Received: 21 September 2017 | Revised: 21 November 2017 | Accepted: 17 January 2018

DOI: 10.1002/pro6.35

ORIGINAL ARTICLE

WILEY

Interfraction movement and clinical outcome of immobilization for thoracic irradiation: A randomized controlled trial

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Funding information
The New South Wales Cancer Council

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Abstract

Objective: To evaluate the impact of immobilization on set-up errors and clinical outcomes in patients receiving radiation therapy to the thorax.

Methods: Patients receiving curative intent radiation therapy to the lung and esophagus were randomized to no immobilization (control) or immobilization (chest jig or vacuum bag), and treatment verification images were acquired within 3 days of commencing treatment and then weekly. The primary outcome was the proportion of patients having a deviation >5 mm from the isocenter. Assessment was carried out blinded to immobilization assignment.

Results: Of the 77 patients, 75 patients were allocated to either immobilization or control. No statistical difference in the proportion of patients with bony displacements >5 mm from the isocenter were observed ($P = 0.5$), as was the case for both systematic and random errors between the groups. There was an increased risk of local failure in the immobilized control group (HR 1.46, 95% CI 0.78–2.71, $P = 0.23$) based on a competing risk analysis. The median overall survival was 18.4 months and 27.0 months in the control and immobilized groups, respectively (HR 0.73, 95% CI 0.51–1.04, $P = 0.08$).

Conclusions: The results failed to show benefit with immobilization in reducing set-up errors, local control, and overall survival.

KEYWORDS

chest, immobilization, radiation therapy, randomized controlled trial, thorax

1 | INTRODUCTION

Reproducibility of patient position is vital in the accurate delivery of radiation therapy. In recent years, with the introduction of stereotactic radiotherapy, patient positioning has become even more important where treatment volumes are minimized to reduce normal tissue toxicity.

The thorax is subject to a number of set-up variations that are related to physiological factors, such as breathing and swallowing, and also set-up factors, which are related to the immobilization or stabilization devices. Patients receiving radiotherapy to the thorax with curative intent are positioned with the arms raised above the head to allow for multifield access. When thoracic immobilization was first introduced into modern radiotherapy practice, several immobilization devices were devised to assist in thoracic irradiation. These included the expanded foam immobilization device, alpha cradle, and polyurethane foam cast, as well as adjustable thoracic immobilization, which includes arm support and T-bar immobilization devices. In the past decade, a whole-body stereotactic frame with abdominal compression has been used in an effort to not only reduce

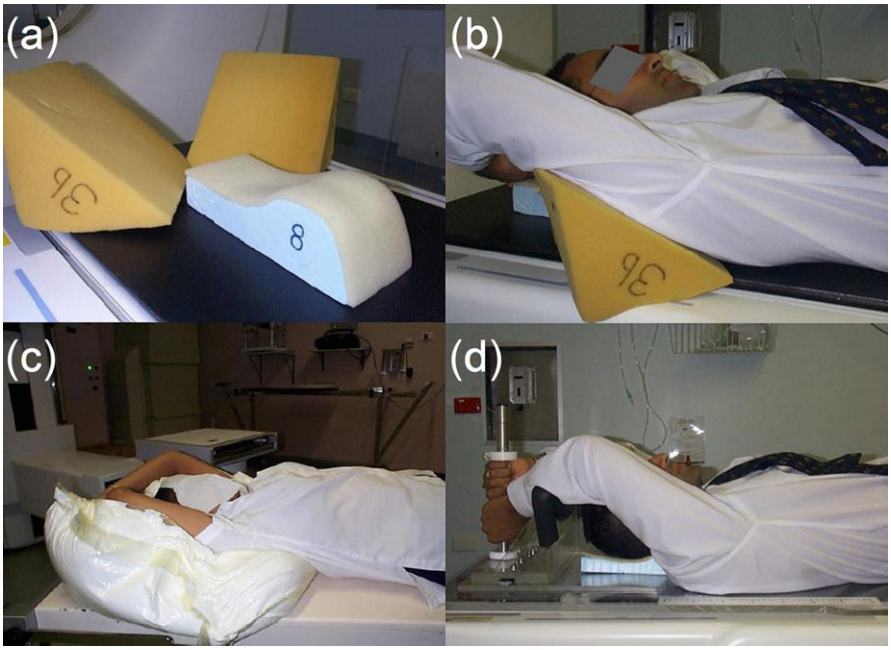

FIGURE 1 Immobilization techniques. (a,b) Control group set-up. Positioning was with right-angled sponges (3B) and a standard headrest (shape 8). (c) Immobilization with vac-bag. In its semi-deflated state, it is molded around the patient's external body contours, as air is drawn out it becomes rigid providing support to the patient. (d) Immobilization with chest jig. The device has adjustable handgrips and adjustable arm support, which can be moved in a left–right direction. There are options of three different headrests fitted.

set-up errors, but also to reduce tumor movement with respiratory motion.

The current literature on thoracic immobilization does not provide a consensus as to effective immobilization methods/techniques. Furthermore, the published studies have methodological limitations, including non-randomized comparisons, small sample sizes, comparisons that do not account for confounding factors (age, weight, disease extent, etc.), poor study conduct (unblinded assessment), and control groups that were not present.

The present study was designed to investigate the benefit of immobilization in reducing the systematic and random errors in the treatment of patients receiving radiation therapy to the thorax. Secondary aims were to examine clinical outcomes of locoregional failure overall survival and toxicity.

2 | METHODS

2.1 | Patient population

Eligible patients were those for whom the primary treatment modality was thoracic radiotherapy with curative intent. This included patients with small cell and non-small cell carcinoma of the lung and esophagus, those aged >18 years, and those who were able to provide written informed consent.

2.2 | Immobilization and stabilization techniques

Patients randomized to immobilization at the Nepean Cancer Care Center (Sydney, NSW, Australia) used a personally contoured device that molds around the chest and arms (vac-bag), whereas patients randomized to immobilization at Crown Princess Mary Cancer Center (Sydney, NSW, Australia) used an adjustable thoracic immobilization device with adjustable head rests, handgrips, and arm support ("chest jig"). Patients in the control arm were positioned using right-angled sponges to support the arms (refer to Figure 1). These positioning devices were the standard of care at these centers during the study period for patients receiving radiotherapy to the thorax.

2.3 | Radiation treatment planning

Treatment was planned between 2001 and 2008 using either a two-dimensional planning system (Radplan^{TM}) or a three-dimensional planning system Pinnacle (Philips Radiation Oncology Systems, Fitchburg, WI, USA) or Eclipse (Varian Medical Systems, Palo Alto, CA, USA). The treatment was prescribed to a radical dose of 45–60 Gy in 5–7 weeks' treatment duration. The planning target volume margin was at the discretion of the treating radiation oncologist, and was 12.5 mm for the lung and 20 mm for the esophagus. A plan is accepted if 95% of the planning target volume is receiving the prescribed dose. To achieve this, 5–7.5-mm margins are placed around the planning target volume to form the field size for the lung and esophagus.

2.4 | Study outcomes and end-points

For each patient, treatment verification images on 1 day or daily for the first 3 days of treatment and weekly were obtained. The treatment radiation therapists reviewed the images during the treatment course to determine whether adjustments were required to the patient/treatment bed if differences between the planned and actual

images deviated by ≥5 mm in any direction. At the completion of treatment, there was a blinded clinical review of the images to determine the extent of patient movement during the treatment course. This review provided the outcome measurements in anterior-posterior (AP), superior-inferior (SI), and left-right (LR) directions. Measurements were taken from a reference point along the vertebrae on the planned image (digitally reconstructed radiograph or simulator film), and compared with the distance on the same point on the treatment image (port film or electronic portal image). The difference between the planned and treatment images were used to calculate the systematic and random errors.[1] The SI and LR deviations were measured on the anterior/posterior image, and the AP deviations were measured on the lateral image for interfraction errors. No intrafraction error was measured.

The primary end-point of the study was the proportion of patients whose overall bony anatomy displacements from the isocenter were >5 mm. Secondary outcomes included total uncertainty in displacement, systematic error, and random error in isocenter displacement, toxicity, progression-free survival, and overall survival.

Skin toxicity was assessed weekly during treatment, and radiation pneumonitis was assessed retrospectively using the Radiation Therapy Oncology Group grading systems.[2] Patients that had a pneumonitis Radiation Therapy Oncology Group grading of ≥3 were recorded. Local failure was defined as patients whose first relapse was in the treatment field or who relapsed both within the treatment field and distally simultaneously. Patients whose first failure was distant or death from other causes were considered as a competing risk.[3]

2.5 | Randomization

Randomization was carried out with a 1:1 allocation using the method of minimization stratified by sex and treating institution. Allocation concealment was maintained by personnel not associated with the study carrying out the randomization.

2.6 | Sample size

Prior experience suggested that with no immobilization, 80% of readings would be expected to be within 5 mm of the planned isocenter. With immobilization, the percentage with deviations >5 mm from the original simulation film could be reduced by 15%, and this was a clinically significant reduction. A sample size of 170 patients would detect a 15% reduction in the displacement rate using immobilization allowing for up to 10% non-compliance.

2.7 | Statistical analysis

All analyses were carried out according to the intention-to-treat principle, and comparisons were carried out using generalized estimating equations. A 5% level was chosen to determine statistical significance, and all comparisons were two-sided. Displacement was measured by calculating the difference of the reference point from the simulator film to the treatment image along the AP, SI, and LR directions. The Euclidean distance in three dimensions was then calculated. Overall survival was described using the Kaplan–Meier method, and comparisons made using the log–rank test and proportional hazards model.[4] Time to locoregional failure was described using the cumulative incidence curves, and comparisons were carried out using the Fine and Gray method.[3]

The Western Sydney Local Health District Human Research Ethics Committee and Wentworth Area Health District Human Research Ethics Committee approved the protocol. Informed consent was obtained from all study participants.

3 | RESULTS

Between 2001 and 2008, 152 patients of the planned 170 patients were randomized, 77 patients to no immobilization and 75 patients to immobilization (Figure 2). Accrual to the study became increasingly difficult, and the trial was stopped after 152 patients were randomized due to emerging technologies (electronic portal imaging device and cone beam computed tomography [CBCT]) and changes in treatment practices (e.g. respiratory gating). The decision to stop accrual to the study was based solely on the ability to recruit, and no outcome results were available. One patient allocated to the control group was treated with an immobilization device. The median follow-up period of the cohort was 75 months.

Patient characteristics are provided in Table 1, which shows a good balance between the groups with respect to age, sex, weight, and Eastern Cooperative Oncology Group performance status.[5]

3.1 | Primary outcome

Table 2 further shows there was no difference in the frequency of isocenter displacement of >5 and >10 mm being observed during the course of treatment.

3.2 | Secondary outcomes

The average systematic error for overall isocenter position was 4.4 mm and 3.4 mm in the control and the immobilized group, respectively (difference 1 mm, 95% CI −0.06–0.25, $P = 0.27$). The average random error was 4.1 mm in the control group and 3.7 mm in the immobilized group (difference 0.4 mm, 95% CI −0.16–0.25, $P = 0.59$; Table 2). Permanent isocenter moves were made in 46.8% of the control group and 22.7% of the immobilized group, which was statistically significant (difference 24.1%, $P < 0.01$). There were no differences in displacements in the SI, LR, or AP direction between groups. The median number of treatment verification images taken per patient was seven (range 1–14).

The present study was carried out over 8 years, and because of the poor prognosis of patients with this disease, many clinical outcomes became available due to the extended accrual period. Thus, we were offered a unique opportunity to assess the impact of a policy of immobilization on clinical outcomes of locoregional control and overall survival in this disease, as well as documenting toxicity. If immobilization allowed more accurate targeting of the disease, then we would expect

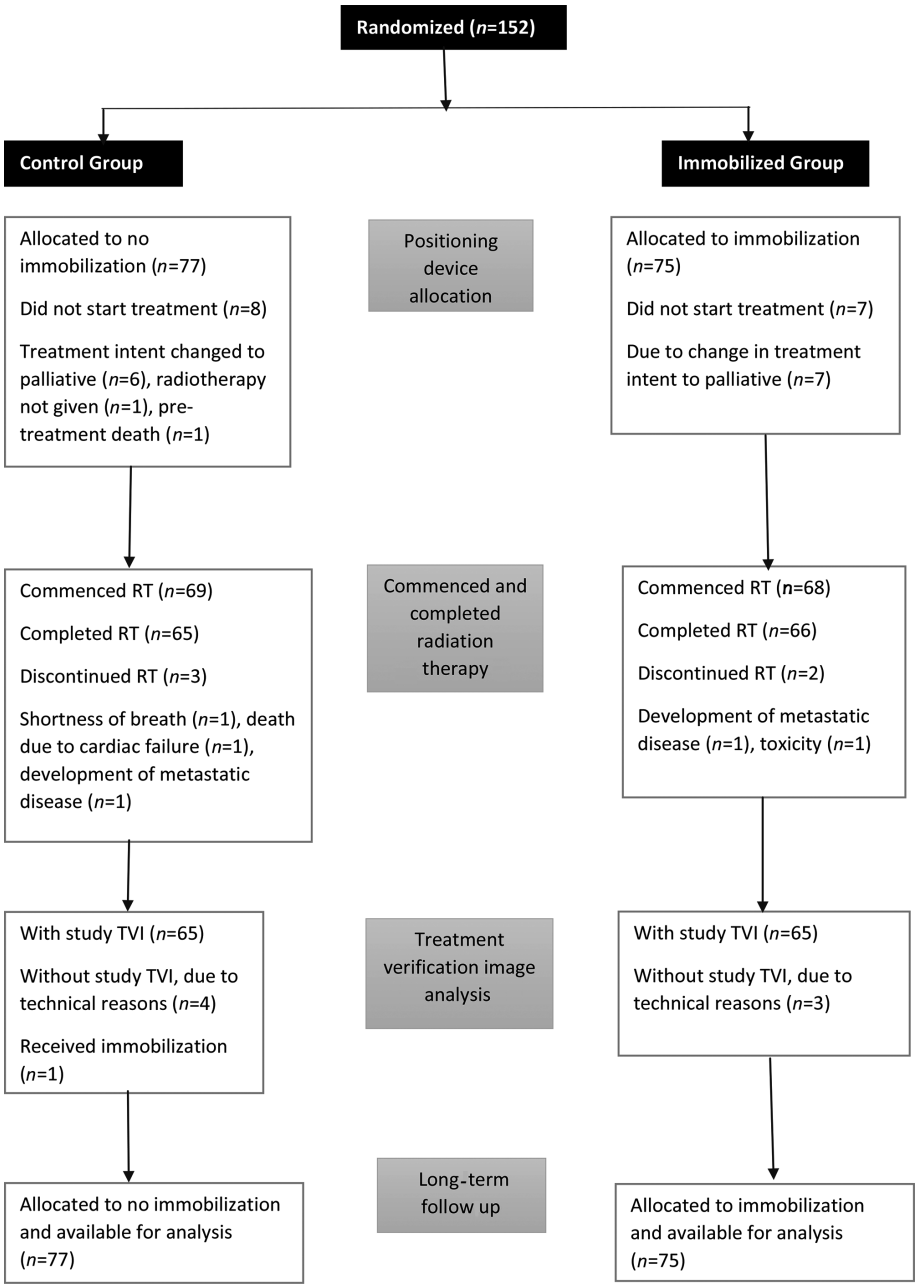

FIGURE 2 CONSORT diagram of patient allocation, follow up and analysis. RT, radiation therapy; TVI, treatment verification image

a reduction in the risk of locoregional recurrence and possibly a lower toxicity profile.

There was a 46% increased incidence of locoregional failure in the group receiving immobilization (HR 1.46, 95% CI 0.78–2.71, $P = 0.23$); however, this was not significant. There was also no significant difference between the two groups in overall survival, median 18.4 months (control) and 27.0 months (immobilized; HR 0.73, 95% CI 0.51–1.04, $P = 0.08$; Figure 3). There was an imbalance in the number of deaths due to other causes between the groups. A total of 14 patients (18%) in the control group and seven patients (9%) in the immobilized group died from non-malignant causes, showing the comorbidities prevalent in this patient cohort; patterns of failure are shown in Table 3.

Grade III skin toxicity was uncommon, occurring in only one patient in the immobilized group and no patients in the control group. Grade III pneumonitis was documented in three patients (4%) of the control group and no patients in the immobilized group.

4 | DISCUSSION

Patients receiving thoracic irradiation with multiple beams must have their arms positioned above their head, so that they are away from the radiation beam. Intuitively, one would expect that rigid or molded immobilizations to support the arms, and better reproduce a patient's position. However, the present study showed that using simple sponges to support the arms is as effective as immobilization devices using a vacuum bag or chest jig. There is no significant benefit in patients receiving immobilization for thoracic irradiation in

TABLE 1 Patient characteristics at baseline

	Control, *n* (%) *n* = 77	Immobilized, *n* (%) *n* = 75
Age (years)		
≤65	39 (51%)	36 (48%)
>65	38 (49%)	39 (52%)
Sex		
Male	49 (64%)	48 (64%)
Primary diagnosis		
Lung	75 (97%)	69 (92%)
Esophagus	2 (3%)	6 (8%)
ECOG performance status		
0	48 (62%)	51 (68%)
1	26 (34%)	19 (25%)
2	2 (3%)	5 (7%)
3	1 (1%)	0
Weight (kg)		
Mean	71 kg	75 kg
Standard Deviation	17.8	14.8
Range	41–163 kg	43–102 kg
Positioning device/ immobilization	Sponges 77 (100%)	Chest jig 60 (80%)
		Vac-bag 15 (20%)
Type of treatment verification images	45 (30%) patients, EPI	
	107 (70%) patients, port films	

ECOG, Eastern Cooperative Oncology Group; EPI, electronic portal images.

TABLE 2 Systematic error, random error mean (SD), and frequency of displacement in the control and immobilized groups

Displacement	Control group	Immobilized group	*P* for difference
Systematic error (mm)	4.4 (3.6)	3.4 (5.1)	0.27
Random error (mm)	4.1 (6.2)	3.7 (5.8)	0.59
>5 mm	65/66 (98%)†	63/65 (97%)†	0.50
>10 mm	34/66 (52%)†	31/65 (48%)†	0.59

†No. patients with displacements/no. patients evaluated (%).

terms of lower systematic or random errors, and improvements in local control or overall survival. Our pre-defined criterion of clinical benefit of 15% was not met; however, we only accrued 152 of the planned 170 patients. Although accrual to such studies is challenging, even if the planned sample size was attained, we would expect the results not to appreciably change and conclusions would remain the same.

At inception, it was estimated that 80% of readings would be within 5 mm of the planned isocenter, which was not the case. The reason for this might be that the estimate was based on retrospective data and there might have been uncaptured events, as this was before weekly imaging protocols were in place. The magnitude of the systematic deviations from the isocenter was consistent with previous studies,[6,7] and this trial also suggests that many non-randomized studies might overstate the effect of immobilization. One of the benefits of immobilization is to reduce the need for permanent isocenter moves.[8] This highlights the need to adhere to robust imaging verification protocols. If images are taken daily and if the action threshold was <5 mm, it is possible that a greater frequency of isocenter movements would be recorded. Hence, by having daily image guidance with low action threshold protocol, one can effectively correct for potential deficiencies in the set-up.[9,10]

Early publications examined the effect of thoracic immobilization compared with unstabilized control groups. In one retrospective review, the alpha cradle immobilization was found to improve reproducibility by 28.5% in the transverse direction and 48% in the superior-inferior direction compared with patients without immobilization; however, this only accounted for an improvement of 1–2 mm.[11] Whereas Bentel *et al*. showed that immobilization with the alpha cradle reduced the frequency of isocenter shifts from 33% to 12% compared with no immobilization.[8] Halperin compared a T-bar device with a vacuum-sealed device and found no difference in isocenter displacement when evaluated with port films.[12] A more modern study utilizing daily CBCT to make a similar comparison comparing a chestboard with an evacuated cushion found that in the absence of image guidance, the chestboard was slightly superior to the evacuated cushion in set-up reproducibility. However, once corrected with image guidance, the positioning error or residual displacements between the groups were similar.[9]

The present study was a pragmatic trial evaluating the standard techniques of immobilizing patients receiving radiotherapy to the thorax during the study period, with the major strength being completeness of the data with both set-up and clinical parameters, and the randomized nature of the study design. This is the first randomized controlled trial that establishes a relationship between patient positioning set-up errors and clinical outcomes of local control and overall survival. However, a major limitation was neither daily treatment image verification nor fluoroscopy nor other more modern three- or four-dimensional imaging techniques to verify tumor movement with bony anatomy and respiration carried out. In the present study, only patient set-up errors could be calculated, and not tumor positioning errors relative to bony anatomy. A second limitation was that rotational errors are difficult to estimate on port films or electronic portal imaging device (EPID) alone. Studies have suggested that set-up errors measured from CBCT scans are larger than those measured by EPID images for lung cancer patients.[10] A secondary outcome of the present study was to examine toxicity, which one might expect to be reduced if immobilization resulted in more accurate tumor targeting. All incidences of radiation pneumonitis occurred in the control group. However, a potential limitation of this study was the modest sample size and the retrospective collection of this toxicity end-point.

Thoracic immobilization remains an important consideration with the implementation of stereotactic body radiotherapy. The use of stereotactic body frames is not only to position the arms and body accurately, but many organizations have used various methods including breath-hold and abdominal compression as a method to minimize tumor motion with respiration. Studies suggest that attempts

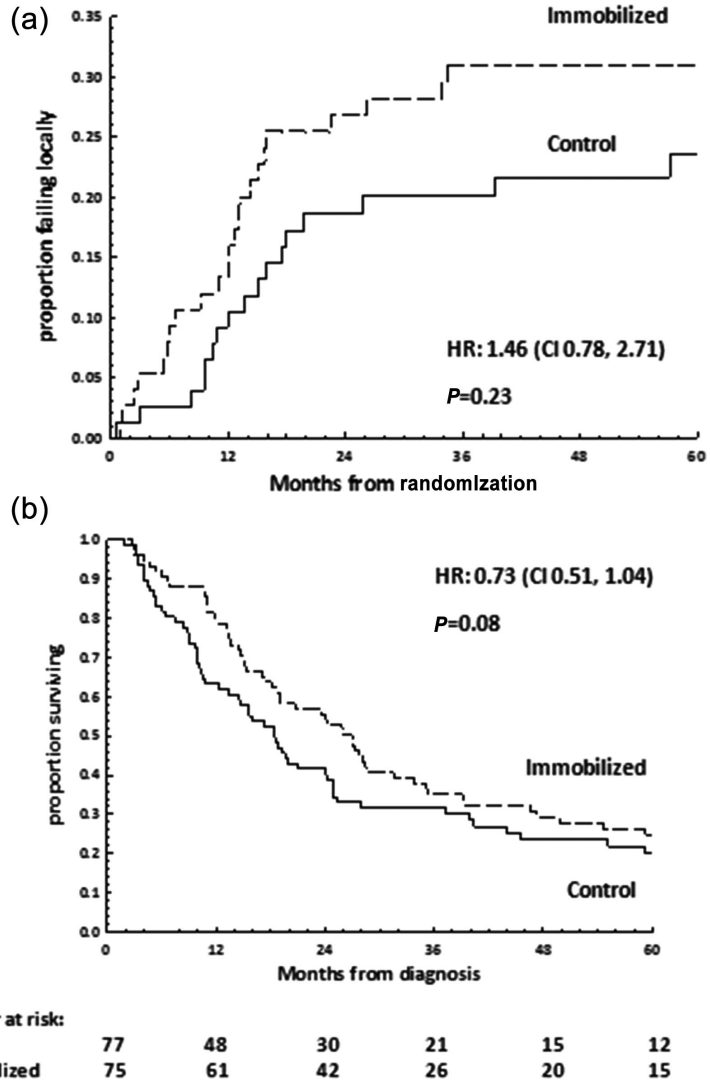

FIGURE 3 Kaplan–Meier analysis. (a) Cumulative incidence: local/regional failure in control and immobilized groups. (b) Overall survival in control and immobilized groups. CI, confidence interval; HR, hazard ratio

TABLE 3 Patterns of first failure and median survival

	Control group, *n* (%)	Immobilized group, *n* (%)
No failure	13 (17%)	16 (21%)
Local/regional	11 (14%)	17 (23%)
Distal	31 (40%)	25 (33%)
Local and distal	6 (8%)	6 (8%)
Death from other causes	14 (18%)	7 (9%)
New primary	2(3%)	4 (5%)
Total	77	75
Median survival	18.4 months	27 months

to reduce tumor movement with respiration might have only modest effects.[13,14] However, the effects of techniques, such as abdominal compression, might be more apparent in tumors of the lower lobe and where respiratory tumor movement is >5 mm.[15,16]

Stereotactic body frames that mobilize the arms and body were reported to show similar set-up errors as our positioning device and other studies that did not utilize stereotactic frames and measured bony anatomy position to detect movement.[10,17] In patients positioned with stereotactic body frames, it was found that 29.4% of the patients had ≥5-mm deviations in one or multiple directions.[18] Thus, regardless of the type of immobilization, image guidance, and assessing the set-up errors daily, before and during treatment is integral to account for interfraction and intrafraction movements, respectively.

The use of immobilization devices would become less important with the use of EPID daily to localize bony anatomy to assess the planned and treatment positions. Using CBCT daily to localize the position of the tumor and the surrounding anatomy puts less emphasis on the use of thoracic immobilization when CBCT images are taken at different times during the delivery of each treatment fraction.[19] In addition, the combination of daily imaging and six degrees of freedom robotic treatment couch enables small treatment position adjustments in all directions before treatment. Thoracic immobilization would also become less important with daily localization with fiducials and photogrammetry patient position systems. These innovations, once refined for easy clinical application, can greatly improve the outcome

of patients' treatment. However, in many centers this is not common practice, as cost and local expertise come into consideration. Furthermore, although these devices might assist in minimizing interfraction movement, there is still a concern regarding intrafraction movement. Thoracic immobilization has undergone an evolution of the past two decades. From no immobilization using sponges to support the arms above the head, to full body casts to immobilize the arms and body with abdominal compression to control breathing. However, the literature shows only modest gains with regard to positioning, hence daily image guidance should be given priority over the method of immobilization.

Despite the differences in treatment technology that was in routine use during the study period compared with current practice, our study remains relevant and can assist in clinical decision-making. The present study did not show a clear benefit of immobilization use. Hence, our study can give confidence to cancer centers that do not utilize expensive thoracic immobilization, but have the latest treatment verification imaging tools, that the clinical outcomes of patients are not being compromised.

To our knowledge this is the only randomized trial investigating both clinical and patient set-up parameters. In our study, where we used bony anatomy and orthogonal verification images to measure patient positioning error, the results failed to show clinical or set-up benefits of immobilizing patients, and no benefit in local control or overall survival.

ACKNOWLEDGMENTS

The New South Wales Cancer Council for their financial support. The University of Sydney's Summer Research Scholarship, which was awarded to Cindy XinXin Hills who assisted with the data entry of this study. We thank the radiation therapists at Nepean and Westmead for their support.

CONFLICT OF INTEREST

The authors declare that they had read the article and there are no competing interests.

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How to cite this article: Pulvirenti T, Agustin C, Tamas M, et al. Interfraction movement and clinical outcome of immobilization for thoracic irradiation: A randomized controlled trial. *Prec Radiat Oncol*. 2018;2:4–10. https://doi.org/10.1002/pro6.35