Clinical and Translational Radiation Oncology 39 (2023) 100575

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Institutional experience of using active breathing control for paediatric and teenage patients receiving thoraco-abdominal radiotherapy

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ARTICLE INFO

Keywords:
ABC
active breathing control
paediatric radiotherapy
thoracic radiotherapy
motion management

ABSTRACT

Introduction: Active Breathing Control (ABC) is a motion management strategy that facilitates reproducible breath-hold for thoracic radiotherapy (RT), which may reduce radiation dose to organs at risk (OARs). Reduction of radiation-induced toxicity is of high importance in younger patients. However, there is little published literature on the feasibility of ABC in this group. The purpose of this study was to report our experience of using ABC for paediatric and teenage patients.

Methods: Patients ≤18 years referred for thoracic RT using ABC at our centre from 2013–2021 were identified. Electronic records were retrospectively reviewed to obtain information on diagnosis, RT dose and technique, OAR dosimetry, tolerability of ABC, post-treatment imaging and early toxicity rates.

Results: 12 patients completed RT and were able to comply with ABC during planning and for the duration of RT. Median age was 15.5 years (10–18 years). Diagnoses were: Hodgkin lymphoma (n = 5), mediastinal B-cell lymphoma (n = 1), Ewing sarcoma (n = 5) and rhabdomyosarcoma (n = 1). For mediastinal RT cases (n = 6), median dose delivered was 30.6Gy(19.8–40Gy), median mean heart dose was 11.4Gy(4.8–19.4Gy), median mean lung dose was 9.9Gy(5.7–14.5Gy) and mean lung V20 was 10.9%. For ipsilateral RT cases, (n = 6), median hemithorax and total doses to primary tumour were 18Gy(15–20Gy) and 52.2Gy(36–60Gy) respectively. Median mean heart dose was 19.5Gy(10.6–33.2Gy) and median mean lung dose was 17.7Gy(16.3–30.5Gy). Mean bilateral lung V20 was 39.6%. Median mean contralateral lung dose was 5.2Gy(3.5–11.6Gy) and mean contralateral lung V20 was 1.5%. At a median follow-up of 36 months, only 1 patient had symptomatic radiation pneumonitis having received further thoracic RT following relapse.

Conclusions: ABC is feasible and well tolerated in younger patients receiving RT. Children as young as 10 years are able to comply. Use of ABC results in OAR dosimetry which is comparable to similar data in adults and can facilitate RT for extensive thoracic sarcoma

Introduction

The management of respiratory-related tumour motion remains one of the key challenges in delivering highly conformal radiotherapy to targets in the thorax and abdomen. Strategies for management of respiratory motion using breath-hold to temporarily 'immobilise' internal anatomy have become widely adopted in adult radiotherapy practice. Self-controlled breath-holding is one such technique used for thoracic and upper abdominal radiotherapy in adults. However, without direct respiratory monitoring this method is vulnerable to inconsistency. Furthermore, this method relies upon the ability to repeatedly comply with breathing instructions, which might be more challenging for children and younger patients.

Active breathing control (ABC) addresses this problem by combining respiratory monitoring with non-invasive equipment that is capable of inducing breath-holds at a pre-determined inspiration or expiration threshold. No surface surrogate is required as a spirometer is used to monitor the patient's lung volume. ABC can therefore facilitate reproducible breath-holds which can improve accuracy in radiotherapy where respiratory motion is likely to affect treatment delivery.

By achieving consistent breath-hold, image clarity is improved, and internal organ motion is reduced and more predictable, which can

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https://doi.org/10.1016/j.ctro.2022.100575
Received 7 April 2022; Received in revised form 23 December 2022; Accepted 29 December 2022
Available online 2 January 2023

facilitate reduced planning target volume margins. This can enable the therapeutic ratio to be maximised in the thorax or upper abdomen, by delivering higher radiation doses to the target, and minimising dose to surrounding critical organs at risk (OARs) including the lungs, heart, liver and kidneys.

ABC is used routinely in adults for treatment of thoracic and upper abdominal tumours, and is generally well tolerated, although elderly patients or those with severe COPD can find it challenging. Where it has been used in the treatment of lung cancer, studies have demonstrated reduced tumour motion, in addition to reduced mean lung dose and V20, key predictors for pneumonitis [1]. When used in adjuvant radiotherapy for breast cancer, mean heart dose can be reduced in the vast majority of patients [2–5] and ipsilateral lung dose may also be reduced [4,5]. Utilising ABC for treatment of upper abdominal (predominantly liver) tumours has also facilitated target margin reductions and better sparing of OARs [6,7].

Accuracy of radiation delivery is arguably of even greater concern in younger patients where there are additional considerations compared with adults, due to growth and the high chance of long survival after treatment. There is greater opportunity for the development of long-term effects when radiation is given at a young age to these anatomical sites, including lung dysfunction, cardiovascular side effects, as well as secondary malignancies in later life [8–16]. Children frequently receive intensive chemotherapy regimens as part of treatment for their cancer, which include agents known to be associated with long term heart and lung toxicity, e.g., anthracyclines and bleomycin. With this in mind, it becomes even more important to limit radiation dose to these normal tissues.

Evidence for the risk of radiation induced effects associated with specific radiation doses has informed guidelines on normal tissue dose constraints for adults (e.g. QUANTEC) [17,18] and a collaborative effort (PENTEC) is underway to produce equivalent guidance for children [19].

Besides the challenges of treatment delivery in breath-hold, radiotherapy can potentially be a stressful and anxiety-provoking time for younger patients [20,21] and there is a risk that the addition of ABC to the radiotherapy workflow may heighten these feelings. The aim of this article is to describe our institutional experience of using ABC for paediatric and teenage patients receiving thoraco-abdominal radiotherapy, in order to contribute to an area where documented experience is limited.

Materials and methods

Following local institutional review board approval, all paediatric and teenage patients referred for thoracic or abdominal radiotherapy using ABC at The Royal Marsden Hospital from 2013 to 2021 were identified. Patients $\leq$ 18 years were included.

Hospital electronic patient records, radiotherapy planning software records and Picture Archiving Communication Systems (PACS) were retrospectively reviewed to obtain information on diagnosis, radiotherapy dose and technique, OAR dosimetry, tolerability of ABC, post-treatment imaging and early toxicity.

Radiotherapy doses and fractionations were delivered according to departmental protocols which are consistent with national and international guidelines.

Patients were followed up clinically and radiologically according to local guidelines.

Toxicity data was collected at 3 months (defined as early toxicity) and at the time of last documented follow-up. Toxicity was graded using CTCAE v5.0.

For the purposes of reporting OAR dosimetric results, patients were separated into two groups: those who received mediastinal radiotherapy and those who received ipsilateral hemithoracic radiotherapy and descriptive statistics were used.

Results

Patient characteristics

In total, 12 patients in total were treated with ABC at The Royal Marsden Hospital between October 2013 and November 2021. The median age treated was 15.5 years (range, 10–18 years). Patient characteristics are summarised in Table 1. Patients were selected for treatment after review of their diagnostic imaging suggested a likely dosimetric benefit from the use of ABC and selection was in line with departmental protocols for ABC in adults, which is predominantly used for inspiratory breath-hold for thoracic tumours.

Of note, treatment with ABC for all patients at our centre was temporarily suspended during the COVID-19 pandemic in 2020/early 2021 due to concerns regarding potential virus transmission.

Five patients had a diagnosis of Hodgkin Lymphoma (HL), five had Ewing sarcoma and the remainder had primary mediastinal B cell lymphoma and thoracic rhabdomyosarcoma.

All children had received prior systemic chemotherapy according to relevant collaborative group or national protocols prior to radiotherapy and had received prior anthracycline containing regimens. One patient with Ewing sarcoma had undergone surgery to the primary tumour prior to commencing radiotherapy.

All patients received radiotherapy to the thorax. Of those being treated for HL, the radiotherapy field extended into the abdomen for two patients to encompass all sites of disease.

The most common radiotherapy technique used was VMAT (n = 9) and the remainder were treated using IMRT (n = 1) or conformal RT (n = 2). Of those that received Phase 1 hemithorax radiotherapy, this was delivered using a parallel opposed beam arrangement for 2 patients. Examples of VMAT plans delivered for patients receiving mediastinal radiotherapy and hemithoracic radiotherapy are shown in Figs. 1 and 2 respectively.

Planning target volume (PTV) margins

PTV margins were 0.5 cm isometrically in almost all cases. For 2 patients, 0.7 cm margins were applied in the superior-inferior direction as it was felt that residual motion would be greatest in this plane. Without ABC, standard PTV margins in our centre for free breathing are at least 1 cm isometrically, unless an internal target volume (ITV) approach is used. For sarcoma patients, where doses are higher, these margins would have resulted in unacceptably high OAR doses, particularly to the lungs.

OAR dosimetry

OAR dosimetric values are reported for the two groups: mediastinal radiotherapy (lymphoma patients, n = 6) and ipsilateral thoracic radiotherapy (sarcoma patients, n = 6). Results for each group are reported in Tables 2 and 3.

Outcomes

At a median follow up of 36 months (range, 0–86 months), nine patients were alive and disease free (two have completed treatment within the last 6 months). Three have died from disease progression.

Five patients in total have relapsed (4 relapsed locally and 1 relapsed with widespread systemic disease). The median time to local relapse was 15.5 months (range, 2–21 months). Survival analysis was not done due to the small total number of patients and heterogeneity of cases.

Of those that relapsed locally, three patients relapsed inside the high dose region, suggesting this was due to the aggressive nature of the tumour. One patient (patient 8) relapsed just outside the hemithoracic radiotherapy field but approximately 8 cm inferior to the site of the original tumour and high dose region. Although this was a loco-regional

Table 1
Patient characteristics.

Patient	Age	M/F	Diagnosis	Anatomical site treated	Dose and fractionation
1	10	Female	Ewing Sarcoma	Right hemithorax Primary site (right 7th rib)	Phase 1: 15 Gy/10# to whole lung, 18Gy/10# to primary tumour Total dose to primary tumour: 45 Gy/25#
2	13	Female	Hodgkin Lymphoma	Neck, axillae, mediastinum, hila, spleen	19.8 Gy/11#
3	13	Female	Ewing Sarcoma	Right hemithorax Primary site (right thorax and hilum)	Phase 1: 15 Gy/10# to hemithorax Total dose to primary tumour: 54 Gy
4	14	Female	Hodgkin Lymphoma	Neck, axillae, mediastinum, hila, retroperitoneum	19.8 Gy/11#
5	15	Female	Hodgkin Lymphoma	Neck, mediastinum	30.6 Gy/17#
6	15	Male	Ewing Sarcoma	Primary site (upper thorax)	60 Gy/30#
7	16	Female	Rhabdomyosarcoma	Mediastinum, hemithorax	36 Gy/20#
8	16	Male	Ewing Sarcoma	Left hemithorax Primary site (left chest wall)	Phase 1: 20 Gy/12# Total dose to tumour: 55 Gy
9	17	Male	Primary mediastinal B cell lymphoma	Mediastinum	40 Gy/20#
10	17	Male	Hodgkin Lymphoma	Mediastinum	40 Gy/20#
11	17	Male	Hodgkin Lymphoma	Mediastinum	30.6 Gy/17#
12	18	Female	Ewing sarcoma	Right hemithorax Primary (Right hemithorax) Metastases (Pleura, vertebra and axilla)	Phase 1: 18 Gy/10# to hemithorax Total dose to tumour: 50.4 Gy

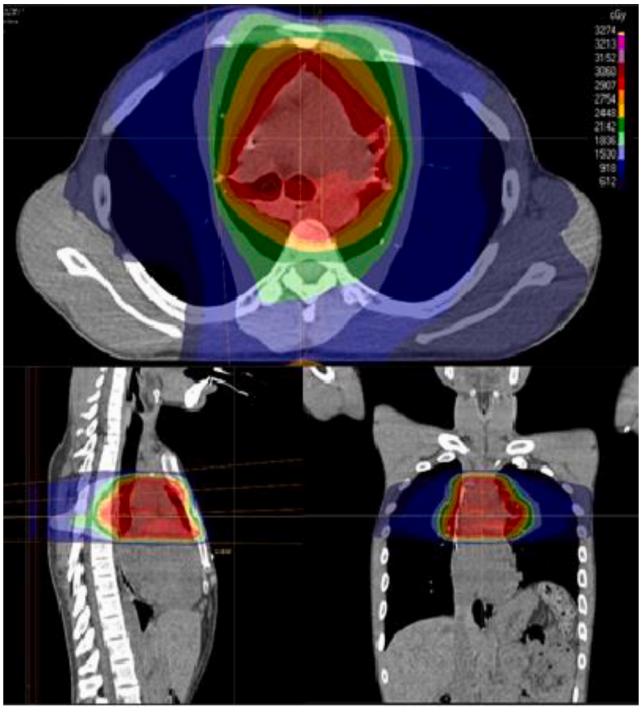

Fig. 1. VMAT plan for a 17 year old patient treated for mediastinal lymphoma with 30.6 Gy in 17 fractions, using ABC to increase the bilateral lung volume and displace heart away from the planning target volume.

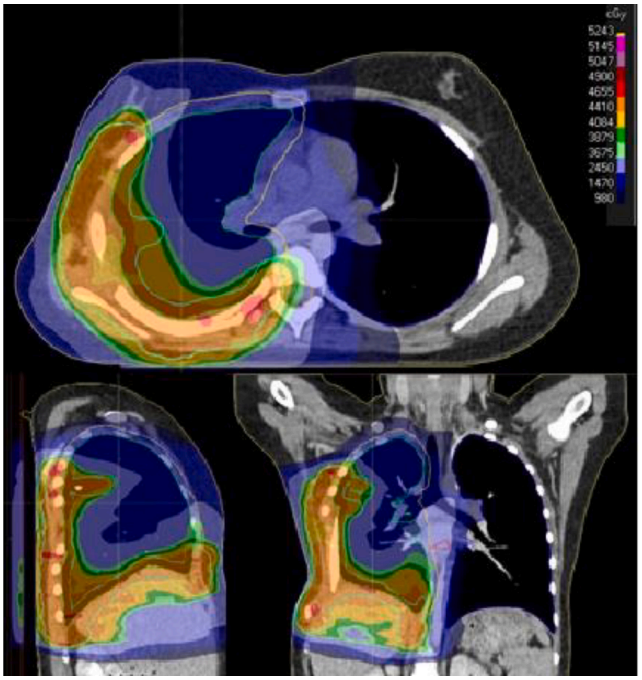

Fig. 2. VMAT plan for a 10 year old patient treated using ABC for Ewing Sarcoma. A combined plan for the Phase 1 treatment (15Gy in 10 fractions to whole lung and 18Gy in 10 fractions to chest wall primary) and Phase 2 boost to primary site (27 Gy in 15 fractions) is shown.

relapse the use of a smaller PTV margin was not considered to be a significant factor.

Toxicity

Of the eleven patients who have reached at least 3 months of follow up, four patients had evidence of acute radiation induced pulmonary toxicity. Of these, three patients were treated for sarcoma, where higher doses were delivered. Three patients had only radiological evidence of radiation pneumonitis and were asymptomatic (grade 1 toxicity). Only one patient was symptomatic (patient 8), a 16 year old with Ewing sarcoma initially treated with VIDE chemotherapy and thoracic

Table 2
Target and OAR dosimetric values for Lymphoma patients (n = 6) who received mediastinal radiotherapy.

Parameter	Median (range)
Dose delivered to target volume (Gy)	30.6 (19.8–40)
Heart	
Mean heart dose (Gy)	11.4 (4.8–19.4)
Lungs	
Mean lung dose (Gy)	9.9 (5.7–14.5)
Lung V20 (%)	10.9 (0–14)
Breasts (n = 3)	
Mean breast dose (Gy)	10.0 (4.78–10.0)

Table 3
Target and OAR dosimetric values for sarcoma patients who received ipsilateral hemithoracic radiotherapy (n = 6).

Parameter	Median (range)
Dose delivered to target volume	
Hemithorax (Gy)	18 (15–20)
Total dose to primary tumour (Gy)	52.2 (36–60)
Heart	
Mean heart dose (Gy)	19.5 (10.6–33.2)
Lungs	
Mean bilateral lung dose (Gy)	17.7 (16.3–30.5)
Mean contralateral lung dose (Gy)	5.2 (3.5–11.6)
Bilateral lung V20 (%)	39.6 (34.6–44)
Contralateral lung V20 (%)	1.5 (0–18.7)
Breasts (n = 4)	
Mean breast dose (Gy)	11.5 (7.3–19.4)
Contralateral breast (Gy)	5.1 (1.3–9)

radiotherapy, who developed shortness of breath on exertion and dry cough after his initial course of radiotherapy (grade 2) which responded to oral corticosteroids. There was no prior history of any respiratory conditions.

At 36 months, the same patient had ongoing mild respiratory symptoms (grade 2) and radiological changes consistent with pulmonary fibrosis. He had originally received a mean lung dose of 16.6 Gy, bilateral lung V20 of 43 %, contralateral mean lung dose of 3.5 Gy and contralateral lung V20 of 0 %. However, this patient had received further chemotherapy (ifosfamide/etoposide) and radiotherapy for a locoregional relapse at the crus of the diaphragm (as discussed above) one year after his initial radiotherapy. He received 54 Gy in 30 fractions to the site of relapse also delivered with ABC, with a mean bilateral lung dose of 5.6 Gy, bilateral lung V20 of 0 %, contralateral mean lung dose of 5 Gy and contralateral lung V20 of 0 %.

Only one other patient showed late radiological signs of radiation induced lung toxicity at the time of last follow-up, but this patient has remained asymptomatic.

All patients were routinely monitored with echocardiograms/electrocardiograms for development of late cardiotoxicity following treatment. One patient had developed reduced ejection fraction, which has been attributed to anthracycline chemotherapy and required treatment with ACE inhibitors. However, it is recognised that the duration of follow up is likely too short to capture late onset radiation-induced cardiac effects.

Patient experience of ABC

Assessment prior to treatment

Each patient referred for radiotherapy to the thorax or abdomen using the ABC technique was formally assessed for compliance at the time of their CT simulation. All were scheduled for a longer CT appointment (additional 30 minutes) to allow time for training and familiarisation with ABC equipment. As numbers of young patients referred were small, there were no difficulties in arranging longer appointment times.

The ABC apparatus (the Elekta ABC™ device (Elekta Oncology Systems ltd, Crawley, UK)) consists of a single use mouthpiece and filter connected via tubing to a respiratory volume transducer and a balloon valve which can be inflated to suspend inspiration or expiration. No specific modifications were required from the standard set-up used for adult patients. Patients wear a nose clip during use. This equipment is used during the entire radiotherapy process, including planning and delivery.

All patients were familiarised with the radiotherapy department prior to their scanning appointment and commencing treatment, as per standard departmental practice for younger patients. The exact process during this session was child and age dependent. For younger patients, additional time was taken to allow demonstration of the equipment and talk through each step using age- appropriate language. Play specialists attended sessions to support younger children during the planning process and later with treatment. Radiographers did not feel that any adaptation to the usual adult explanation, demonstration or practice session was required for patients over 15 years. The youngest patient (aged 10 years) was an inpatient at the time of treatment and an experienced paediatric radiographer visited the child on the ward to explain the ABC process and demonstrate the equipment prior to her attendance at the CT scanner.

All patients were positioned supine and immobilised in the radiotherapy treatment position for this session. A lung board was used and arms were raised above the head, with the legs immobilised. Intravenous cannulation was undertaken for contrast administration, and permanent skin marks were utilised to aid reproducible set-up. No thermoplastic immobilisation shells were used for treatment to the lower neck as this was impractical in addition to the ABC equipment used.

After the ABC apparatus was positioned, radiographers would observe the patient's normal respiration for a short time to allow them to settle into a comfortable breathing pattern. After this, patients were asked to inhale as deeply as possible, so that the volume of maximum inspiration could be assessed. As per the adult protocol, the threshold for the valve to shut was set to 70 % of maximum inspiration, to maximise comfort and consistency during treatment. Patients were reminded not to voluntarily breath-hold, but to allow the ABC device to suspend breathing at the pre-defined point.

The ABC device was used to monitor breathing and the balloon valve then closed to stop inspiration at the same point within this phase of respiration. Standardly, patients were asked to breath-hold for 20 s each time. Patients were deemed to be compliant if breath-hold was tolerated during the simulation session. The CT image was acquired over a single breath-hold.

Patient experience in room

All patients were immobilised and treated in the same position as during their simulation session (Fig. 3).

A monitor was placed inside the room, which displayed the respiratory trace and timer. However, because patients were positioned supine with a nose clip/mouthpiece in situ, with the head of the linear accelerator in close proximity during treatment delivery, the monitor was not clearly visible. Therefore, patients were reliant on verbal cues from radiographers to time their breathing.

There were no issues with the ability of the equipment in detecting a respiratory trace in these younger patients where respiratory motion is anticipated to be of lower amplitude. Radiographers were uncertain

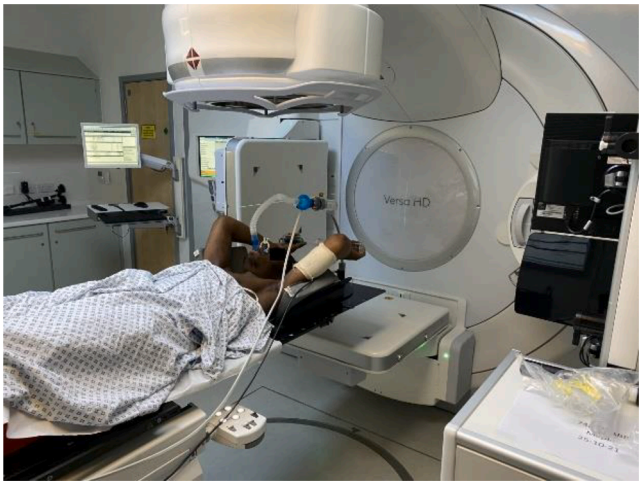

Fig. 3. Clinical photograph demonstrating pre-treatment patient set-up, immobilisation and positioning of the ABC equipment.

whether the standard adult mouth-bite provided would be suitable for much smaller children and felt that a paediatric mouthpiece may be required.

None of the 12 patients treated described experiencing any significant discomfort, anxiety or issues during treatment. All patients deemed suitable for ABC at simulation CT managed to complete treatment using ABC without any problems or interruption during treatment. No patients required re-scanning or re-planning for any reason.

Although treatment times were lengthened by approximately ten minutes each day by using ABC, this did not cause any additional anxiety for any patients. Two younger patients perceived the use of ABC on treatment as a challenge to see how long they could breath-hold and the majority of children found that ABC became easier with each subsequent treatment.

Discussion

Our experience shows that the use of ABC is feasible in younger patients receiving thoracic or abdominal radiotherapy. With the necessary pre-treatment training, play specialist/radiographer support and explanation, all patients were able to complete planning and the full course of radiotherapy with ABC and it did not cause further anxiety.

We have also demonstrated that the late toxicity rate is low in patients treated with this technique both children with mediastinal lymphoma or thoracic sarcoma. Only one patient was symptomatic of late radiation induced pulmonary fibrosis at the time of last follow up, having received a second course of thoracic radiotherapy for relapse.

A number of articles have described the dosimetric benefits of treating with ABC vs free breathing in adults [2,22]. One article has described improved dosimetry using ABC to treat a mixed adult and paediatric population with mediastinal lymphoma [22], where the use of ABC results in a mean heart dose and mean lung dose of 11.8 Gy and 9.5 Gy respectively. These are very similar values to those we report above. However, they report a median lung V20 of 22 %, whereas it was possible to achieve a median lung V20 of only 10.9 % in our patient group. Claude et al [23] describe their experience of delivering radiotherapy using ABC for seven adolescents with HL aged 13–18 years. They compared dosimetry between ABC and free breathing and found that use of ABC reduced volume of lung irradiation and slightly reduced the mean heart dose, although the latter was not statistically significant. They raised concerns regarding treatment of very young patients, who may not easily be able to comply with instruction and breath-holding with ABC.

No article has yet described the experience of treating children as young as 10 years old using ABC. Furthermore, most published experience to date has been on the use of ABC in mediastinal radiotherapy, whereas half of the patients treated with ABC in our centre had received hemi-thoracic radiotherapy for sarcoma, some of whom would have been untreatable without use of ABC. Radiation doses required in the treatment of sarcoma are higher than those routinely used for lymphoma. We have shown that using ABC, it was possible to achieve a low contralateral mean lung dose of 5.2 Gy and contralateral lung V20 of 1.5 %, despite delivery of high doses to extensive target volumes.

There are a small number of articles that describe treatment of younger patients with Deep Inspiration Breath-Hold (DIBH), as opposed to ABC. The majority of those treated with DIBH underwent respiratory monitoring, but DIBH was voluntary. However, there is very little published experience in treating this group of patients with any type of breath-hold method, hence they are included for the purposes of discussion.

An article by Lundgaard et al (8) demonstrated feasibility of treating paediatric patients as young as five years old with a voluntary DIBH approach. In total, 33 children aged 5–15 were included (18 healthy and 15 hospitalised children with cancer diagnoses). They found that 28 (85 %) children were DIBH compliant and 8 were conditionally DIBH compliant. Children were deemed to be DIBH compliant if they were able to perform 3 DIBHs of 20 s, whilst remaining motionless. However, the aims of this study were to assess feasibility and compliance with the DIBH approach. No children in this study received radiotherapy using this technique and over half were healthy volunteers. It is possible that compliance was over-estimated as healthy children may be better positioned to cope with voluntary DIBH and its additional challenges.

The youngest patient reported to receive radiation in DIBH was 8.6 years [25] was part of a retrospective dosimetric and feasibility study comparing treatment in free breathing with DIBH. This study provided further evidence that treatment with breath-hold improves normal tissue toxicity as irradiated liver volumes was statistically significantly lower in DIBH than in free breathing.

All of the patients included in the studies by Lundgaard et al [24] and Demoor-Goldschmidt et al [25] were planned with voluntary DIBH, which suggests even younger children may also be able to comply with ABC. Patient selection should not be based entirely on age but rather on the individual child. The feasibility of DIBH in these studies has also led to the development of a prospective trial (TEDDI) in Denmark. This study will assess the dosimetric benefit and tolerability of treating in DIBH compared with free breathing for patients aged 5–17 requiring radiotherapy to the mediastinum/upper abdomen.

In our centre, children did not have access to visual feedback due to proximity of the ABC monitor in relation to the linear accelerator head. In the study by Lundgaard et al, 88 % of children found visual feedback (either via screen or goggles) helpful and these were also used in the study by Demoor-Goldschmidt et al. There are commercially available goggles which allow projection of the ABC monitor display. This may improve the process, by allowing even further engagement from children who would be able to self-monitor their breathing and prepare accordingly.

More recently, updated equipment has been acquired which integrates with the linear accelerator automatically. This switches on the radiotherapy beam when the pre-determined respiratory threshold is reached. Gating was previously a manual process, so automation will enable even more streamlined treatment delivery.

Understandably, there are some limitations to this single centre study. We were not able to perform a dosimetric comparison between ABC and free-breathing because only one CT was acquired for radiotherapy planning to minimise ionising radiation exposure. Secondly, no contemporaneous patient questionnaires were completed detailing experience of ABC, so the experiences described here reflect only compliance with treatment, documented toxicities from medical records and observations of the radiotherapy staff. In addition, the median follow-up time of 36 months is likely to be too short to capture some late radiation-induced side effects, which are known to potentially occur much later.

Conclusion

In this article, we have demonstrated that ABC is a feasible strategy for motion management in paediatric and adolescent patients receiving thoracic or upper abdominal radiotherapy. Given that those as young as 10 years old were able to comply, children should be assessed for suitability for ABC on an individual basis.

The use of ABC in younger patients results in heart and lung doses which are comparable to similar data in adults treated for mediastinal lymphoma. Furthermore, ABC can facilitate the delivery of radiotherapy for extensive thoracic sarcoma.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study represents independent research supported by the National Institute for Health and Care Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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