and ABC CT data. The mean lung dose resulting from a prescription dose of 64 Gy and resultant, escalated iso-lung toxic prescription doses with associated TCPs (local progression-free survival at 30 months) are also shown.