Breathing guidance in radiation oncology and radiology: a systematic review of patient and healthy volunteer studies

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Purpose: The advent of image-guided radiation therapy (IGRT) has led to dramatic improvements in the accuracy of treatment delivery in radiotherapy. Such advancements have highlighted the deleterious impact tumor motion can have on both image quality and radiation treatment delivery. One approach to reducing tumor motion irregularities is the use of breathing guidance systems during imaging and treatment. These systems aim to facilitate regular respiratory motion which in turn improves image quality and radiation treatment accuracy. A review of such research has yet to be performed; it was therefore our aim to perform a systematic review of breathing guidance interventions within the fields of radiation oncology and radiology.

Methods: From August 1 – 14, 2014 the following online databases were searched: Medline, Embase, PubMed, and Web of Science. Results of these searches were filtered in accordance to a set of eligibility criteria. The search, filtration, and analysis of articles were conducted in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses). Reference lists of included articles, and repeat authors of included articles, were hand-searched.

Results: The systematic search yielded a total of 480 articles, which were filtered down to 27 relevant articles in accordance to the eligibility criteria. These 27 articles detailed the intervention of breathing guidance strategies in controlled studies assessing its impact on such outcomes as breathing regularity, image quality, target coverage, and treatment margins, recruiting either healthy adult volunteers or patients with thoracic or abdominal lesions. In 21/27 studies significant ($p < 0.05$) improvements from the use of breathing guidance were observed.

Conclusions: There is a trend towards the number of breathing guidance studies increasing with time, indicating a growing clinical interest. The results found here indicate that further clinical studies are warranted that quantify the clinical impact of breathing guidance, along with the health technology assessment to determine the advantages and disadvantages of breathing guidance.

I. INTRODUCTION

The advent of image-guided radiation therapy (IGRT) has led to dramatic improvements in the accuracy of treatment delivery in radiotherapy, with the reduction of both random and systematic uncertainties.[1-6] While IGRT has improved the accuracy of radiotherapy by utilizing information about tumor motion and positioning throughout a patient's treatment, it has also shed light on the deleterious impact tumor motion can have on both image quality and radiation treatment delivery.[2, 4, 7-10] Anatomic motion due to breathing in the thoracic and abdominal regions is of great concern due to their proximity to the thoracic diaphragm, where respiratory-induced motion can be up to 5 cm.[11] In addition, heightened patient anxiety levels during imaging and treatment,[12, 13] can result in increasingly irregular breathing, leading to erratic breathing motion of both internal anatomy and the tumor itself.[8, 14, 15]

The widespread utilization of IGRT has led to the investigation of an increasing number of methods to address breathing motion and therefore tumor and organ movement and the resultant uncertainties they cause. A number of image reconstruction methods and tracking systems have been developed to ameliorate these uncertainties.[16-19] However such techniques can be expensive and don't directly manage the problem of irregular breathing motion. Addressing irregular tumor motion directly at the source by managing the patients' breathing has been of increasing interest in recent times, with several breathing guidance techniques being developed from simple buzzer signals to interactive guiding interfaces to facilitate regular and predictable tumor motion.

I.A. Irregular Breathing in Radiation Oncology and Radiology

The deleterious impact of irregular motion during image acquisition has been well documented for across a range of medical imaging modalities.[8, 14, 20-28] During radiation treatment there are two fundamental types of errors: the errors occurring during treatment preparation (systematic) and the errors occurring during treatment delivery (random);[5, 29-31] both these types of errors are exacerbated by irregular breathing-motion.[9, 10, 27]

Systematic errors typically arise from errors in the images used to plan the patient's treatment; *Figure 1* demonstrates the irregular tumor motion and errors present in images due to such irregular breathing-motion.

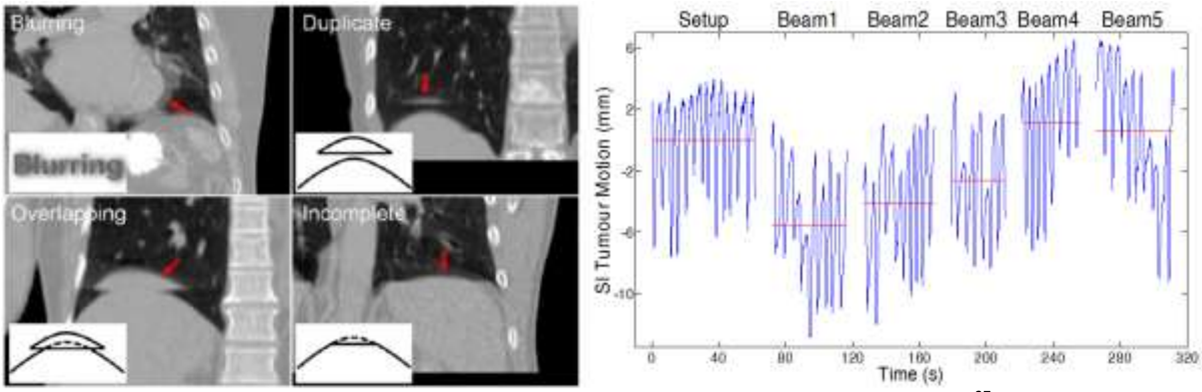


Figure 1. Left: Examples of 4D-CT image artefacts due to irregular breathing (Yamamoto (2008)[27])*. Right: Example of irregular respiratory-induced tumor motion during treatment setup and delivery (Adapted from Worm (2013)[10]) †.

Random errors typically arise from variations in target position throughout the patient's treatment. Irregular breathing leads to larger variations in target position not only during treatment, but between treatments,[9, 10] as shown in *Figure 2*.

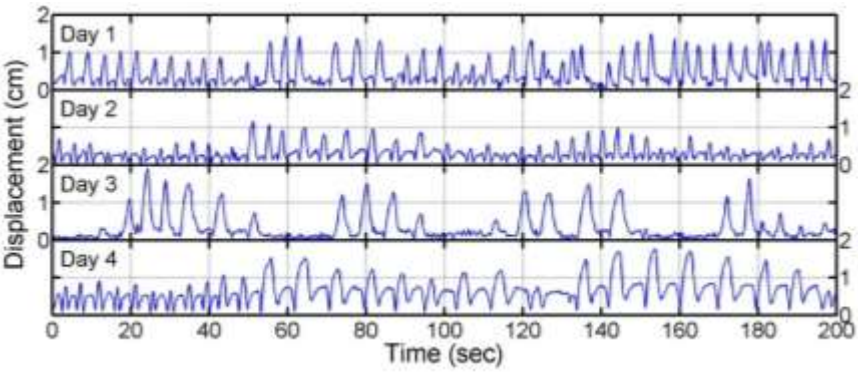


Figure 2. Example of interfraction breathing variations (from Shah (2013)[9]) ‡.

To account for irregular breathing-motions' exacerbation of systematic and random errors, the treatment volume is expanded;[32] increasing radiation dose to the healthy surrounding tissue thus increasing the risk of post-treatment radiation complications such as radiation pneumonitis.[33-39] Such complications occur in over 60% of lung cancer patients after treatment, with 47% developing at least grade 2 pneumonitis requiring clinical intervention.[34] Such clinical interventions involve the prescription of anti-inflammatory pharmaceuticals thereby increasing health-care costs for that patient's course of treatment.[36, 40] To combat the increase of these systematic and random errors a number of strategies directly engaging with the patient have been investigated to minimize the irregularity of patient breathing motion. These breathing guidance strategies have the advantage of being non-invasive, requiring minimal modifications to existing facilities and protocols.

Given the relatively recent widespread interest in such breathing guidance strategies, a review of such research has yet to be performed. It was therefore our aim to perform the first systematic review of breathing guidance intervention strategies within the fields of radiation oncology and radiology.

‡Adapted from Publication the International Journal of Radiation Oncology* Biology* Physics , Vol 86, Issue 3, Shah, *et al*., Title: Real-Time Tumor Tracking in the Lung Using an Electromagnetic Tracking System, Pages No., Copyright (Year), with permission requested from Elsevier

II. METHODS

This systematic review follows the PRISMA-Statement reporting standard (Preferred Reporting Items for Systematic reviews and Meta-Analyses).[41] *Table 1* presents our research questions in the PICOS approach (Patients, Intervention, Comparison, Outcome, Study design); given the relatively recent interest in such breathing guidance strategies, healthy volunteer studies were also considered in addition to patient studies.

Table 1: PICOS approach to the systematic review following the PRISMA statement

P - patients/participants	• Cancer patients with tumors affected by breathing-motion (e.g. thoracic and abdominal tumors) receiving radiotherapy and/or medical imaging. • Healthy volunteers participating as surrogates for the above patient population.
I - intervention	Breathing guidance – technologies which monitor patient breathing and provide feedback to the patient informing them on how to adjust their own breathing in real-time on their own accord.
C - comparison	No breathing guidance of the same breathing type (i.e. non-guided breath-holds for breath hold studies, and free breathing for breathing guidance studies)
O - outcome	Regularity of breathing signal & anatomic/tumor motion, medical image quality, radiation treatment margins & coverage, medical imaging &radiation treatment times
S - study design	Quantitative and controlled prospective or retrospective trials.

Once eligible articles were identified they were filtered in accordance to the selection criteria. The objective of the selection criteria was to acquire scientific articles describing in sufficient detail a breathing guide intervention's utilisation towards some aspect of abdominal or thoracic radiology and radiotherapy application. Articles were extracted by two authors using an electronic (Microsoft Excel 2010) pro forma specifying the identified articles. Where there was disagreement between the reviewers, discussion was undertaken amongst all authors until consensus was reached.

II.A. Selection Criteria

Articles were included if they satisfied the following inclusion criteria:

1) Quantitatively evaluate the intervention of breathing guidance relevant to the practice of either medical imaging or thoracic/abdominal radiotherapy (prospective or retrospective)
2) Participants were human over the age of 18 (retrospective data was from adult human study)
3) Reported in the English language
4) Published in a peer-reviewed journal between the years 1994 – 2014
5) Had a control group for the same breathing type:
    - For guided breathing studies control group performed unguided free breathing
    - For guided breath hold studies control group performed unguided breath-holds

Articles which excluded, even if satisfying the above inclusion criteria, if they:

1) Did not have a control group comparing intervention to no intervention for the same breathing type (free breathing *or* breath hold)
2) Lacked a statement of statistical significance
3) Did not describe, or reference to an article, in sufficient detail of the breathing guidance intervention
4) Was not a scientific paper (e.g. conference abstract, conference proceeding, book, patent)

II.B. Search Strategy

From August 1 – 14, 2014 the following online databases were searched: Medline, Embase, PubMed, and Web of Science. The search for articles initially included the fields of radiation oncology and radiology using the terms: (radiation therapy OR radiotherapy OR imaging). These search results were then refined towards breathing guidance by using the terms: (respiration OR breathing) AND (audio OR visual) AND (guidance OR training OR feedback OR biofeedback).

The findings from the above mentioned databases, in addition to articles identified through hand searching of their reference lists and cross-referencing for previously unidentified articles which met the inclusion criteria. These articles were exported to a citation manager, Endnote X5 where duplicate articles were also removed. The process tree for attaining the search strategies results in shown in *Figure 3*. After duplication and filtering through the selection criteria five articles identified by this hand searching method made it into the final 27 articles.

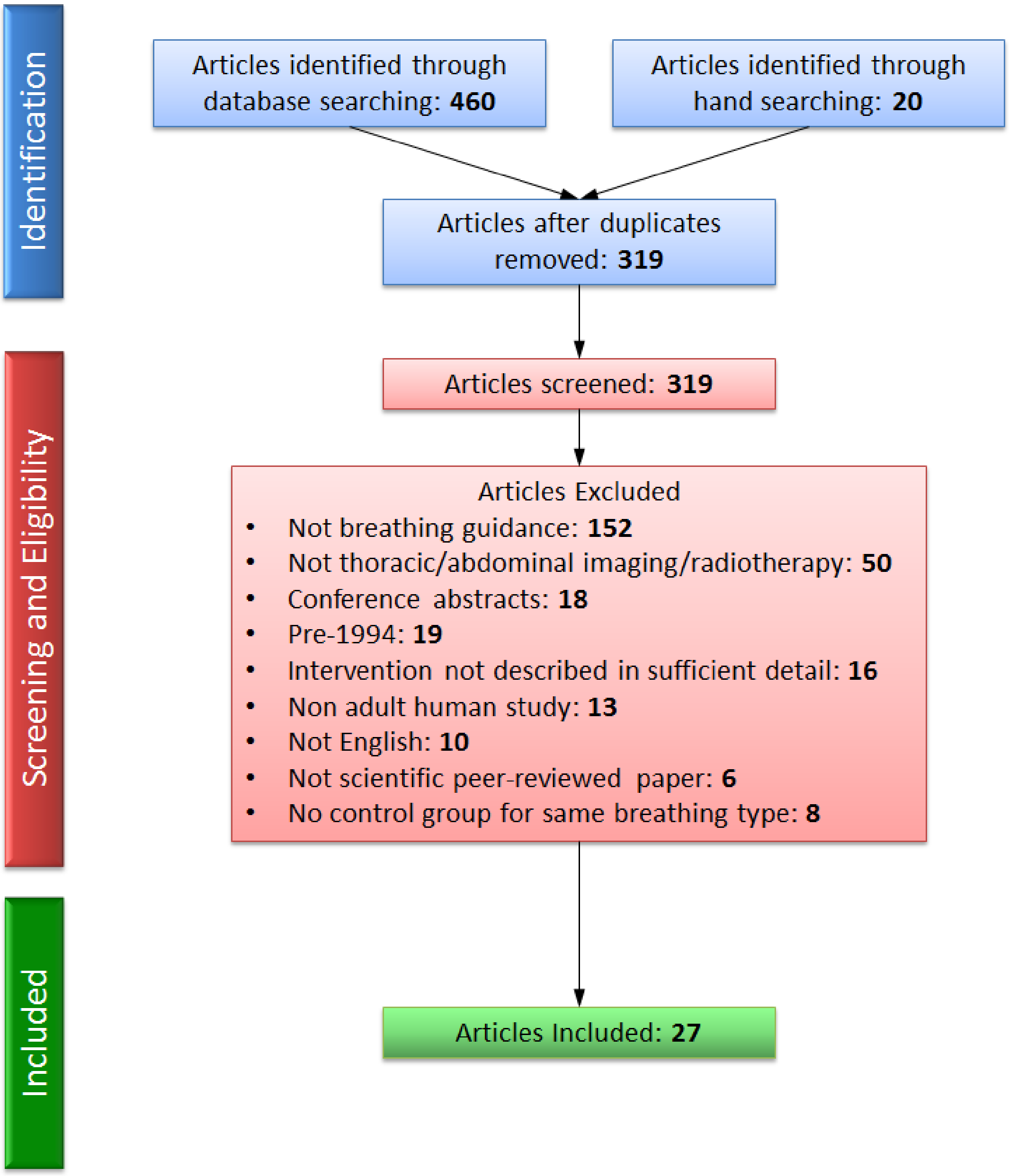


Figure 3. Search Strategy Results. Screening and Eligibility based on inclusion and exclusion criteria.

Information extracted from each included article included: (1) purpose of intervention (breath-holds, regular breathing); (2) study participants (healthy volunteers and/or patients, number recruited, disease type (if patients)); (3) nature of audio prompt (verbal, tones, music); (4) nature of visual prompt (breathing limits, guiding-wave, etc.); (5) imaging performed (if any); (6) treatment performed (if any); (7) main findings of intervention strategy compared to control group; (8) visual display of intervention (if any).

II.C. Analysis of Articles

Due to the diverse applications and results used to determine the efficacy of breathing guidance strategies a meta-analysis was not performed; however the main findings from each of these articles were organised in terms of statistical significance: achieving positive significant results, non-significant results, or negative results.

Quality assessment scoring of the identified and included articles was also performed in accordance with the *Standard Quality Assessment Criteria for Evaluating Primary Research Papers From a Variety of Fields*.[42] Quality Assessment Score is given based on 14 questions about the article, the reviewers award yes (2 points), partial (1 point) and no (0 points) or not applicable (N/A - question not counted in score). Overall a score out of 28 (or less if N/A is chosen) is found and then converted to a percentage. Articles were scored by two authors and when discrepancies arose in the scores allocated a discussion was then undertaken until a consensus was reached.

III. RESULTS

Twenty-seven articles were included as a part of this systematic review as shown in *Figure 3*. After duplication and filtering through the selection criteria four articles identified by this hand searching method made it into the final 27 articles. *Table 2* and *Table 3* detail the development of such strategies over the past 20 years, in addition to the quality assessment score of each article. The average quality assessment score was 79% (range: 54% - 95%). *Figure 4* also illustrates the timeline of these studies.

Table 2(i). Details of radiology breathing guidance studies. *Retrospective analysis.

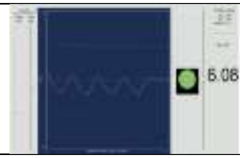
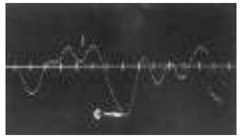
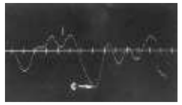
Study author (Year)	Purpose of intervention	Participants	Visual prompt	Audio prompt	Imaging / Treatment	Breathing motion sensor	Quality Assessment Score	Display
Wang[43] (1995)	Breath Holds	11 healthy volunteers	None	Buzzer tone	MRI	Bellows belt	54%	No display used
Locklin[44] (2007)	Breath holds	16 cancer patients	Breathing signal	None	CT	Bellows belt	75%	
Okada[45] (2009)	Regular breathing & Breath holds	13 healthy volunteers	Breathing signal	None	MRI	MRI navigator echo	88%	
Jhooti[46] (2011)	Regular breathing	10 healthy volunteers	Video game-type interface	None	MRI	MRI navigator echo	79%	

Table 2(ii). Metrics and Results of radiology breathing guidance studies. *Retrospective analysis.
$^{\alpha}$ $P < 0.05$ (significant) $^{\beta}$ $P \geq 0.05$ (non-significant)
□ No p-value, but significance stated × No p-value, no statement of significance

Study author (Year)	Metric(s) used	Result(s)	Display
Wang[43] (1995)	Standard deviation of superior-inferior (SI) position of cardiac structures	• Without breathing guidance: standard deviation of right coronary artery SI position was 2.0 mm × • Breathing guidance: standard deviation of right coronary artery SI position was 0.9 mm ×	No display used
	Slice misregistration	• Without breathing guidance: the total number of slices was 35 • Breathing guidance: the total number of slices was 19, much less than no breathing guidance □ • Total number of breath-holds needed reduced by almost a factor of 2 □	

	Improving Image Quality	• With breathing guidance there was less missing cardiac structures [□] • Image quality improved in 6 (of 8) subjects whose image quality was evaluated by a radiologist and a physicist [×]	

Locklin[44] (2007)	Standard error of the mean (SEM) of breath hold position readings	• With breathing guidance:
		  ○ SEM reduced for inspiratory breath holds ($p = 0.0693$) [β]
		  ○ SEM reduced for expiratory breath holds ($p = 0.0083$) [α]
		  ○ SEM reduced for mid-breath breath holds ($p = 0.053$) [β]
			

Okada[45] (2009)	Five point grading system of image quality by assessors	• Worse scores were observed for breathing guidance compared to free breathing ($p < 0.05$) [α]
		  ○ Of the 15 coronary artery segments that were scored, 5 were scored significantly worse for breathing guidance
		  ○ Of the 15 coronary artery segments that were scored, None were scored significantly better for breathing guidance
			

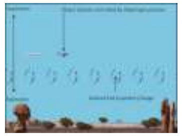
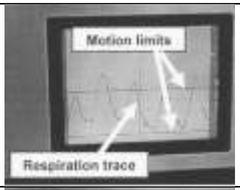
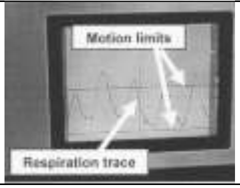
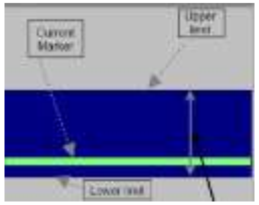
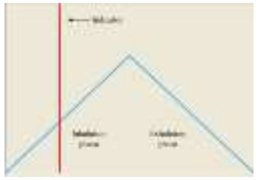
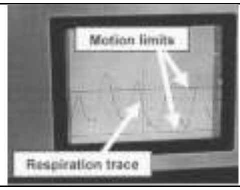
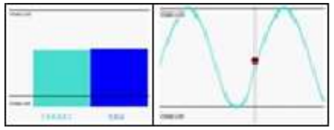
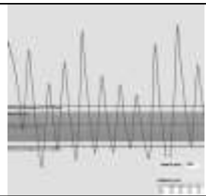
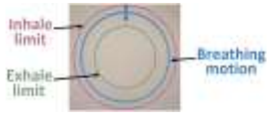
	Scan time	• Free breathing: mean scan time was 10.0 ± 2.2 minutes • Breathing guidance: mean scan time was 10.0 ± 2.5 minutes, no significant difference compared to free breathing [β]	
Jhooti[46] (2011)	Respiratory efficiency (the minimum time required to acquire a full dataset within a 5 mm range of respiratory motion)	• Free breathing: respiratory efficiency was 45% • Breathing guidance: respiratory efficiency was 56%, significantly improved over free breathing ($p = 0.006$) [α]	
	Scan time	• Free breathing: scan time was 7 minutes 44 seconds • Breathing guidance: scan time was 5 minutes 43 seconds, significantly shorter than free breathing ($p = 0.026$) [α]	
	Image quality	• No different in image quality [β]	

Table 3(i). Details of radiation oncology breathing guidance studies. *Retrospective analysis.								
Study author (Year)	**Purpose of intervention**	**Participants**	**Visual prompt**	**Audio prompt**	**Imaging / Treatment**	**Breathing motion sensor**	**Quality Assessment Score**	**Display**
Vedam[47] & Kini[48] (2003)	Regular breathing	5 lung cancer patients	Breathing signal & limits	Verbal commands	Fluoroscopy	Real-time position management system (RPM)	Vedam: 73% Kini: 55%	
Neicu (2006)[49]	Regular breathing	5 healthy volunteers & 33 lung cancer patients	Breathing signal & limits	Verbal commands	4D-CT & treatment simulation	RPM	68%	
George (2006)[50, 51] & An[52] (2013)*	Regular breathing	24 lung cancer patients	Breathing limits	Ascending & descending tones	None	RPM	George (a): 91% George (b): 95% An: 55%	
Chen[53] (2007)	Regular breathing	Phantom & 8 healthy volunteers	Cyclic moving pattern	None	IMRT delivered to phantom	RPM	59%	
Lim[54] (2007)	Regular breathing	10 healthy volunteers	Breathing signal & waveguide	Verbal commands or tones	None	Respiratory monitoring mask with thermocouple	77%	

Vedam[55] (2007)	Regular breathing	90 lung cancer patients	Breathing signal & limits	Verbal commands	CT	RPM	82%	
Haasbeek[56] (2008)	Regular breathing	22 lung cancer patients	None	Verbal commands	4D-CT	RPM	77%	No display used
Persson[57] (2008)	Regular breathing	13 healthy volunteers	None	Verbal commands	None	RPM	91%	No display used
Venkat[58] (2008) & Yang[59] (2012)*	Regular breathing	10 healthy volunteers	Waveguide or bar-model	Ascending & descending tones	Venkat: None Yang: PET	RPM Phantom programmed with RPM motion	Venkat: 77% Yang: 86%	
Linthout[60] (2009)	Regular breathing	25 lung & liver cancer patients	Breathing signal & limits	Verbal commands	Treatment delivery	ExacTrac	82%	
Masselli[61] (2009)	Regular breathing	10 healthy volunteers & 5 lung cancer patients	Breathing limits	None	None	Pneumatic strain gauge	73%	
Nakamura[62] (2009)	Regular breathing	6 lung cancer patients	None	Verbal commands	Fluoroscopy	RPM	91%	No display used

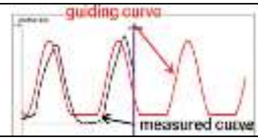
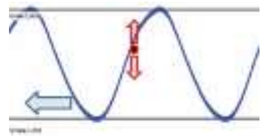
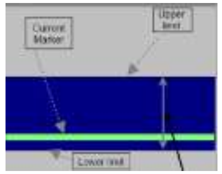
Cerviño[63] (2009)	Deep Inspiration Breath Holds	15 healthy volunteers & 5 breast cancer patients	Breathing signal & limits.	None	None	GateCT-RT	91%	
Park[64] (2011)	Quasi-breath hold	10 healthy volunteers	Breathing signal & waveguide	Verbal commands	Simulated IMRT plan	Infrared-based stereo camera	82%	
Kim,[65] Pollock,[66] & Steel[67] (2012-2014)	Regular breathing	15 healthy volunteers	Waveguide & breathing limits	Music which varies in speed	MRI	RPM (abdominal motion) & MRI (thoracic diaphragm motion)	Kim: 95% Pollock: 86% Steel: 82%	
Damkjær[68] (2013)	Deep Inspiration Breath Holds	24 breast cancer patients	Breathing limits	Verbal commands	CT	RPM	91%	
Lu[69] (2014)	Regular breathing	13 lung & Liver cancer patients	Breathing limits	Ascending & descending tones	4D-CT	RPM & Active Breathing Coordinator	83%	

Table 3(ii). Metrics and Results of radiation oncology breathing guidance studies. *Retrospective analysis.
$^{\alpha}$ P < 0.05 (significant) $^{\beta}$ P ≥ 0.05 (non-significant)
$^{□}$ No p-value, but significance stated $^{\times}$ No p-value, no statement of significance

Study author (Year)	Metric(s) used	Result(s)
Vedam[47] & Kini[48] (2003)	Standard deviation of thoracic diaphragm motion	• Free breathing: standard deviation of 0.36 cm • Audio guidance: standard deviation of 0.71 cm, higher than free breathing $^{\times}$ • Visual guidance: standard deviation of 0.47 cm, comparable to free breathing $^{\times}$
	Measure of ability to predict	• Free breathing: standard deviation of 0.09 cm

	diaphragm motion (standard deviation of relative position between actual and predicted motion traces)	• Audio guidance: standard deviation of 0.09 cm • Visual guidance: standard deviation of 0.11 cm • Breathing guidance comparable to free breathing ×
	Vedam: Relationship between respiratory signal and diaphragm motion	• Strong linear relationship between respiratory signal and diaphragm motion ($p < 0.001$) over all sessions, regardless of the type of breathing guidance or whether it was used at all ($p = 0.19$)
	Kini: Average and standard deviation in breathing period	• Audio breathing guidance: reproducible breathing frequency compared to free breathing × • Visual breathing guidance: further improved reproducibility in breathing frequency compared to free breathing ×
	Kini: Average and standard deviation in breathing range of motion	• Audio guidance: higher variations and magnitude in breathing range of motion compared to free breathing × • Visual guidance: lower variations in breathing range of motion compared to audio guidance □
Neicu (2006)[49]	User acceptance of breathing guidance	• All 5 healthy volunteers were able to follow audio-visual breathing guidance • Of the 33 lung cancer patients: ○ 10 could follow audio-visual breathing guidance ○ 13 could follow only audio breathing guidance ○ 4 were not able to follow breathing guidance ○ 6 had naturally regular breathing, so breathing guidance was deemed unnecessary
	SMART duty cycle	• Lung cancer patients: ○ Free breathing: only 3 patients had duty cycles higher than 60% ○ Audio-visual breathing guidance: most patients had duty cycles around 80% or larger, and all patients had duty cycles higher than 60% × ○ Audio breathing guidance: 5 patients had duty cycles higher than 80%, and higher than 60% for 7 patients ×

	Duty cycles for simulated amplitude gating	• Healthy volunteers: ○ Simulated amplitude gating: ▪ Free breathing: average duty cycle was 32% ▪ Audio-visual breathing guidance: average duty cycle was 36%, an improvement over free breathing [×] ▪ Audio breathing guidance: With the exception of Patients 6, 8, and 11, breathing guidance reduced intra-session variations in period from about 23% to 11% [×] ○ Simulated hybrid amplitude/phase gating: ▪ Free breathing: average duty cycle was 21% ▪ Breathing guidance: average duty cycle was 32%, an improvement over free breathing [×] • Lung cancer patients: ○ Simulated amplitude gating and hybrid amplitude/phase gating: ▪ Audio-visual breathing guidance: 4 patients demonstrated good improvements over free breathing, 1 patient demonstrated worse results with breathing guidance, the rest of the patient demonstrated similar results to free breathing [×] ▪ Audio breathing guidance: 6 patients demonstrated slight improvements over free breathing, 1 patient demonstrated worse results, and the rest of the patient demonstrated similar result to free breathing [×]
	Intra-session breathing amplitude variations	• Healthy volunteers: ○ Breathing guidance reduced intra-session standard deviations in amplitude by a factor of 3 [×] ○ Baseline drift almost entirely removed from the use of breathing guidance [×] • Lung cancer patients: ○ Audio-visual breathing guidance: ▪ Breathing guidance did not have much difference to free breathing for intra-session variations in amplitude [×] ▪ Breathing guidance typically increase breathing amplitude [×]
	Intra-session breathing period variations	• Healthy volunteers: ○ Breathing guidance reduced intra-session standard deviations in period by a factor of 2 [×] • Lung cancer patients: ○ Audio-visual breathing guidance: ▪ Breathing guidance reduced intra-session variations in period by about 12% [×] ▪ Breathing guidance typically increase breathing period [×] ○ Audio breathing guidance:

		▪ With the exception of Patients 6, 8, and 11, breathing guidance reduced intra-session variations in period from about 23% to 11% × ▪ Breathing guidance typically increase breathing period ×
	Intra-session breathing end-of-inhale and end-of-exhale variations	• Healthy volunteers: ○ Breathing guidance reduced standard deviations of the end-of-inhale and end-of-exhale positions, normalized to the average amplitude, by a factor of 2 to 3 × • Lung cancer patients: ○ Audio-visual breathing guidance: ▪ With the exception of Patient 6, breathing guidance reduced standard deviations of end-of-exhale positions by a factor of 2.5 × ▪ Breathing guidance produced mixed results for the standard deviations of end-of-inhale positions ×
	Inter-session breathing variations	• Healthy volunteers: ○ Inter-session standard deviations of amplitude and period for breathing guidance were about 3 times smaller than free breathing ×
George (2006)[50, 51] & An[52] (2013)*	George (a): Residual breathing motion (standard deviation of displacement) within a duty cycle at inhale and exhale for phase-based gating	• Gating at inhale with 40% duty cycle: ○ Free breathing: mean residual motion was 0.47 cm ○ Audio breathing guidance: mean residual motion was 0.47 cm, no significant difference to free breathing × ○ Audio-visual breathing guidance: mean residual motion was 0.36 cm, significantly improved over free breathing and audio guidance □ • Gating at exhale with 40% duty cycle: ○ Free breathing: mean residual motion was 0.32 cm ○ Audio breathing guidance: mean residual motion was 0.31 cm, no significant difference to free breathing × ○ Audio-visual breathing guidance: mean residual motion was 0.27 cm, significantly improved over free breathing and audio guidance □ • Duty cycles of 30% and 50% were also tested and demonstrated similar results

	George (a):
	Residual breathing motion (standard deviation of displacement) within a duty cycle at inhale and exhale for displacement-based gating
		• Gating at inhale with 40% duty cycle:
		  ○ Free breathing: mean residual motion was 0.42 cm
		  ○ Audio breathing guidance: mean residual motion was 0.44 cm, no significant difference to free breathing [×]
		  ○ Audio-visual breathing guidance: mean residual motion was 0.31 cm, significantly improved over free breathing and audio guidance [□]
		• Gating at exhale with 40% duty cycle:
		  ○ Free breathing: mean residual motion was 0.27 cm
		  ○ Audio breathing guidance: mean residual motion was 0.27 cm, no significant difference to free breathing [×]
		  ○ Audio-visual breathing guidance: mean residual motion was 0.21 cm, significantly improved over free breathing and audio guidance [□]
		• Duty cycles of 30% and 50% were also tested and demonstrated similar results

	George (b):
	Relationship between patient, tumour and treatment variables with breathing residual motion
		• Inhale based gating:
		  ○ Correlation between residual motion and visual training displacement ($p < 0.05$) [α]
		  ○ Correlation between residual motion and breathing guidance types ($p < 0.05$) [α]
		• A number of other correlations were investigated, however, they were independent from breathing guidance (e.g. Karnofsky performance status, dose-per-fraction, etc.) and therefore were not included in these results

	An: Breathing reproducibility of internal motion (variation of range of motion in the first session compared to the subsequent 4 session)	• Free breathing: breathing reproducibility of range of motion decreased by 28.5% ± 27.9% • Audio-visual breathing guidance: breathing reproducibility of range of motion improved by 21.4% ± 20.7%, significantly more reproducible than free breathing ($p < 0.05$) [α]
	An: CTV coverage	• Free breathing: CTV coverage decreased by 7.0% • Audio-visual guidance: CTV coverage improved by 20.2%, an improvement over free breathing [×]
Chen[53] (2007)	Mean percent error in breathing	• Free breathing: mean percent error was 21% • Breathing guidance: mean percent error was 1.8%, considerably less than free breathing [×]
	Intrapatient breathing standard deviation	• Intrapatient standard deviations decreased with breathing guidance [□]

Lim[54] (2007)	Standard deviation of breathing amplitudes	• Free breathing: standard deviations of amplitudes was 0.0029 (arbitrary units) • Breathing guidance: standard deviation of amplitudes was 0.00139 (arbitrary unites), significantly improved over free breathing (p = 0.029) [α]
	Standard deviation of breathing periods	• Breathing guidance reduced standard deviation of periods from 0.359 s to 0.202 s (p = 0.002) [α]

Vedam[55] (2007)	Difference between simulated and delivery gate threshold determined by using the mean displacement from within the phase interval	• Gating phase interval of 40%-60%:
		  ○ Free breathing: mean difference was 0.14
		  ○ Breathing guidance: mean difference was 0.08, significantly improved compared to free breathing [α]
		• Gating phase interval of 30%-70%:
		  ○ Free breathing: mean difference was 0.08
		  ○ Breathing guidance: mean difference was 0.04, significantly improved compared to free breathing [α]
		• The above improvements due to breathing guidance had p-values between 0.01 and 0.02

	Difference between simulated and delivery gate threshold determined by using the maximum of average displacements from within the selected phase	• Gating phase interval of 40%-60%:
		  ○ Free breathing: mean difference was 0.18
		  ○ Breathing guidance: mean difference was 0.11, significantly improved compared to free breathing [α]
		• Gating phase interval of 30%-70%:
		  ○ Free breathing: mean difference was 0.17
		  ○ Breathing guidance: mean difference was 0.11, significantly improved compared to free breathing [α]
		• The above improvements due to breathing guidance had p-values between 0.01 and 0.02

Haasbeek[56] (2008)	Lung volume	• End-inspiration lung volume:
		  ○ Audio breathing guidance increased lung volume by 415 mL (10.2%) compared to free breathing (p = 0.001) [α]
		• End-expiration lung volume:
		  ○ Audio breathing guidance increased lung volume by 131 mL (2.9%) compared to free breathing (p = 0.08) [β]
		• Between inspiration and expiration lung volume:
		  ○ Audio breathing guidance increased lung volume by 671 mL (19.2%) compared to free breathing (p < 0.001) [α]

	Displacement of internal target volume (ITV)	• Free breathing: mean displacement of 3D ITV center of mass was 9.2 ± 8.3 (range: 0–27 mm) • Breathing guidance: mean displacement of 3D ITV center of mass was 13.0 ± 12.9 (range, 0–46 mm), significantly larger compared to free breathing (p = 0.008) [α]

Persson[57] (2008)	Breathing amplitude	• Compared to free breathing, more volunteers had larger breathing amplitudes (p values between < 0.0001 and 0.0237): [α]
		  ○ 7 of 12 volunteers (and 6 of 12) had significantly larger amplitude for type 1 (and type 2) audio guidance
		  ○ 2 of 12 (and 2 of 12) volunteers had significantly lower amplitude for type 1 (and type 2) audio guidance

	Standard deviation of breathing amplitude intrafractionally	• No significant difference in the standard deviation of the breathing amplitude distribution between guidance and free breathing [β]
Venkat[58] (2008) & Yang[59] (2012)*	Venkat: Root mean square (RMS) variations in breathing motion displacement	• Free breathing: mean RMS variations in displacement was 0.16 cm • Bar-model breathing guidance: mean RMS variations in displacement was 0.10 cm, 40% more regular than free breathing (p = 0.005) [α] • Wave-model breathing guidance: mean RMS variations in displacement was 0.08 cm, 55% more regular than free breathing, and significantly more regular than bar-model breathing guidance (p = 0.006) [α]
	Venkat: RMS variations in breathing motion period	• Free breathing: mean RMS variations in period was 0.77 s • Bar-model breathing guidance: mean RMS variations in period was 0.33 s, 50% more regular than free breathing (p = 0.002) [α] • Wave-model breathing guidance: mean RMS variations in period was 0.2 s, 75% more regular than free breathing and significantly more regular than bar-model breathing guidance (p = 0.005) [α]
	Yang: Motion blurring (quantified by target size)	• Free breathing: average increase in target diameter was 1.3 ± 2.2 mm • Breathing guidance: average increase in target diameter was 0.6 ± 1.6 mm, a significant improvement in target size compared to free breathing (p < 0.001) [α]
	Yang: Dice coefficient	• Free breathing: average Dice coefficient was 0.88 ± 0.10 • Breathing guidance: average Dice coefficient was 0.90 ± 0.07, a significant improvement compared to free breathing (p < 0.001) [α]
	Yang: Recovery coefficient	• For all targets, breathing guidance had consistently higher recovery coefficients than free breathing [×] • Target size had a greater impact on recovery coefficient values than breathing motion [×] • For the largest target: ○ Free breathing: recovery coefficient was 0.97 ± 0.04

		○ Breathing guidance: recovery coefficient was 1.00 ± 0.04 • For the smallest target: ○ Free breathing: recovery coefficient was 0.36 ± 0.05 ○ Breathing guidance: recovery coefficient was 0.39 ± 0.03
Linthout[60] (2009)	Delivery time of gated treatment	• Free breathing: 1.7 ± 0.6 min/100 MU • Visual breathing guidance: 1.4 ± 0.4 min/100 MU, a non-significant reduction in delivery time compared to free breathing ($p = 0.249$) [β] • Audio-visual breathing guidance: 0.9 ± 0.2 min/100 MU, a significant reduction in delivery time compared to free breathing ($p = 0.004$) [α] and a significant reduction in treatment time compared to visual breathing guidance ($p = 0.008$) [α]
Masselli[61] (2009)	Baseline shift	• Removal of baseline drift [×]
	Average amplitude	• Healthy volunteers: ○ Free breathing: average amplitude was 10 ± 2 mm ○ Breathing guidance: average amplitude was 6 ± 1 mm, lower compared to free breathing [□] • Lung cancer patients: ○ Free breathing: average amplitude was 8 ± 2 mm ○ Breathing guidance: average amplitude was 5 ± 1 mm, lower compared to free breathing [□]
	Variability of breathing amplitude	• No significant difference in standard deviation of amplitude [β]
	Average breathing frequency	• Healthy volunteers: ○ Free breathing: breathing frequency was 17 breaths per minute ○ Breathing guidance: breathing frequency was 37 breaths per minute, more than free breathing [□] • Lung cancer patients: ○ Free breathing: breathing frequency was 15 breaths per minute ○ Breathing guidance: breathing frequency was 45 breaths per minute, more than free breathing [□]
Nakamura[62] (2009)	Mean SI tumor displacement	• Free breathing: mean SI tumor displacement was 10.4 mm • Breathing guidance: mean SI tumor displacement was 23.0 mm, a significant increase compared to free breathing ($p < 0.01$) [α]
	Mismatches between SI lung tumour position and abdominal position	• Free breathing: the average position mismatch was 1.70 mm • Breathing guidance: the average position mismatch was 2.09 mm ○ Compared to free breathing, SI lung tumor position mismatches became larger in 75% of sessions with breathing guidance ($p = 0.01$) [α]

	Correlation between abdominal displacement and lung tumor motion	• Free breathing: correlation coefficients ranged from 0.89 – 0.97 • Breathing guidance: correlation coefficients ranged from 0.93 – 0.99, significantly improved compared to free breathing ($p < 0.01$) [α]
Cerviño[63] (2009)	Reproducibility of breath holds: maximum difference between difference breath hold levels	• Without guidance: average reproducibility was 2.1 mm • Breathing guidance: average reproducibility was 0.5 mm, significantly improved compared to free breathing ($p < 0.001$) [α]
	Stability of breath holds: maximum of the amplitude change between initial and end time points of a breath hold	• Without guidance: average stability was 1.5 mm • Breathing guidance: average stability was 0.7 mm, significantly improved compared to free breathing ($p < 0.01$) [α]
Park[64] (2011)	Simulated treatment time	• Free breathing: average treatment time was 530.4 ± 9.0 s • Quasi-breath hold with 3 second exhale (QBH_3) guidance: average treatment time was 466.8 ± 26.5 s, significantly lower than free breathing ($p < 0.001$) [α] • QBH_5 guidance: average treatment time was 452.3 ± 29.9 s, significantly lower than free breathing ($p < 0.001$) [α] • QBH_7 guidance: average treatment time was 430.8 ± 8.3 s, significantly lower than free breathing ($p < 0.001$) [α]
	Mean absolute error (MAE) between the guiding wave and measured breathing signal	• Free breathing: average MAE was 0.9 ± 0.7 s • QBH_3 guidance: average MAE was 0.8 ± 0.6 s, lower than free breathing ($p = 0.497$) [β] • QBH_5 guidance: average MAE was: 0.7 ± 0.6 s, significantly lower than free breathing ($p = 0.013$) [α] • QBH_7 guidance: average MAE was 0.6 ± 0.7 s, significantly lower than free breathing ($p = 0.021$) [α]
	Mean absolute deviation (MAD) of the measured breathing signal	• Free breathing: average MAD was 0.7 ± 0.7 s • QBH_3 guidance: average MAD was 0.5 ± 0.5 s, motion variations lower than free breathing ($p = 0.144$) [β] • QBH_5 guidance: average MAD was 0.5 ± 0.4 s, motion variations significantly lower than free breathing ($p = 0.006$) [α] • QBH_7 guidance: average MAD was 0.5 ± 0.6 s, motion variations significantly lower than free breathing ($p = 0.029$) [α]
Kim,[65] Pollock,[66]	Kim: Root mean square error	• Abdominal breathing motion: ○ Free breathing: average RMSE in displacement was 1.3 mm

& Steel[67] (2012-2014)	(RMSE) of breathing motion displacement	○ Breathing guidance: average RMSE in displacement was 0.7 mm, 46% more regular than free breathing ($p < 0.0001$) $^{\alpha}$ • Thoracic diaphragm breathing motion: ○ Free breathing: average RMSE in displacement was 2.6 mm ○ Breathing guidance: average RMSE in displacement was 1.6 mm, 38% more regular than free breathing ($p < 0.0001$) $^{\alpha}$
	Kim: RMSE of breathing period	• Abdominal breathing motion: ○ Free breathing: average RMSE in period was 1.6 s ○ Breathing guidance: average RMSE in period was 0.3 s, 81% more regular than free breathing ($p < 0.0001$) $^{\alpha}$ • Thoracic diaphragm breathing motion: ○ Free breathing: average RMSE in period was 1.7 s ○ Breathing guidance: average RMSE in period was 0.3 s, 82% more regular than free breathing ($p < 0.0001$) $^{\alpha}$
	Kim: Spectral power dispersion metric (SPDM) of thoracic diaphragm breathing motion	• Free breathing: average SPDM was 2.1 • Breathing guidance: SPDM was 0.7, 67% more regular than free breathing ($p = 0.005$) $^{\alpha}$
	Kim: Baseline drift of breathing motion	• Abdominal breathing motion: ○ Free breathing: average baseline drift was 0.21 mm/min ○ Breathing guidance: average baseline drift was 0.05 mm/min, 75% more regular than free breathing ($p < 0.0001$) $^{\alpha}$ • Thoracic diaphragm breathing motion: ○ Free breathing: average baseline drift was 1.6 mm/min ○ Breathing guidance: average baseline drift was 0.9 mm/min, 44% more regular than free breathing ($p = 0.012$) $^{\alpha}$
	Kim: Breathing regularity difference from breathing session 1 to breathing session 2	• Abdominal breathing motion: ○ $RMSE_{AV}/RMSE_{FB}$ in displacement: ▪ Breathing session 1: 0.700 ▪ Breathing session 2: 0.509, a larger discrepancy between free breathing and breathing guidance regularity ($p = 0.053$) $^{\beta}$ ○ $RMSE_{AV}/RMSE_{FB}$ in period: ▪ Breathing session 1: 0.386

		▪ Breathing session 2: 0.237, a larger discrepancy between free breathing and breathing guidance regularity (p = 0.093) [β] ○ Baseline drift$_{AV}$/Baseline drift$_{FB}$: ▪ Breathing session 1: 0.904 ▪ Breathing session 2: 1.684, a larger discrepancy between free breathing and breathing guidance regularity (p = 0.230) [β] • Thoracic diaphragm breathing motion: ○ RMSE$_{AV}$/RMSE$_{FB}$ in displacement: ▪ Breathing session 1: 0.875 ▪ Breathing session 2: 0.639, a larger discrepancy between free breathing and breathing guidance regularity (p = 0.170) [β] ○ RMSE$_{AV}$/RMSE$_{FB}$ in period: ▪ Breathing session 1: 0.426 ▪ Breathing session 2: 0.269, a larger discrepancy between free breathing and breathing guidance regularity (p = 0.212) [β] ○ Baseline drift$_{AV}$/Baseline drift$_{FB}$: ▪ Breathing session 1: 1.426 ▪ Breathing session 2: 0.926, a larger discrepancy between free breathing and breathing guidance regularity (p = 0.212) [β]
	Pollock: RMSE between breathing signal and predicted breathing position	• Abdominal breathing motion: ○ Free breathing: average RMSE was 1.4 ± 1.0 mm ○ Breathing guidance: average RMSE was 1.0 ± 0.8 mm, 26% more accurate than free breathing (p < 0.001) [α] • Thoracic diaphragm breathing motion: ○ Free breathing: average RMSE was 2.8 ± 2.1 mm ○ Breathing guidance: average RMSE was 2.0 ± 1.4 mm, 29% more accurate than free breathing (p < 0.001) [α]
	Steel: Correlation between abdominal and thoracic diaphragm breathing motion	• Free breathing: average correlation was 0.96 ± 0.02 • Breathing guidance: average correlation was 0.96 ± 0.03, no significant difference to free breathing (p = 0.88) [β]
	Steel: Correlation between RMSE in	• Free breathing: minimal correlation between RMSE values and motion correlation values (R = 0.079) • Breathing guidance: minimal correlation between RMSE values and motion correlation values (R = −0.33)

	displacement and abdomen-diaphragm correlation	
	Steel: Correlation between SPDM and abdomen-diaphragm correlation	• Free breathing: weak correlation between SPDM values and motion correlation values ($R = -0.0633$) • Breathing guidance: weak correlation between SPDM values and motion correlation values ($R = -0.0471$)
Damkjær[68] (2013)	Mean inspiration level	• Unguided: mean inspiration level was 16.6 ± 1.66 mm • Guided breath holds: mean inspiration level was 20.5 ± 0.38 mm, a significant increase compared to unguided ($p < 0.002$) $^{\alpha}$
	Mean dose to CTV ($D_{mean, CTV}$)	• Unguided: mean $D_{mean, CTV}$ was 50.1 Gy • Guided breath holds: mean $D_{mean, CTV}$ was 50.0 Gy, a non-significant difference compared to unguided ($p > 0.05$) $^{\beta}$
	Relative volume receiving more than 95% of the prescribed dose ($V_{95\%, CTV}$)	• Unguided: mean $V_{95\%, CTV}$ was 93.9% • Guided breath holds: mean $V_{95\%, CTV}$ was 92.6%, a non-significant difference compared to unguided ($p > 0.05$) $^{\beta}$
	If internal mammary nodes (IMN) were included in the target volume, relative volume receiving 90% of the prescribed dose ($V_{90\%, IMN}$)	• IMN included in target area for 19 of 24 patients • Unguided: mean $V_{90\%, IMN}$ was 70.6% • Guided breath holds: mean $V_{90\%, IMN}$ was 76.1%, a non-significant difference compared to unguided ($p > 0.05$) $^{\beta}$
	Volume receiving more than 107% of the prescribed dose ($V_{107\%, body}$)	• Unguided: mean $V_{107\%, body}$ was 7.3 cm^3 • Guided breath holds: mean $V_{107\%, body}$ was 7.3 cm^3, a non-significant difference compared unguided ($p > 0.05$) $^{\beta}$
	Absolute volume of the left lung ($V_{left\ lung}$)	• Unguided: mean $V_{left\ lung}$ was 1982 cm^3 • Guided breath holds: mean $V_{left\ lung}$ was 2286 cm^3, 11% larger than unguided ($p < 0.0004$) $^{\alpha}$
	Relative volume of the lung receiving 20 Gy or more ($V_{20\ Gy, left\ lung}$)	• Unguided: mean $V_{20\ Gy, left\ lung}$ was 29.6% • Guided breath holds: mean $V_{20\ Gy, left\ lung}$ was 27.1%, a 9% decrease in lung dose compared to unguided ($p < 0.002$) $^{\alpha}$
	Maximum dose to the left anterior descending coronary artery (LAD) ($D_{max, LAD}$)	• Unguided: mean $D_{max, LAD}$ was 16.1 Gy • Guided breath holds: mean $D_{max, LAD}$ was 16.1 Gy, a non-significant difference compared to unguided ($p > 0.05$) $^{\beta}$
	Mean dose to the heart	• Unguided: mean $D_{mean, heart}$ was 2.41 Gy

	($D_{mean, heart}$)	• Guided breath holds: mean $D_{mean, heart}$ was 2.49 Gy, a non-significant difference compared to unguided ($p > 0.05$) $^{\beta}$
	Volume of heart receiving more than 25 Gy ($V_{25 Gy, heart}$)	• Unguided: mean $V_{25 Gy, heart}$ was 0.8% • Guided breath holds: mean $V_{25 Gy, heart}$ was 0.7%, a non-significant difference compared to unguided ($p > 0.05$) $^{\beta}$
Lu[69] (2014)	Volume ratio between two methods of internal target volumes (ITV) generation: ITV_{10} and ITV_{MIP}	• Free breathing: ITV_{10}/ITV_{MIP} was 1.19 • Breathing guidance with RPM: ITV_{10}/ITV_{MIP} was 1.21 • Breathing guidance with ABC: ITV_{10}/ITV_{MIP} was 1.19 • No significant impact of breathing guidance ($p > 0.05$) $^{\beta}$
	Centroid difference between ITV_{10} and ITV_{MIP}	• Free breathing: centroid difference between ITV_{10} and ITV_{MIP} was 1.9 mm • Breathing guidance with RPM: centroid difference between ITV_{10} and ITV_{MIP} was 1.7 mm • Breathing guidance with ABC: centroid difference between ITV_{10} and ITV_{MIP} was 2.3 mm • No significant impact of breathing guidance ($p > 0.05$) $^{\beta}$
	Overlap between ITV_{10} and ITV_{MIP} quantified by Dice coefficient	• Free breathing: Dice coefficient was 0.87 • Breathing guidance with RPM: Dice coefficient was 0.88 • Breathing guidance with ABC: Dice coefficient was 0.86 • No significant impact of breathing guidance ($p > 0.05$) $^{\beta}$
	Root mean square (RMS) difference between surfaces of ITV_{10} and ITV_{MIP}	• Free breathing: RMS distance was 2.7 mm • Breathing guidance with RPM: RMS distance was 2.6 mm • Breathing guidance with ABC: RMS distance was 3.0 mm • No significant impact of breathing guidance ($p > 0.05$) $^{\beta}$
	Correlation coefficient between the best cosine fit and the original breathing signal	• Free breathing: correlation coefficient was 0.66 • Breathing guidance with RPM: correlation coefficient was 0.72, a non-significant difference compared to free breathing $^{\beta}$ • Breathing guidance with ABC: correlation coefficient was 0.77, significantly more regular than free breathing ($p < 0.05$) $^{\alpha}$
	Power dominant frequency (PDF) of breathing signal	• Free breathing: the PDF was 0.04 • Breathing guidance with RPM: the PDF was 0.08, significantly more regular than free breathing ($p < 0.05$) $^{\alpha}$ • Breathing guidance with ABC: the PDF was 0.08, significantly more regular than free breathing ($p < 0.05$) $^{\alpha}$

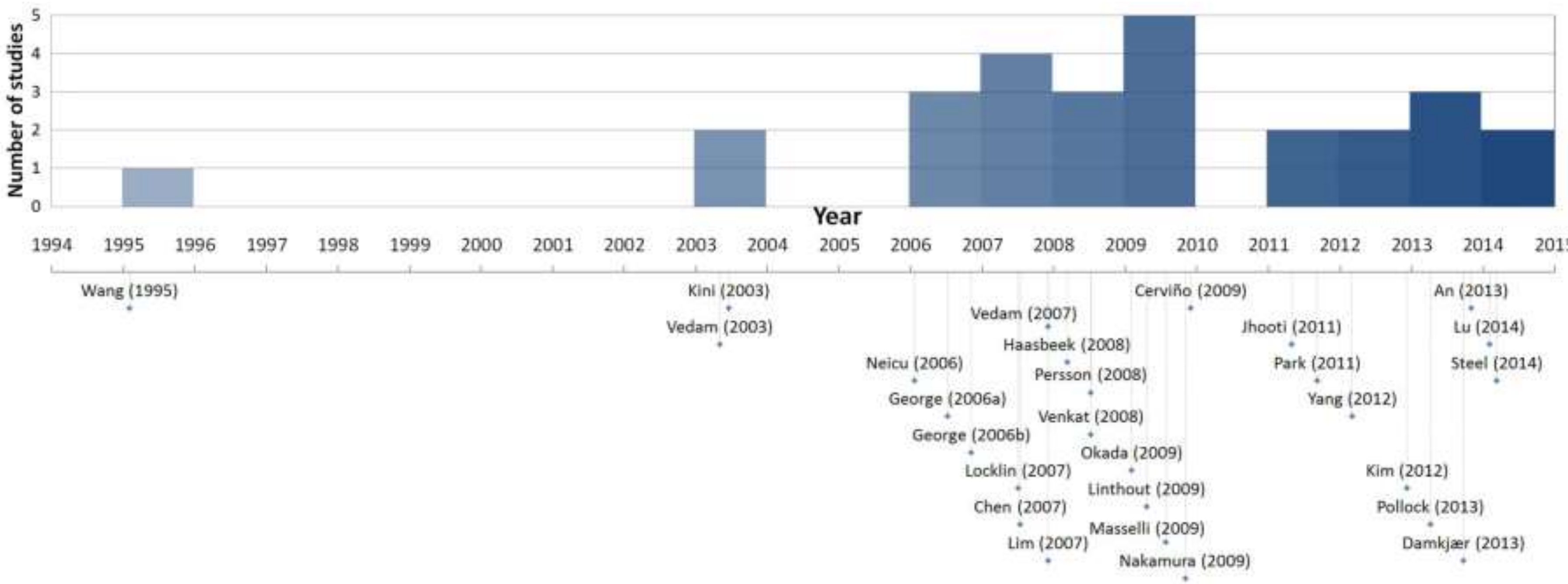


Figure 4. Timeline of the number of breathing guidance studies (top) and the study publications (bottom) from 1995 – 2014, detailed above in *Tables 2* and *Table 3*.

Table 4 is an assembly of these 27 articles' findings and whether their results were significantly positive, negative, or non-significant. It should be noted that the number of outcomes exceeds the number of identified articles because most articles investigated more than one outcome.

Table 4. Number of study outcomes investigated and their statistical significance (references in brackets)

	Positive Results	Non-Significant Results $^{\Delta}$	Negative Results
Breathing Regularity & Tumor Motion	27 / 60 (48, 52-54, 58, 61, 64, 65, 69)	28 / 60 (48, 49, 53, 56, 57, 61, 64, 65, 69)	5 / 60 (56, 57, 62)
Breath hold stability & reproducibility	3 / 6 (44, 63, 68)	3 / 6 (43, 44)	
Gating efficiency	17 / 42 (46, 50, 55)	25 / 42 (47, 49, 50)	
Image Quality	3 / 7 (43, 59)	3 / 7 (43, 46, 59)	1 / 7 (45)
Reduced Margins		8 / 8 (69)	
Reduced dose to healthy tissue	2 / 6 (68)	4 / 6 (68)	
Improved target coverage		4 / 4 (52, 68)	
Reduced Treatment / Imaging time	6 / 8 (43, 46, 60, 64)	2 / 8 (45, 60)	
Other*	5 / 11 (51, 62, 66)	5 / 11 (47, 67)	1 / 11 (62)
Total	63	82	7

$^{\Delta}$ Or significance of results not stated

* Motion correlation, motion prediction, correlation with disease type

IV. DISCUSSION

Findings from the 27 identified articles yielded a diverse range of breathing guidance intervention strategies being utilized on a range of different cancer types. Breathing guidance strategies ranged from buzzer signals to customized, interactive guides. Of the 27 included articles in this systematic review, 21 yielded at least one statistically significant positive outcome from the use of breathing guidance, with a further 2 articles reporting non-significant improvements (or not reporting the significance of improvements) from the use of breathing guidance, and 4 articles reporting at least one statistically significant negative result. Of the 4 studies that yielded negative results, 3 investigated audio-only guidance, which resulted in larger breathing motion amplitudes, an undesirable trait in most radiation oncology and radiology procedures.[22, 62, 70-75] Of the findings assembled in *Table 4*, 63 were positive statistically significant, 82 were non-significant (or significance not reported), and 7 were negative statistically significant. It should be noted that of the 82 non-significant (or significance not reported) results, 35 noted improvements from the use of breathing guidance, 12 of which were reported to be non-significant, and 23 did not report the significance.

Of the 27 identified articles 12 were healthy volunteer studies and 12 were patient studies, with 3 studies recruiting both healthy volunteers and patients; the most investigated cancer type was lung cancer (12 studies), followed by breast (2 studies) and liver cancer (2 studies). Of the breathing guidance intervention strategies, most were designed to facilitate regular breathing (21 articles); 4 articles detailed breath-hold guidance, 1 study investigated both regular breathing and breath-hold guidance, and 1 study investigated quasi-breath-hold breathing guidance where each exhale was extended to 3, 5, or 7 seconds. Medical imaging was performed in 15 studies, and radiation treatment was performed (or simulated) in 4 studies. Given these numbers, and as evident from *Table 4*, there are areas of breathing guidance which require more investigation. For example, research into the impact of breathing guidance on radiation treatment margins and target coverage is limited and largely inconclusive, with all results thus far being non-significant. Further investigation into this area would be valuable as such findings would also give insight to the impact of breathing guidance strategies on patient outcomes. Further to this, of the 27 identified articles, none were randomized studies, indicating that future study designs should incorporate randomization.

20 of the 27 identified articles did not explicitly control for confounding, however the authors of this review paper did not consider this to bias their results. Of the 27 articles, none declared any conflicts of interest; however two articles acknowledged at least partial funding from either Phillips (Lu *et al*. (2014)) or VisionRT (Cerviño *et al*. (2009)), and two articles acknowledged research agreements with either Varian Medical Systems (Persson *et al*. (2008)) or Phillips Medical Systems (Locklin *et al*. (2009)). However, these articles received positive quality assessment scores, as such, the authors of this review paper did not consider the results presented in these articles to be biased.

IV.A. Breathing Guidance for Breath-Holds

Breath-holds are a well-documented and frequently utilized strategy for minimizing anatomic motion during imaging and treatment.[43, 63, 68, 76-84] To further improve the efficacy and reproducibility of breath-holds, measures have been taken to provide guidance to the patient to maintain breath-hold stability.[43, 44, 68, 85] Wang (1995) utilised a buzzer signal to prompt patients to perform their breath-hold; such simple additions in this MR imaging study resulted in improved consistency of breath-holds resulting in achieving their goal of improving image quality.[43] Locklin (2007) investigated a more-comprehensive guidance system by showing the patient their own breathing signal as well as the intended breath hold level.[44] These studies also resulted in improved image quality and intra-fraction motion management.

Breathing guidance has also been developed for deep-inspiration breath holds (DIBH).[63, 68] DIBH is often performed by the patient in left breast cancer radiotherapy to minimize the radiation damage to the lung and heart.[79, 80, 82, 86 83] Given the increased difficulty in achieving deep-inspiration and maintaining it for the adequate duration of imaging and treatment, DIBH an attractive technique to implement with a breathing-guidance strategy. The use of breathing guidance for DIBH improved the consistency of breath holds as demonstrated by Cerviño (2009), leading to an increased sparing of organs at risk in breast radiation therapy, as demonstrated by Damkjær (2013).[63, 68]

IV.B. Breathing Guidance for Regular Breathing

While breath-holds have positively impacted imaging and radiotherapy, they can be taxing on the patient who often has compromised respiratory function, and are typically not feasible beyond 20 seconds. As such, techniques to dynamically control breathing during imaging and treatment have been developed to, rather than immobilize the tumor, minimize the irregular motion of the tumor, which would otherwise compromise the accuracy of radiation targeting,[7, 8, 14, 22, 87] and image quality.[8, 14, 21, 22, 24-27]

Prompts used to guide patient towards regular breathing have undergone considerable development and refinement over the years as detailed in *Table 2* and *Table 3*. Audio-only guidance typically appeared in the form of verbal instructions or tones,[50-52, 56, 57, 62] and while the regularity of breathing was improved, it also increased the amplitude of breathing-motion.[48, 56, 57, 62] Increased tumor motion, even if it's regular, is undesirable in a patient's treatment planning and delivery.[22, 62, 70-75] Visual guidance has garnered positive results not only over free breathing,[44, 63] but also over audio-only guidance.[47, 48, 50, 62, 68, 81] However, utilizing both audio and visual guiding prompts together has yielded the most significant improvements over free breathing.[47, 48, 50-52, 58, 60, 64-66, 69] Both audio and visual guiding prompts have led to significant improvements over audio-only and visual-only guidance as well.[50, 60] On top of this, as noted by Venkat (2008), utilising audio and visual prompts together poses no increase in the patient's cognitive load; i.e. it does not require additional concentration for the patient to incorporate two different sensory forms of guidance at once.[58]

The guiding prompts of breathing guidance have developed from a buzzer sounding to provide a queue for breath-holds, to a patient display presenting breathing-surrogates superimposed with a guiding interface. Additional constraints have been added to the visual prompts to further manage respiration, such as the displaying of inhale and exhale limits,[47, 48, 50, 60] a waveguide with fixed period and amplitude for the patient to match their own breathing to,[54] and combinations thereof.[58, 64, 65]

In addition to the nature of guiding prompts utilized, study design has also factored into influencing patient acceptance and compliance with the breathing guidance intervention. Studies in which patients used breathing guidance multiple times demonstrated improved breathing consistency with time.[50, 58, 65] Hence, to achieve optimal compliance with breathing guidance, patient training and repeated sessions are of importance to bolster their familiarity with the system; such elements have been absent in previous patient studies which yielded non-significant results.[69, 88, 89]

While this systematic review yielded 27 articles, it should be noted that some articles that were in contention required considerable discussion between the authors to conclude on their exclusion from the final selection. The main factor influencing the decision to exclude these articles was the control group criterion; while several studies investigated a breathing guidance intervention strategy, the control group was not of the same breathing type (see inclusion criterion 5).[81, 84-86, 89-92]

While the search undertaken and review of articles by the authors was performed as objectively as possible it should be noted that two of the authors of this systematic review: Sean Pollock and Paul Keall are either first- or co-authors of 3 and 9 of the 27 included articles, respectively, investigating the breathing guidance intervention: audiovisual biofeedback. Their familiarity with breathing guidance strategies led to the identification that a gap in the literature existed in that a review of such research had yet to be performed; however, unintentional bias may have permeated this review towards audiovisual biofeedback. To minimize this bias, co-author Robyn Keall was invited to review and screen the identified 319 (see *Figure 3*); where there was disagreement between reviewers, a discussion was undertaken amongst all authors until consensus was reached.

While 21 of the 27 included articles reported at least one statistically significant positive finding from the use of breathing guidance interventions, bias should also be noted that papers reporting on positive results are more likely to be published than papers with negative results.[93, 94] This notes the systemic bias in scientific reporting and the possibility that negative results on breathing guidance may not have been published.

The largely positive results found in this systematic review indicate that further clinical studies are warranted, and should be focussed on (1) utilizing training and multiple sessions to maximize patient compliance with the breathing guidance system, and (2) further determining the clinical impact of breathing guidance interventions by investigating outcomes pertaining to treatment margins, toxicity, and patient outcomes. Such factors are being explored in ongoing and upcoming studies, with some preliminary results presented thus far.[95-97]

V. CONCLUSION

A systematic review of breathing guidance intervention strategies in radiotherapy and radiology has been performed and 27 studies were identified. In 21 studies statistically significant improvements from the use of breathing guidance were observed. No studies observed worse breathing consistency with guidance; however, audio-only guidance, while facilitating regular breathing, also increased respiratory amplitude which is undesirable in most circumstances. Studies that have repeated breathing guidance across multiple sessions have observed an improvement in participant compliance from one session to the next, emphasising the importance of patient practice and training. Such insights are valuable in designing breathing guidance studies in terms of both guiding prompts used and patient familiarity with the intervention to maximize the effectiveness of the intervention. The largely positive results found here indicate that further clinical studies are warranted to further assess and quantify the clinical impact of breathing guidance, along with the health technology assessment to determine the advantages and disadvantages of the use of breathing guidance strategies.

ACKNOWLEDGEMENTS

This project was supported by an NHMRC Australia Fellowship and the Bob and Nancy Edwards Scholarship. The authors would like to thank Informa Healthcare and Elsevier for allowing us the use of their Figures in our manuscript, as well as the authors of those papers the Figures appeared in for producing such a high quality of work we wished to utilize to improve the clarity of our manuscript's rationale.

CONFLICT OF INTEREST

Paul Keall is one of the inventors of US patent # 7955270 and Paul Keall, Robyn Keall, and Sean Pollock are shareholders of Respiratory Innovations, an Australian company that is developing a device to improve breathing stability. Respiratory Innovations did not provide any support or funding for this project.

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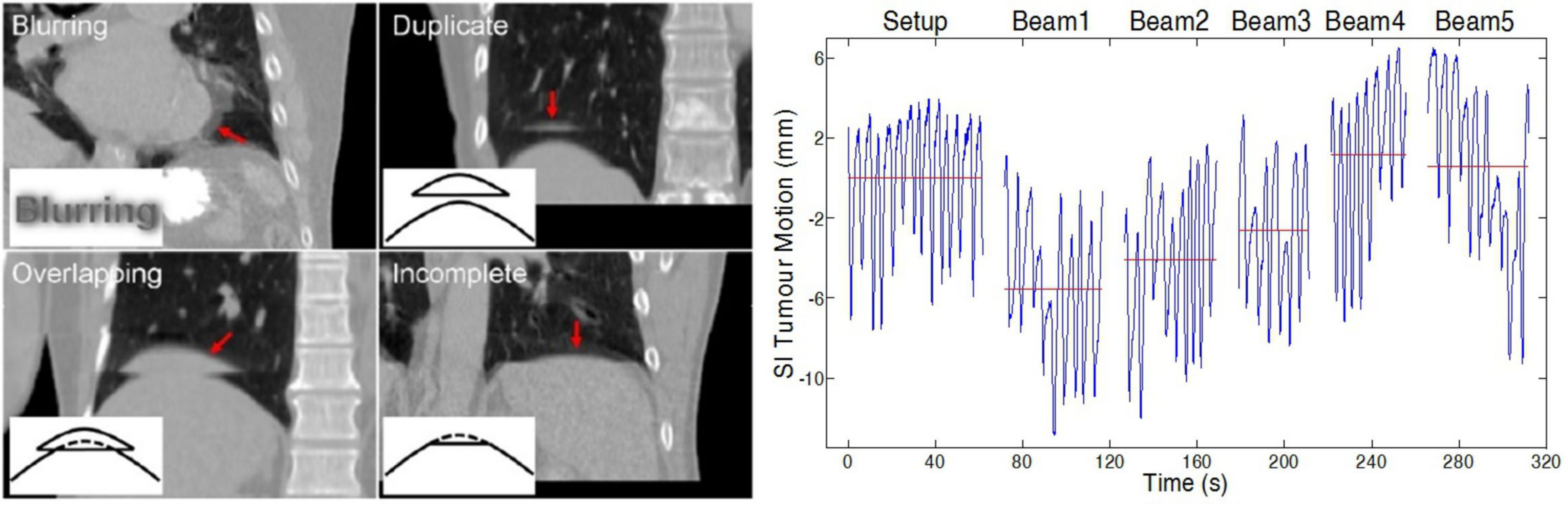
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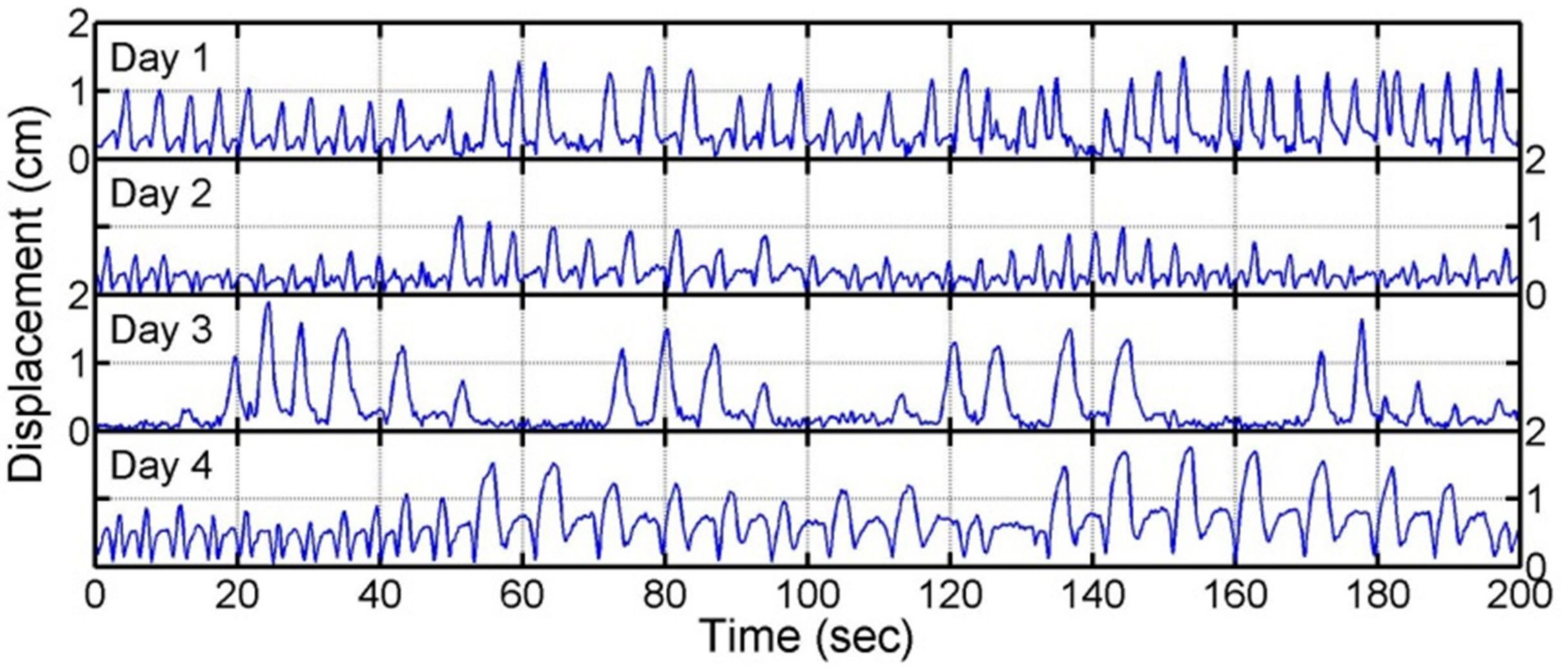

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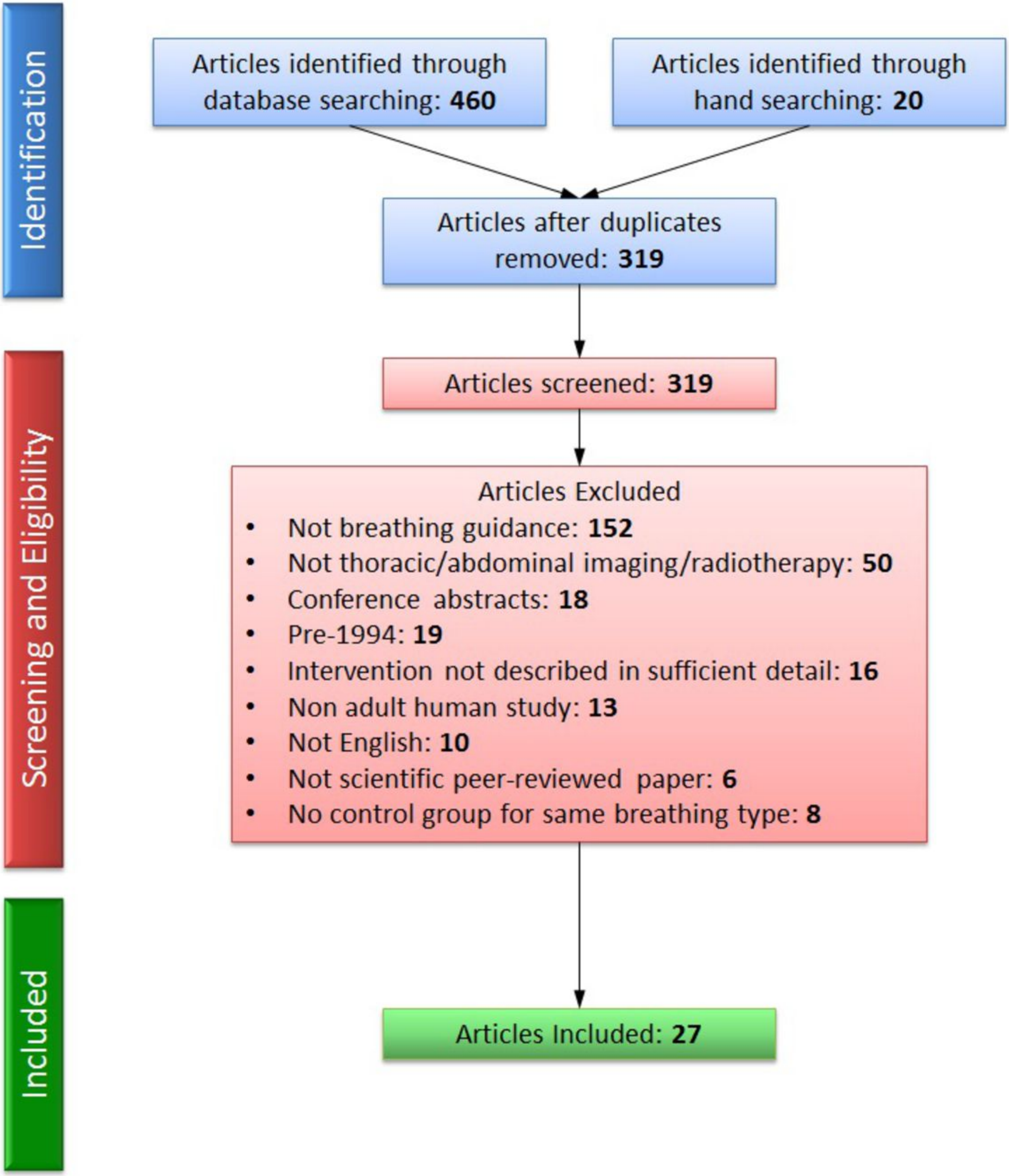
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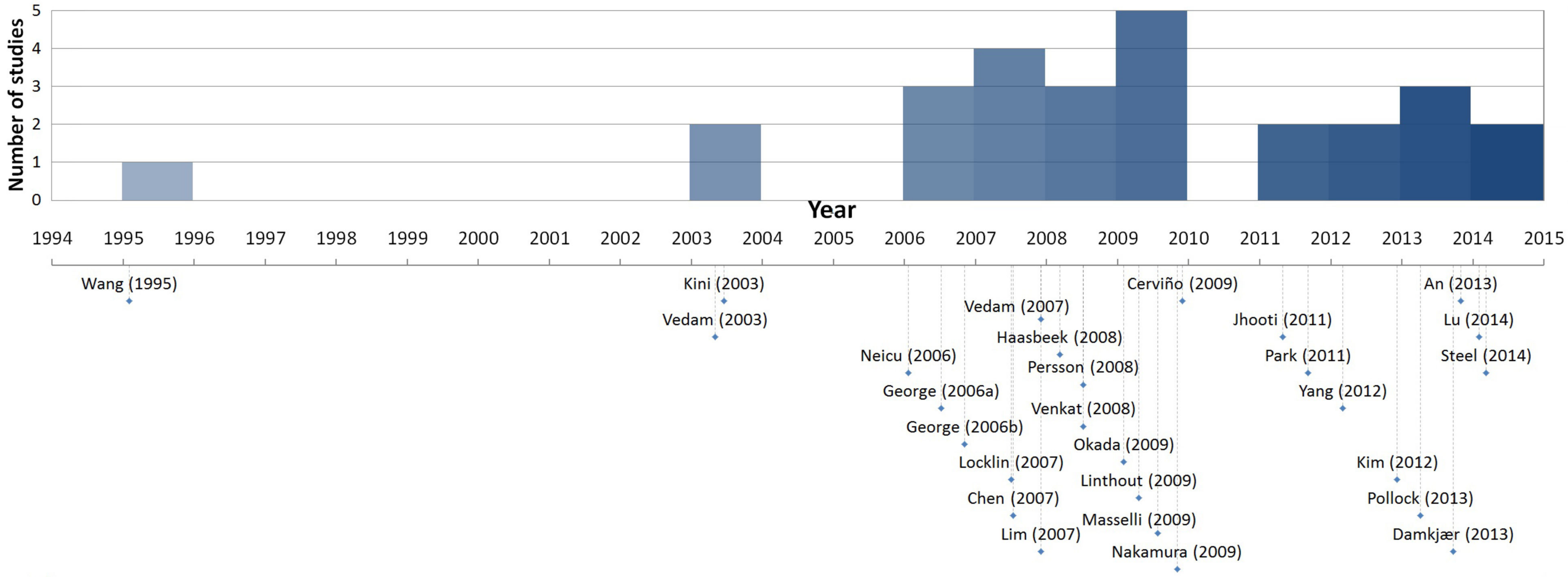
Not thoracic/abdominal imaging/radiotherapy: 50
Conference abstracts: 18
Pre-1994: 19
Intervention not described in sufficient detail: 16
Non adult human study: 13
Not English: 10
Not scientific peer-reviewed paper: 6
No control group for same breathing type: 8
Included
Articles Included: 27



Number of studies
5
4
3
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Year
1994
1995
1996
1997
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2015
Wang (1995)
Kini (2003)
Vedam (2003)
Neicu (2006)
George (2006a)
George (2006b)
Vedam (2007)
Locklin (2007)
Chen (2007)
Lim (2007)
Haasbeek (2008)
Persson (2008)
Venkat (2008)
Cerviño (2009)
Okada (2009)
Linthout (2009)
Masselli (2009)
Nakamura (2009)
Jhooti (2011)
Park (2011)
Yang (2012)
Kim (2012)
An (2013)
Pollock (2013)
Damkjær (2013)
Lu (2014)
Steel (2014)