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PHYSICS CONTRIBUTION

CONE-BEAM COMPUTED TOMOGRAPHIC IMAGE GUIDANCE FOR LUNG CANCER RADIATION THERAPY

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Purpose: To determine the geometric accuracy of lung cancer radiotherapy using daily volumetric, cone-beam CT (CBCT) image guidance and online couch position adjustment.
Methods and Materials: Initial setup accuracy using localization CBCT was analyzed in three lung cancer patient cohorts. The first (n = 19) involved patients with early-stage non–small-cell lung cancer (NSCLC) treated using stereotactic body radiotherapy (SBRT). The second (n = 48) and third groups (n = 20) involved patients with locally advanced NSCLC adjusted with manual and remote-controlled couch adjustment, respectively. For each group, the couch position was adjusted when positional discrepancies exceeded ±3 mm in any direction, with the remote-controlled couch correcting all three directions simultaneously. Adjustment accuracy was verified with a second CBCT. Population-based setup margins were derived from systematic (Σ) and random (σ) positional errors for each group.
Results: Localization imaging demonstrates that 3D positioning errors exceeding 5 mm occur in 54.5% of all delivered fractions. CBCT reduces these errors; post-correction Σ and σ ranged from 1.2 to 1.9 mm for Group 1, with 82% of all fractions within ±3 mm. For Group 2, Σ and σ ranged between 0.8 and 1.8 mm, with 76% of all treatment fractions within ±3 mm. For Group 3, the remote-controlled couch raised this to 84%, and Σ and σ were reduced to 0.4 to 1.7 mm. For each group, the postcorrection setup margins were 4 to 6 mm, 3 to 4 mm, and 2 to 3 mm, respectively.
Conclusions: Using IGRT, high geometric accuracy is achievable for NSCLC patients, potentially leading to reduced PTV margins, improved outcomes and empowering adaptive radiation therapy for lung cancer.

Cone-beam CT, Image-guided radiotherapy, Non-small cell lung cancer, Setup error, Margins.

INTRODUCTION

Achieving local control for lung cancer is technically challenging for several reasons. First, the extent of the disease is significant and often close to several organs at risk, such as the spinal cord, esophagus and heart, thereby limiting coverage dose to the tumor. Lung tissue is another critical organ at risk, with limited tolerance to radiation, but through which beams must pass to reach the tumor (1). Finally, lung tumors are subject to motion induced by breathing (2, 3). High geometric accuracy is particularly important for early stage lung tumors treated stereotactically, where high doses of radiation, from 6 to 20 Gy per fraction, are delivered with few (three to five) fractions (4).

Image-guidance radiotherapy (IGRT) for lung cancer has been performed, using both film and electronic portal imaging devices, using the diaphragm, the carina, or bony structures for image matching (5). Setup errors of a few millimeters have been reported, with maximum deviations ranging up to 22 mm, but online correction strategies were shown to reduce these errors to less than 2 mm (6). The commercial introduction of respiratory-synchronized CT (4DCT) has enabled improved targeting by providing volumetric and motion data at the time of planning (7–9). In turn, kilovoltage cone-beam CT (CBCT) systems mounted on radiation therapy linear accelerator gantries (10) permit the tridimensional verification of the position of the tumor and surrounding organs at risk, relative to the treatment geometry, immediately prior to treatment. Thus, CBCT systems allow online correction of patient setup errors, immediately prior to initiation of radiation therapy.

The IGRT technique was instrumental in the development of stereotactic body radiotherapy (SBRT) techniques applied for the lung, and has made clinicians aware of changes of internal anatomy through the progress of a course of radiation therapy (11–18). IGRT was also applied to locally advanced lung tumors, namely Stage IIIA and IIIB, often with mediastinal involvement (19, 20).

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This article reports our experience with IGRT applied to lung tumors, treated using stereotactic or conventional dose fractionations, building on clinical experience in our center since 2005. Specifically, we report on the geometric accuracy of online, daily CBCT imaging for our lung radiotherapy practice, what frequency of imaging is required to maintain a high level of accuracy, and subsequently derive setup margin requirements for PTV definition. This report is limited to a single iteration of online image-guidance.

METHODS AND MATERIALS

Stereotactic lung image guidance

At Princess Margaret Hospital, CBCT volumetric image-guidance for lung cancer commenced for stage I and II NSCLC tumors treated stereotactically, following the RTOG 0236 protocol. Our imaging technique for lung SBRT patients has been described in detail elsewhere (15, 21). Briefly, stereotactic lung patients are initially setup comfortably and immobilized in an evacuated cushion (VacLok, Civco Medical Solutions, Kalona, IA) and then imaged using fluoroscopy, under free breathing, to assess whether lung tumor motion exceeds 10 mm over a number of respiratory cycles; abdominal compression is applied when this is the case. Subsequently, a respiratory-synchronized planning CT (4DCT; Discovery LS, GE, Waukesha, WI) is acquired for planning; therapists confirm that tumor motion is less than 10 mm on the reconstructed 4DCT images. Images corresponding to the inhale and exhale phases are transferred to the treatment planning system (Pinnacle[3], Phillips, Madison, WI), using the exhale phase as the primary dataset. The treating radiation oncologist defines a gross tumor volume (GTV) on both the inhale and exhale phases, fusing both contours to yield an internal target volume (ITV) accounting for the observed tumor motion. The planning treatment volume (PTV) is then defined by adding a 5-mm margin to the ITV (17, 22). The ITV and PTV contours are transferred, through DICOM RT protocol, to the treatment unit (Synergy and Synergy S accelerators using the XVI software, Elekta Oncology Systems, Crawley, UK).

On the treatment day, the patient is positioned within their cushion and aligned to the room lasers using skin tattoos. A *localization* CBCT (XVI, Elekta Oncology Systems, Crawley, UK) is acquired and registered to the planning 4DCT (exhale phase). Image registration is a two-stage process. First, rigid image registration is performed on a user-defined rectangular volume (i.e., clip box) placed around the spine to get the daily CBCT registered quickly to bony anatomy. Therapists then manually adjust the registration to ensure that the tumor is registered to the ITV defined on the planning 4DCT. If a discrepancy between the localization CBCT and the planning 4DCT exceeds ± 3 mm in any direction, the patient position is corrected by manually translating the couch according to the results of the image registration. Our ± 3-mm threshold was initially established on analysis of the geometric accuracy of out CBCT system (23, 24) and to reflect safety margins used clinically around organs at risk, such as the spinal cord, during planning. Any discrepancy exceeding 5° of rotation is corrected by manually repositioning the patient. After correcting the patient position, a verification CBCT scan confirms the accuracy of the manual correction and measures the residual setup error. Treatment does not commence until therapists assure that the patient position is within our ± 3-mm threshold, sometimes requiring additional iterations of image guidance, until the residual error meets our ± 3 mm tolerance. Therapists also ensure that pertinent organs at risk are away from critical isodose lines prior to initiating therapy; this is achieved by creating contours from isodose levels of interest and importing these contours in the XVI workstation using DICOM-RT import.

Localization and verification images from 19 SBRT lung patients were analyzed according to the terminology defined by van Herk (25), including the group systematic error (M), the standard deviation in this systematic error (Σ), and the standard deviation of the random error (σ). The M statistic is the average of all discrepancies measured for all patients; unless significant biases are present in the equipment or procedures, one expects discrepancies to be equally distributed around the ''zero'' position defined from the planning CT, and M should be close to 0. The Σ statistic is a measure of the patient-to-patient variation in the systematic error, indicating how reproducible setup is, on average. Finally, the σ statistic represents the standard deviation of the random setup uncertainty. For these 19 SBRT lung patients, a total of 114 CBCT scans were analyzed using this methodology; our analysis was restricted to the first iteration of image-guidance; thus, at most, only one couch shift is considered in the calculation of our statistics.

Several ''margin recipes'' have been proposed to define appropriate PTV margins from the M, Σ, and σ statistics (25). In our clinic, the ITV concept is used to explicitly account for tumor motion; while this approach involves more lung than approaches proposed by Hugo *et al*. (19) and van Herk (25), we believe that it is a conservative approach to dose calculation, as the ITV concept ensures that the treatment aperture encloses the tumor using the motion amplitude recorded at CT simulation time. Also, planning on the exhale dataset ensures that the normal lung dose criteria (V20, mean lung dose) result in conservative values since these parameters are expected to decrease as the lung volume expands. Therefore, to estimate a uniform setup margin for lung patient based on our population, we have been applying the general margin recipe from van Herk (25, 26), using

$$\text{Setup margin} = 2.5\,\Sigma + 0.7\,\sigma \tag{1}$$

This margin recipe has been validated for lung cancer (27).

Image guidance for conventional lung protocols: manual couch correction

In conventionally fractionated, locally advanced lung cancer, tumors often involve the mediastinum and therefore they cannot be used directly for image guidance at the present time, given the limited visualization of the entire GTV borders (28). Therefore, daily CBCT datasets for these patients are registered to the spine of the patient, thus mimicking the portal imaging practice. Subsequently, therapists assess the position of the carina on the resulting image registration, and evaluate whether the target seen on the daily CBCT is included within the ITV contour imported on the CBCT workstation; since the CBCT is acquired with the patient breathing freely, the image of the tumor will be blurred because of breathing motion, thus representing a surrogate of the ITV. Similarly to our lung SBRT practice, any rotation exceeding $\pm 5^\circ$ is corrected by lifting the patient off the couch and recommencing the setup.

The CBCT scans from a cohort of 48 patients with locally advanced NSCLC were analyzed, involving 1256 localization and 689 verification CBCT datasets. These patients were selected sequentially to avoid any biases. For this cohort, the number of radiotherapy fractions ranged from 14 to 35, with a median of 30. Similarly to the lung SBRT process, the position of the patient was corrected when discrepancies exceeded ± 3 mm in any direction. The correction was performed by manually displacing the treatment couch according to registration of the localization CBCT to the planning CT; verification scans were subsequently obtained.

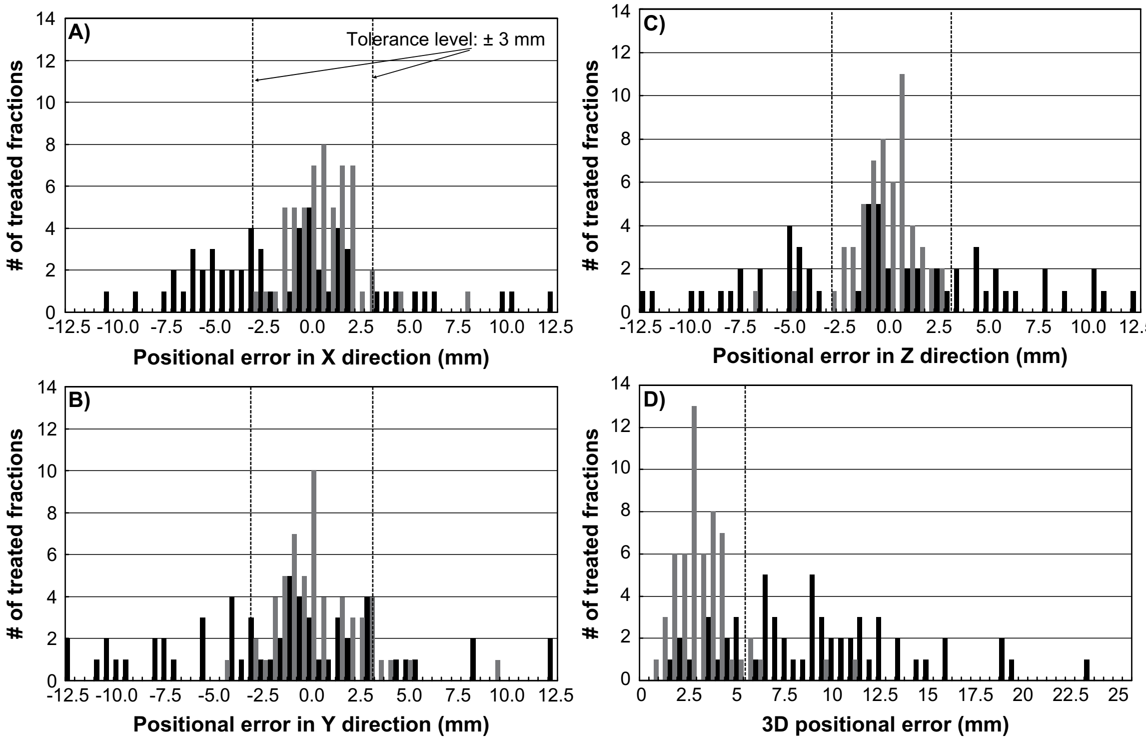


Fig. 1. Difference between the daily localization (black bars) or verification (grey bars) volumetric cone-beam computed tomography (CBCT) scans and the reference planning CT for 19 stereotactic body radiotherapy (SBRT) lung patients. These differences are shown for the mediolateral direction (A), the craniocaudal direction (b), and the anteroposterior (c) directions.<COMP: Please set all alphabetical figure labels lower case in keeping with journal style.> Three-dimensional differences are shown in panel (d). Discrepancies exceeding ±3 mm in any direction were corrected by therapists entering the treatment room and adjusting the couch position manually. A total of 114 volumetric CBCT were analyzed.

Similarly to the SBRT lung cases described above, M, Σ, and σ statistics were derived, allowing only one iteration of image guidance, for this cohort ($n = 48$), and uniform setup margins were calculated.

Image guidance for conventional lung protocols: Remote couch correction

This analysis was performed for a third group of 20 patients treated with conventional radiotherapy for locally advanced NSCLC, after the commissioning of the remote-controlled couch installed on several of our units (29). For this population, a total of 416 localization CBCT and 260 verification CBCT scans were analyzed. All discrepancies were corrected, and not just those exceeding ±3 mm as the remote-controlled couch corrected discrepancies in all three directions, simultaneously. The median number of fractions ranged between 15 and 35, with a median of 31. Similarly to the other two cohorts, the analysis considers only the first iteration of image guidance.

The data for all three groups were acquired under a protocol approved by local research ethics board.

Justifying online image guidance for NSCLC

For each of these groups, the percentage of daily positional discrepancy that was within a tolerance level varying between 1 and 10 mm was determined from the localization and verification CBCT's. These data were further reorganized to identify the proportion of patients who benefit from daily CBCT imaging.

RESULTS

We analyzed volumetric CBCT data for three groups of patients, and report here the accuracy of initial patient setup, from localization CBCT, and residual setup errors after couch correction, from the verification CBCT. For each of the three groups, four distributions of positional setup errors were obtained from localization and verification CBCT scans, in the three directions [X (mediolateral); Y (craniocaudal); Z (anteroposterior)] as well as expressed as a 3D vector. These plots are shown in Fig. 1 for the SBRT lung cases ($n = 19$), Fig. 2 for locally advanced lung cancer patients with position corrected manually ($n = 48$), and Fig. 3 for locally advanced lung cancer patients treated on units equipped with a remote-controlled couch ($n = 20$). In all cases, the distributions obtained from the verification scans are narrower than those obtained from localization scans, often lying within the ±3 mm tolerance level for SBRT patients (82% of all setups) and patients with locally advanced disease (76% with manual couch correction and 82% for remote-controlled couch correction). For a tolerance level of ±5 mm, the compliance level was raised to 95%, 95%, and 98%, respectively.

For all three cohorts, comparison of the statistics obtained from localization and verification CBCT (Table 1) shows that IGRT allows a noticeable reduction of both the group systematic (Σ) and random (σ) positional errors that may lead to a reduction of the margins allowed for setup uncertainties, as calculated from equation 1. A larger reduction of Σ and σ are observed for the patients repositioned using the automatic couch. This may be a result of the shorter time taken to correct patient position, in combination with the remote

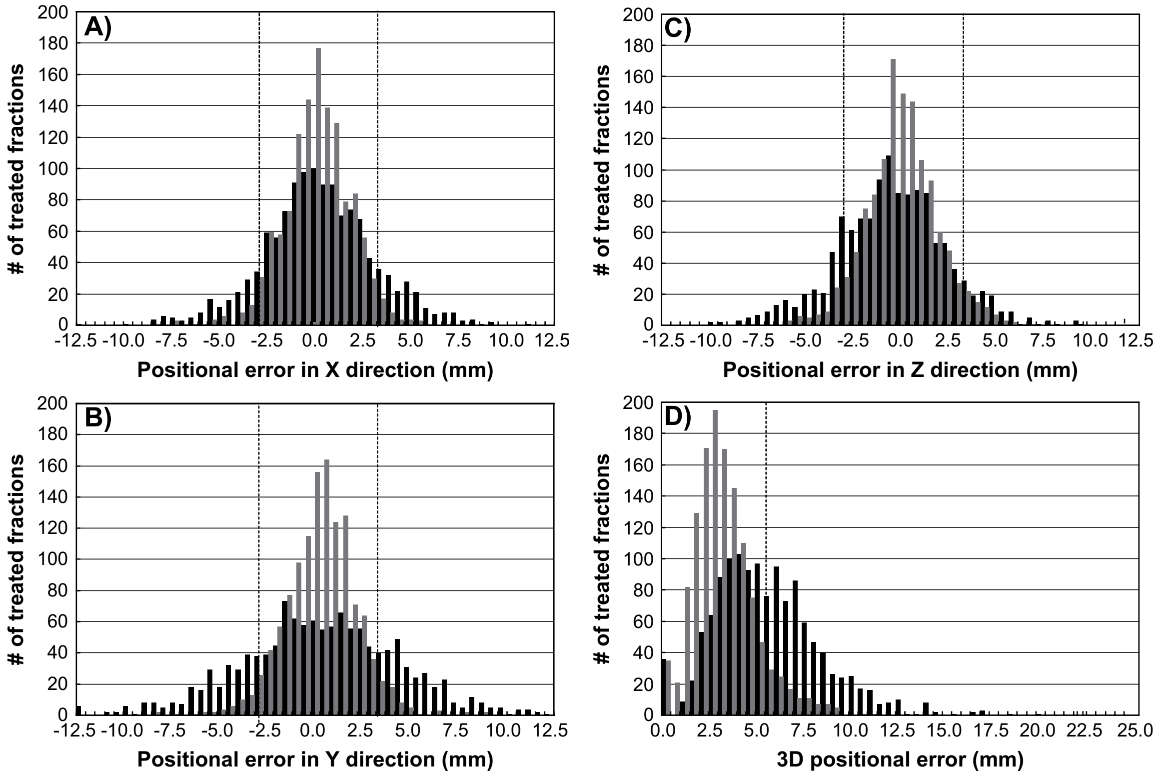


Fig. 2. Difference between the daily localization (black bars) or verification (grey bars) volumetric cone-beam computed tomography (CBCT) scans and the reference planning CT for 25 patients treated for locally advanced lung cancer. These differences are shown for the mediolateral direction (A), the craniocaudal direction (B), and the anteroposterior (C) directions. Three-dimensional differences are shown in panel (D). Discrepancies exceeding ±3 mm in any direction were corrected by therapists entering the treatment room and adjusting the couch position manually. A total of 665 localization and 367 verification CBCT datasets were analyzed.

controlled couch correcting setup discrepancies smaller than the initial clinical tolerance level of ±3 mm. Larger systematic errors are observed for stereotactic lung patients, because of the higher mobility of these tumors, making skin marks a poor surrogate for tumor location.

Figure 4 shows the efficacy of the IGRT procedure, as a function of the tolerated geometric error. Figures 1d and 4a show that, for our SBRT lung protocol requiring high geometric accuracy, patients were setup within our ±3-mm tolerance on only 16% of all fractions; 25% of all fractions had the patient setup more than 10 mm away from the intended position, which would exceed even standard PTV margins. Indeed, 4% of patients always set up initially within ±3-mm, 8% of patients always set up within ±5 mm, and 52% of patients initially set up within ±10 mm. Discrepancies greater than 15 mm were observed in a minority of fractions. Similarly, conventional lung patients set up within the ±3-mm tolerance on 30% of all fractions. Manual couch correction raised this proportion to 76%; using the remote couch further raised this proportion to 84%, a value comparable to that obtained with the 82% obtained with stereotactic lung patients.

Combining the distributions from the localization CBCT scans from the two groups of locally advanced lung cancer patients ($n = 68$), one obtains the plot shown in Fig. 5, where the proportion of patients that were set up within a specified tolerance level varying from ±1 to ±10 mm, in any of the X, Y, and Z directions, is shown as a function of the proportion of treatments where the tolerance level was met. Our volumetric analysis of the localization CBCT scans shows that positional errors occur frequently. None of the patients met our clinical tolerance of ±3 mm, on initial setup, for all treatments. Only 52% of all patients would always initially set up within ±10 mm. Likewise, at a tolerance level of ±5 mm, 21.5% of patients would require a couch correction for, at most, half of their treatment fractions. For the patients with locally advanced lung cancer treated on a unit equipped with a remote-controlled couch, 15 out of 20 patients *always* set up within 5 mm after a single cycle of image-guidance. A tolerance level of ±3 mm is always achievable with the remote-controlled couch at the cost of correcting patient position half the time. Therefore, high geometric accuracy is achievable with little time penalty with a remote-controlled couch.

DISCUSSION

Compared with portal imaging, CBCT images offer high subject contrast, facilitating image interpretation and rendering automatic image matching more reliable. Therefore, in combination with automatic image registration and remote-controlled treatment couch, lung radiotherapy performed

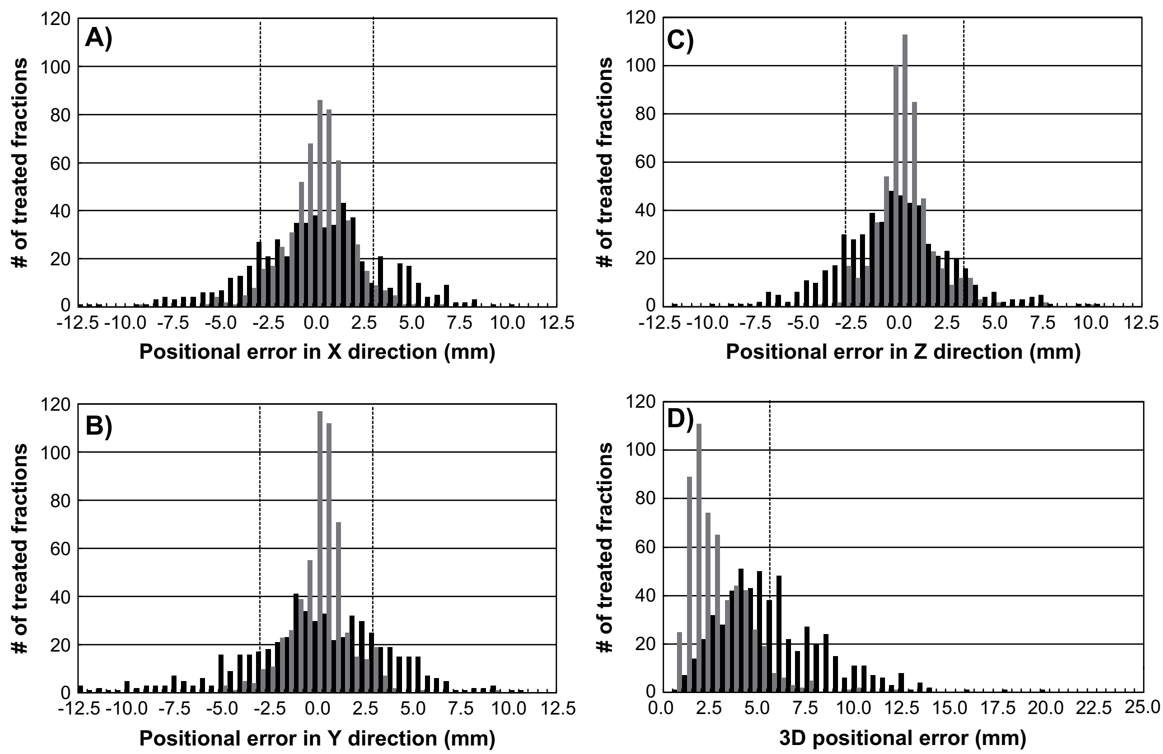


Fig. 3. Difference between the daily localization (black bars) or verification (grey bars) volumetric cone-beam computed tomography (CBCT) scans and the reference planning CT for 20 patients treated for locally advanced lung cancer. These differences are shown for the mediolateral direction (A), the craniocaudal direction (B), and the anteroposterior (C) directions. Three-dimensional differences are shown in panel (D). Discrepancies exceeding ±3 mm in any direction were corrected by adjusting the couch position using a remote-controlled couch. A total of 416 localization and 260 verification CBCT datasets were analyzed.

under CBCT guidance offers opportunities for faster and more accurate positioning (15, 18, 21, 30).

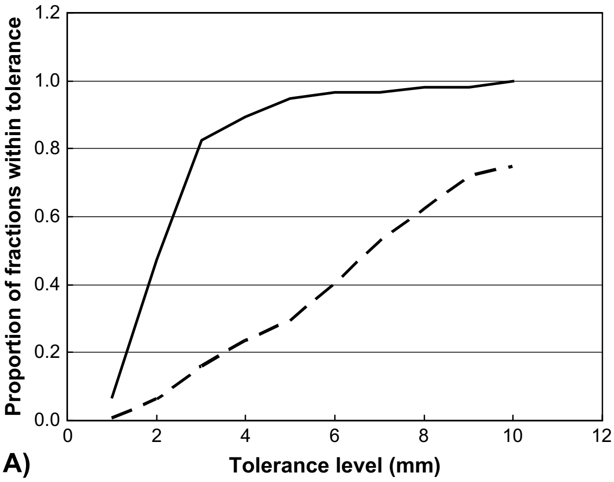
For the data obtained from the verification CBCT scans, a bias is apparent because of our ±3 mm tolerance level; for the SBRT patients, when daily CBCT revealed that the geometry was within tolerance, no correction was made, and no verification scan was acquired to reduce the likelihood of an intrafraction shift (15). When the residual setup error still exceeded ±3 mm in any direction, patients were imaged once more; no patient was treated unless the ±3 mm clinical tolerance was met. Therefore, the results presented in this manuscript reflect the accuracy of a single IGRT iteration since data from patients requiring two or more CBCT are not presented.

Although the Σ and σ statistics extracted from the localization CBCT are comparable to those reported from Grills *et al.* (18) for six SBRT lung patients, our Σ and σ statistics are somewhat larger, reflecting the ±2 mm tolerance level used in that institution. Furthermore, the patient population described in that paper was treated with either four or five

Table 1. Systematic and random positional errors measured for three groups of lung cancer patients

		Localization scan			Verification scan		
		ML (mm)	CC (mm)	AP (mm)	ML (mm)	CC (mm)	AP (mm)
Stereotactic protocol	Σ	4.2	5.3	4.9	1.2	1.9	1.2
	σ	2.4	3.4	3.8	1.6	1.6	1.4
	Margin	12	15	15	4	6	4
Conventional, manual couch correction	Σ	1.9	2.6	1.9	1.0	0.8	1.2
	σ	2.6	3.8	2.3	1.6	1.8	1.5
	Margin	7	9	6	4	3	4
Conventional, remote couch correction	Σ	1.4	2.0	1.4	0.4	0.6	0.7
	σ	3.3	3.8	2.7	1.7	1.4	1.4
	Margin	6	8	6	2	2	3

Margins calculated from these statistics are also shown. Statistics are presented from the localization and verification scans.



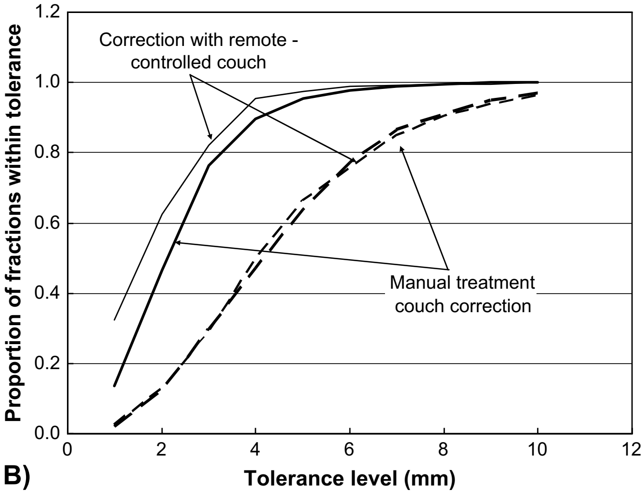


Fig. 4. Efficacy of the image-guidance radiotherapy (IGRT) procedure for stereotactic body radiotherapy (SBRT) (A) and conventional (B) lung radiation therapy, per treatment fraction. Initial (dashed) and residual (solid) positional errors are shown for both treatment techniques. Using a remote-controlled treatment couch further improves accuracy.

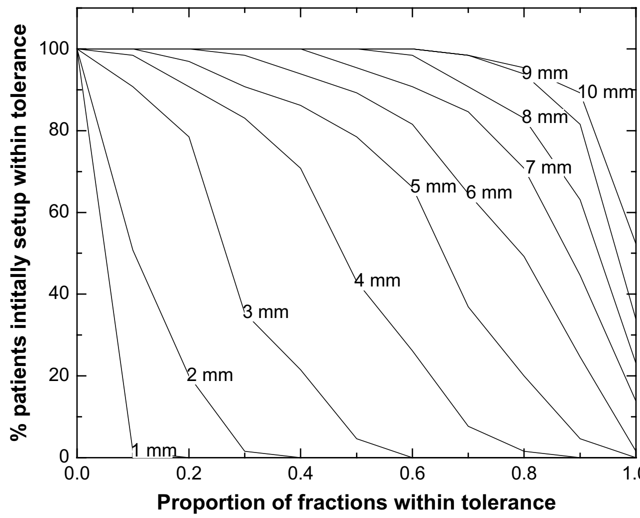


Fig. 5. Initial positional accuracy for conventional lung radiation therapy, per patient, as determined from localization cone-beam computed tomography (CBCT) scans. Initial positional accuracy for conventional lung radiation therapy, per patient, as determined from localization CBCT scans. The graph shows the percentage of patients who were set up within various tolerance levels as a function of the proportion of treatments in which this tolerance was met.

fractions of RT. Based on our statistical analysis, achieving a ±2-mm tolerance for 90% of all fractions would require an additional couch correction on 66% of all fractions. Conversely, achieving a ±3-mm tolerance 90% of the time requires an additional couch correction on 33% of all fractions. These percentages may improve with the introduction of a remote-controlled couch while reducing the overall treatment time.

For the patients with locally advanced NSCLC, our Σ statistics derived from localization CBCT scans are 1.2 to 1.4 mm smaller than those of Borst *et al.* (31) in the X and Y directions, but are similar in the Z direction; the σ statistic, in contrast, is of the same order. However, the Σ and σ statistics derived from verification CBCT scans are systematically smaller than those of Borst *et al.* (31), reflecting the off-line shrinking action level strategy (no correction if the 3D discrepancy was less than ±9 mm/$\sqrt{N}$, where N is the number of consecutive measurements) used to correct for systematic errors. Because our online practice corrects both random and systematic errors, our post-correction statistics are lower, especially in the Y direction, which is associated with the largest Σ and σ statistics defined from the localization scans.

Our data (Figs. 1 and 4a) have shown that, based on localization CBCT, SBRT lung cases often (84.2% of all fractions) setup outside of a ±3-mm tolerance level, and that setup errors larger than 10 mm are common (25.3% of all fractions). Therefore, patient setup based on external landmarks, such as skin tattoos or external markers on a SBRT frame, is likely to result in significant and frequent geometric misses. Fortunately, a single positional correction raised the proportion of fractions within ±3 mm, in any direction, to 82%; a second correction was required in 18% of all fractions achieve this tolerance, affecting 42% of all patients.

Similarly, localization CBCT scans show that conventional lung patients (n = 68) are often subject to geometric discrepancies. Figure 5 shows that none of the patients were always set up within ±5 mm, and that 47.7% of all conventional lung patients encountered a setup error exceeding 10 mm at least once; reaching a confidence interval of 95% for a ±10-mm tolerance, one must adjust at least 20% of all fractions. Traditional patient setup and weekly imaging, using 10 mm PTV margins to account for setup error, do not meet the 95% confidence interval required by the ICRU definition of the PTV. Therefore, initial setup of lung cancer patients using traditional means, using external surrogates such as skin marks, does not guarantee geometric accuracy; our data suggests that geometrical miss occurs frequently, possibly compromising the success of radiation therapy.

Fortunately, daily CBCT can notably improve geometric accuracy for SBRT and conventional lung cancer patients. For SBRT patients, ensuring a geometric accuracy of ±3 mm for all patients required, on average, that setup is corrected on two of three fractions; from our data, all fractions would have required a couch shift to reach a ±2-mm accuracy level. For conventional lung patients, all patients can be set up within ±3 mm at the cost of manual couch correction for at most 80% of their respective fractions. When a remote-controlled couch is used, this cost decreases to 44.5% of all fractions. To achieve always an accuracy level of ±5 mm, these proportions reduce to 53.5% for manual correction, and to 20.9% for the remote-controlled couch. Using a single iteration of IGRT, it is possible to set up all lung cancer patients within ±5 mm of their intended position, 95% of the time. Therefore, a 5-mm setup margin would be achievable for lung cancer RT provided that online image guidance is used.

We have demonstrated that daily IGRT is feasible on a large scale. Using online correction strategies, high geometric accuracy is easily achievable for most lung patients. It remains to be seen if such increases in geometric accuracy, and thus reduction of geographical misses, will eventually improve outcomes and survival. In combination with expected improvements in image quality and the introduction of respiratory-correlated CBCT, IGRT should become a powerful tool to monitor the patient throughout the delivery of a course of radiation therapy, thereby empowering adaptation as changes in tumor volume, centre of mass, and lung tissue density can become detectable.

CONCLUSION

Daily volumetric CBCT image guidance is essential to confirm the high geometric accuracy required for lung radiotherapy; indeed, the vast majority of stereotactic lung patients have required IGRT to ensure a ±3 mm accuracy, and 43.2% of all conventional lung patients will encounter a geometric discrepancy exceeding 10 mm. The IGRT process for stereotactic lung protocols can be easily transported to conventional lung radiotherapy, thereby avoiding geometrical miss of radiation therapy at little cost in terms of time and effort, when using a remote-controlled couch. Reducing both random and systematic positional errors for lung patients may lead to reductions in setup margins used in planning. In turn, such margins reductions may facilitate dose escalation and therefore provide an opportunity for improved local control of lung cancer.

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