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The impact of intra-thoracic anatomical changes upon the delivery of lung stereotactic ablative Radiotherapy

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Abstract

Title: The impact of intra-thoracic anatomical changes upon the delivery of lung stereotactic ablative Radiotherapy

Purpose:

So far, the impact of intra-thoracic anatomical changes (ITACs) on patients treated with stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer (NSCLC) is unknown. Studying these is important as ITACS have the potential to impact the workflow and reduce treatment quality. The aim of this study was to assess and categorise ITACs, as detected on cone beam computed tomography scans (CBCT), and their subsequent impact upon treatment in lung cancer patients treated with SABR.

Methods and materials
CBCTs from 100 patients treated with SABR for early NSCLC were retrospectively reviewed. The presence of the following ITACs was assessed: atelectasis, infiltrative change, pleural effusion, baseline shift, and GTV increase and decrease. ITACs were graded using a traffic light protocol. This was adapted from that developed by Kwint et al. to assess potential target under-coverage or OAR over-dose. The frequency of physics or clinician review was noted. A linear mixed effects model was used to assess the relationship between ITAC grade and set-up time (time from 1st CBCT to beam delivery).

Results
ITACs were observed in 22% of patients. 21% of these were categorised as 'red', implying a risk of underdosage to the GTV. Most were 'yellow' (51%) indicating little impact upon PTV coverage of the GTV. Physics or clinician review was required in 10% of all treatment fractions overall. 3 patients needed their treatment re-planned. Mixed effect model analysis demonstrates that ITACs cause a significant prolongation of set-up time ($\mathbf{X^2}(3)=9.22$, $p=0.02$).

Conclusion
The majority of intra-thoracic anatomical changes were minor but associated with unplanned physics or clinician review, representing a potentially significant resource burden. ITACs also had a significant impact upon set-up time with consequences for the wider workflow and intra-fraction motion. Detailed guidance on the management of ITACs is needed to provide support for Therapeutic Radiographers delivering lung SABR.

Key words: lung cancer, SABR, intra-thoracic anatomical changes

The impact of intra-thoracic anatomical changes upon the delivery of lung stereotactic ablative radiotherapy

Introduction

The last decade witnessed major developments in technical radiotherapy. Innovations such as stereotactic ablative radiotherapy (SABR), magnetic resonance-guided radiotherapy (MRgRT) and proton beam therapy (PBT) hold considerable promise.[1–3] Given the resource implications, careful consideration is needed on how these techniques may be introduced into routine care.

The management of anatomical changes during radiotherapy for lung cancer can be challenging. A recent single institution audit reviewed treatment radiographer requests for physics support.[4] Over 20% were due to concerns regarding anatomical change on cone-beam computed tomography (CBCT), and lung was the dominant tumour site. Kwint recently described intra-thoracic anatomical changes (ITACs) on CBCTs of 72% of lung cancer patients treated with curative-intent fractionated radiotherapy.[5] 12% had changes with potential to significantly impact upon the dose to the planning target volume (PTV). They used a traffic light decision-support system to quantify ITACs on CBCT, which advised when to contact the clinician. Moller reviewed ITACS in 163 lung cancer patients during radiotherapy; similarly 12% were found to benefit from treatment adaptation.[6]

These studies demonstrate ITACS are frequently seen and potentially interfere with the quality of radiotherapy delivered. However, they excluded patients treated with SABR, the standard of care for medically-inoperable patients with early-stage lung cancer.[7,8] Therefore it's unclear to what extent patients with early-stage lung cancer experience these issues and how image guidance workflows should be optimised for SABR delivery.

In this paper we evaluate CBCTs from lung cancer patients treated with SABR across two large institutions with extensive SABR experience. This work will describe the occurrence of ITACs and impact upon treatment.

Materials and methods

One hundred consecutive patients were identified as having been treated with thoracic SABR for peripherally located primary lung cancer at one of two experienced cancer centres; A or B, in 2017. Early non-small cell lung cancer (NSCLC) was previously diagnosed via local thoracic oncology multi-disciplinary team (MDT) meetings. All patients underwent a radiotherapy planning CT (RTP CT) using a free-breathing 4D CT. Motion adapted gross tumour volumes (GTV) were formed by contouring the tumour on the maximum intensity projection (MIP). This was adjusted as required using the breathing phases to account for motion. This volume is the same as the internal target volume (ITV); no extra margin is added for microscopic disease. The ITV was isotropically expanded by 5mm to form the planning target volume (PTV). Treatment plans were created for 6MV flattening filter-free (FFF) volumetric-modulated arc radiotherapy (VMAT) using the Pinnacle planning system (Philips Radiation Oncology Systems, USA) or Monaco (Elekta AB, Stockholm, Sweden). A dose of 54-60 Gy was prescribed to the PTV D95 while ensuring the maximum dose was <140%. Treatment was delivered over 3 – 8 fractions, alternate-days.

Daily on-line CBCTs, acquired using the Elekta XVI system (Elekta AB, Stockholm, Sweden), were used for localisation and to correct rigid setup errors. These were acquired at treatment and 'day zero' (Centre B only) which represents a trial set-up (nontreatment) session. Local protocols were followed at both institutions which involved soft tissue CBCT image registration to the target and manual adjustment if required. 4D CBCTs were acquired on an individual patient basis if tumour motion was considered significant (e.g. >1cm) and/or if 4D CBCT was required for matching.

For each patient, all saved CBCTs registrations were reviewed retrospectively by a research clinical fellow (centre A) or Therapeutic Radiographer (centre B) using in-house software and XVI Version 5.0 (Elekta AB, Stockholm, Sweden). ITACs were assessed using the Traffic Light Protocol devised by Kwint.[5] This tool assists treatment radiographers in CBCT review. A four coloured traffic light was used to grade ITACs depending on how they impact coverage of the GTV (Table 1), thus providing a surrogate for the risk of significant dosimetric changes.

The following ITACs were assessed; atelectasis, infiltrative change, pleural effusion, baseline shift, and GTV increase/ decrease. The treatment fraction at which the ITAC occurred was noted and radiographer notes were reviewed to document whether the patient was treated, physics or clinician review was needed or re-planning required. The time from RTP CT to treatment (1st CBCT) was recorded and a *t* test performed to assess for differences in time to treatment between patients who developed a GTV increase and those who did not.

To evaluate how ITACs impact the workflow a linear mixed effects model was used to assess the fixed effect relationship between set-up time and ITAC traffic light grade. Institution and patient identity were considered as nested random effect intercepts to account for any variability due to differences in process at the different institutes, or effects associated with individual patients respectively. Set-up time was assessed by using a surrogate consisting of the interval between the recorded times of the first CBCT and first treatment beam. CBCT imaging time and time of first treatment beam were acquired from the Mosaiq (Elekta AB, Stockholm, Sweden) record and verify databases at both institutes. At centre A, CBCT image times from Mosaiq and the CBCT databases were combined to minimize missing data. As less data was missing from the CBCT acquisition records than Mosaiq (n=61 and n=82 respectively) these were the data source. There was significant overlap between both datasets enabling imputation of missing CBCT records from the Mosaiq data using a linear fit (intercept 568s, gradient 0.98, R^2 = 0.94, residual standard error 114s). Following imputation n=22 records were missing. This data was normalized by log transformation and statistical significance assessed via the likelihood ratio test of this model against a null model with no fixed effect component.

Results

558 CBCTs were reviewed from 100 patients. Median patient age was 75 years (range 47.1-89.8). Information regarding histology, tumour location and treatment is provided as supplementary information. The majority (72%) were T1 tumours (i.e. size ≤3cm) with adenocarcinoma the commonest histological diagnosis. In over half of patients a biopsy was not attempted due to the risk of complications.

Figure 1 shows ITACs were observed in 22 patients (22%); seven demonstrated a red ITAC. Nine patients demonstrated ITACs of differing severity throughout treatment; two patients had nine ITACs, five had six ITACs and 15 had between one and five. Seventy-eight patients had no ITACs.

Table 2 shows that baseline shift was the most frequent ITAC. The majority were scored yellow (51%). 17 red ITACs were observed in seven patients; one patient had a red ITAC seen over six fractions, 2 patients over 3 fractions, and 4 patients at 1 fraction only. Examples are demonstrated in Figure 2. Table 3 depicts the spread of ITACs according to the treatment fraction.

Atelectasis was observed in two patients (2%), increasing in severity throughout the remainder of one patient's treatment and completely resolving in another.

Infiltrative changes were seen in six patients (6%), on 18 occasions, most frequently at fractions 3-5. These occurred three times in one patient and scored orange (described above in association with atelectasis), twice in another patient and graded orange (also described above, with GTV increase and localised atelectasis), and in one patient was observed in the contralateral lung for all six fractions, graded yellow. In the other three patients infiltrative changes scored yellow (total score; 30% orange, 70% yellow).

On five occasions a pleural effusion was noted, in three patients; three times within the same patient. Apart from one example, the change was minor and scored yellow. However, in one patient, treatment was planned with a large pleural effusion present. This resolved by day zero causing a large baseline shift, moving the tumour outside the PTV; graded red.

GTV decrease was observed 19 times in seven patients (7%), most frequently between the third and fifth fractions. These were minor and scored yellow. An increase in GTV volume was seen 14 times in five patients (5%). Two had GTV increase at all fractions. The other three patients had this noted at either the first or second fraction. Most were scored orange (86%), the rest were yellow (14%). There was no significant difference in time to treatment between patients who developed a GTV increase or decrease and those who did not (p=0.704 and p=0.990, respectively).

Baseline shift was noted in 34 fractions in seven patients (7%). Six had baseline shifts graded as red; 38% of all baseline shifts. Thirty-two percent of baseline shifts were graded orange and 29 yellow.

Seven patients demonstrated red ITACs. Table 4 demonstrates the frequency of clinician and physics contact by radiographers with concern regarding safe delivery of SABR. Over 558 fractions, physics were contacted 27 times (5%). Clinicians were contacted 29 times (5%); 15 of these occasions required the clinician attend the linac and provide guidance online. On the other occasions, advice was sought post-treatment, prior to the next fraction.

Physics support was most often required at the sixth fraction (13%), followed by day zero (10%) and fraction one (9%). Physics were commonly contacted to assess the dosimetric impact of unexpected CBCT changes. The most frequent problem was GTV and/or OAR drift on CBCT when compared to the RTP CT. Others are provided in supplementary data: 4D CBCT artefacts, poor image quality, assessment after noting couch rails were not in place for treatment and review of pacemaker dose. Mostly advice was given after attending the machine for CBCT review. On 7 occasions an adaptive assessment was required, involving a comparison of the CBCT with the RTP CT to quantitatively assess the dosimetric impact of CBCT changes.

Clinician review most commonly occurred at day zero (10%) followed jointly by the first (8%) and third fractions (8%). Clinicians were commonly contacted with concerns regarding adequacy of tumour coverage by the PTV, GTV or OAR drift. PTV coverage assessment was challenging due to difficulty determining the tumour edge (10%), motion (10%) and atelectasis/infiltrative change (17%). Three patients required treatment to be re-planned.

Individual set-up time values are provided as supplementary data. Figure 3 demonstrates, for each institution, how set-up times vary according to ITAC grade. Effect sizes and likelihood ratio tests for the mixed model are shown in Table 5. Effect sizes are estimated from the log transformed time intervals by taking the difference between the inverse transformed model intercept (i.e. time taken for green ITACs) and the inverse transformed model parameters (i.e. offsets of yellow, orange and red ITACs from green in log space) added to the intercept. The likelihood tests show that inclusion of ITACs as a fixed effect explains more of the variance in the data than not including ITACs in the pooled dataset after including hospital and patient IDs as random effects. This demonstrates that ITACs have a significant effect on treatment set-up time ($p=0.02$), with red scores prolongating average treatment time by about 7 minutes.

Discussion

SABR is the standard of care for early NSCLC patients unsuitable for surgery.[8] It is well tolerated, provides local control rates of ~90% at 5 years and has been shown to be superior to radiotherapy using standard fractionation.[9] Safe delivery of SABR is only possible due to advanced radiotherapy developments such as accurate image guidance and intensity modulated radiotherapy (IMRT). These permit delivery of large doses of radiotherapy with high precision and accuracy in the order of 2-3mm. In the UK 54 – 60Gy is typically delivered over 3-8 alternate day fractions.[10] However this is potentially associated with serious risks. Mediastinal OARs (e.g. proximal bronchial tree) have a low alpha/beta ratio and are susceptible to severe toxicity from such hypofractionated treatment.[11] This was shown in early work by Timmerman and colleagues demonstrating excessive rates of grade 3-5 toxicity when treating central tumours with SABR.[12] Therefore strict IGRT workflows are required to protect these critical structures from excessive dose and ensure SABR is delivered safely.[10] To our knowledge, this is the first piece of work to assess the impact of ITACs upon SABR delivery for lung cancer and the wider workflow. Despite finding ITACS in 22% of patients, most were minor and rarely prevented treatment. However, ITACs can represent a significant resource burden with repeated physics and clinician involvement.

The proportion of patients who developed ITACS in this study (22%) is considerably less than other studies including lung cancer patients with more advanced stage of disease. For example Kwint et al reported ITACs in 72%; this is unsurprising as in this study 76% of patients had locally advanced lung cancer.[5,6,13] Larger tumours are more likely to be associated with anatomical changes. In this current study 72% of patients had tumours <3cm and, as per national guidelines, outside of the 'No Fly Zone' (2cm radius from the main airways and proximal bronchial tree).[14] Other studies evaluating ITACs mostly included patients with locally

advanced disease treated with conventional (chemo)radiation.[5,13,15] Such differences undoubtedly influence ITAC frequency.
Changes in tumour size and position led to the most commonly observed ITACs. Baseline shift was observed over 34 fractions (36% of ITACs). GTV decrease was observed on 19 occasions in 7% of patients. Within the literature tumour regression is reported typically in 1/3 of patients treated with (chemo)radiotherapy (however, as above, the majority of these studies involved locally advanced disease).[5,15]

GTV increase was seen on 14 occasions in five patients (8%). Two patients experienced a GTV increase throughout treatment. The other three demonstrated this at the first or second fraction. It did not interrupt treatment. The median time from RTP CT to first treatment was 15 days. No significant difference was seen between this time for the group with GTV increase and without, inferring that the duration of time from planning scan to start of radiotherapy does not influence the development of this ITAC. It is difficult to know what this change represents. It may represent tumour progression, oedema or inflammation. However, early cancers treated with SABR typically grow slowly. Therefore significant growth during the short time between treatment planning and radiotherapy seems unlikely.

Atelectasis was observed in two patients (2%). One was scored red, the other orange and consequently required both physics and clinician review. The patients could still be treated; however, there was difficulty in determining GTV coverage, prompting clinician review. Atelectasis was reported in approximately 15% of patients in the Netherlands Cancer Institute (NKI) and Aarhus studies and led to plan adaptation in 9-12%.[5,6,13] Again these studies included more locally advanced stages and there is a paucity of data looking at this in the context of SABR. A recent case report illustrates how atelectasis can affect the treatment of lung cancer with SABR.[16] The tumour was associated with segmental atelectasis. This resolved after the first dose of 10Gy causing a 15mm tumour baseline shift. Consequently thereafter the tumour was incompletely covered by the PTV, requiring plan adaptation.

The occurrence of ITACs during lung SABR can represent a resource burden. This is demonstrated by the frequency of physics (5%) and clinician (5%) involvement; 52% of fractions requiring clinician involvement necessitated attendance at the linac for online CBCT review. Over half were due to difficulty in establishing PTV coverage or tumour localisation. Physics were mostly requested (78%) to provide guidance on the dosimetric implications of GTV/OAR drift or changes in external contour (e.g. arm positioning). On 7 occasions (26%) this involved an additional adaptive assessment.

The mixed model analysis demonstrates that ITACs have a significant effect upon set-up time in these data ($p=0.02$). Figure 3 suggests that this impact is mostly driven by red ITACs. As discussed in methodology, in order to minimise missing data, CBCT image times from Mosaiq and CBCT acquisition databases at centre A were combined. Following imputation, time to treatment data was missing for 9% and 20% of fractions at centre A and centre B respectively. Figure 3 highlights a notable difference in the set-up time durations between each institution; this is explained by a discrepancy in clock synchronisation between treatment software at centre A. This clock offset translated to a consistent increase in set-up times and greater values compared to centre B where the clocks had previously been synchronised and no offset was present. Figure 3 also demonstrates greater variability in the set-up times at centre A compared to centre B. This would suggest the process of managing the impact of ITACs upon set-up time is more uniform at centre B. This warrants further investigation to assess if there are examples of good practice that can be adopted into future protocols. The analysis of these data accounted for variation between centres such as this, or effects associated with individual patients, by including institution and patient identities as nested random intercepts in the model. Our analysis showed a mean delay of 7 minutes for red compared to green ITAC scores. Such prolongation of treatment time can have important consequences for patient throughput, patient comfort and treatment accuracy. The latter aspect is supported by several publications that show an increase in intra-fraction motion as a function of time.[17]

Tumour baseline shift is usually judged by evaluating the difference in tumour position between the RTP CT and CBCT after bony anatomy registration. Our analysis used saved results from image registrations taken at the time of treatment. This included treatment and OAR contours. However, since the correction reference point within the RTP CT had been set to the isocentre, rather than within the PTV, it was not possible to accurately quantify the baseline shift; it was only possible to identify shifts that appeared grossly different

and/or compromised an adjacent OAR. Additional analysis was undertaken to confirm the presence of baseline shift using dual registration (e.g. bone and soft tissue), if this was suspected.

In addition, review of radiographer notes to assess 'action taken' illustrated that baseline shifts were an issue. This was apparent after the radiographers had undertaken a soft tissue match and would manifest as drifts in OAR position with respect to their contours. 'GTV/OAR drift' was the commonest reason for clinician or physics review and according to radiographer notes frequently prompted senior radiographer review; unfortunately the frequency of this latter outcome was not recorded. Therefore, it's likely the frequency of this ITAC is under-reported. The authors believe additional investigation into the occurrence, magnitude and dosimetric consequences of baseline shift in patients treated with SABR for lung cancer is necessary. This could be achieved by performing new registrations with the correction reference point selected appropriately to correct for rotation. Baseline shifts could be more easily recorded when dual image registration is used.[18]

Soft tissue matching to the GTV allows for correction of inter-fractional baseline shifts in tumour position. However, this can cause critical structures to migrate away from their PRVs (which help to ensure they receive a safe dose) and should be carefully considered when radiographers review image guidance. This risk is exemplified by the 'red' baseline shift observed which led to the PTV overlapping the small bowel, leading to the potentially serious risk of small bowel ulceration given the high dose per fraction. One way to reduce the resource burden of unexpected baseline shifts is to account for this possibility when generating the treatment plan. At the NKI, the impact of a potential 1cm tumour baseline shift in all planes is considered at planning. These shifts are 'pre-authorised' by the clinician, providing these efforts to improve tumour coverage by the PTV do not compromise protection of critical structures by their OARs. This helps to reduce unplanned clinician/physics review should these occur.

Three patients had their treatment re-planned. Given that 22% of yellow and orange ITACs prompted clinician or physics review, this suggests treatment radiographers are overly cautious when seeking this additional support. This represents a significant drain on physics, clinician and radiographer time and risks affecting patient treatment time and departmental workflow. This suggests there is a need to improve guidance for radiographers with an emphasis on dealing with ITACs. This is particularly relevant given the results of the lung SABR survey demonstrating that almost a half of SABR centres lack a protocol to deal with anatomical changes.[19] Detailed advice on how to approach CBCT changes in IGRT workflows will hopefully improve radiographer confidence when treating these patients. This is likely to be of use when treating the thorax irrespective of the type of cancer. Some centres utilise specialist radiographers, trained in the interpretation of CBCTs and the management of ITACs, who can help reduce physics and clinician involvement. Collectively these measures should help reduce the impact upon set-up time and the wider service and may be useful considerations for centres preparing to implement SABR.

This study is limited as CBCTs were scored retrospectively by one observer. There is clearly a subjective element to ITAC assessment and it is likely to be associated with inter-observer variation. A method for evaluating GTV changes by delineating the tumour on the first and last treatment CBCTs has been developed.[20] This allows for an objective assessment of GTV change but at the expense of being significantly more time consuming.

Tumour motion accounted for 17% of the reasons for clinician review, demonstrating that motion should be included in guidance for ITAC assessment. Whilst most CBCTs reviewed in this study were 3D acquisitions, some were 4D. These were acquired if significant motion (>1cm superior – inferior) was seen on the planning CT, or suspected when reviewing the 3D CBCT (e.g. GTV blurring or large shifts) at the time of treatment.

These data clearly support the rationale for improving IGRT protocols. Whilst limited as it is derived from only two centres, these are institutions with considerable lung SABR experience. To further enhance the quality of this work, a dosimetric analysis of cases with ITACS should be undertaken.

Conclusion

In conclusion, intra-thoracic anatomical changes have been observed in 22% of patients undergoing SABR for lung cancer. Over half are minor and rarely interrupt treatment. However, ITACs are associated with unplanned physics or clinician involvement and therefore represent a resource burden. There is a need to

incorporate detailed guidance on the management of ITACs into IGRT workflows. This should help to streamline workflow and reduce ITAC impact.

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Tables

Action level	Descriptor
Red	The GTV is outside the PTV due to ITACs. The radiation oncologist is called immediately and treatment is only given when approved by the radiation oncologist.
Orange	The GTV is just inside the PTV due to ITACs. The radiation oncologist is notified by email and has to respond before the next fraction. Further diagnostics are considered as a result of the ITAC.
Yellow	There is an ITAC visible but the GTV is well inside the PTV. The radiation oncologist is notified by email about the ITAC but no response is necessary and treatment may continue.
Green	No change visible. No action needed.

Table 1. Traffic light scores and descriptors [1]

Anatomical change	Red	Orange	Yellow	Green	Total ITACs *(i.e. non green)*
Atelectasis	3	2	0	553	**5**
Infiltrative change	0	5	13	540	**18**
Pleural effusion	1	0	4	553	**5**
GTV decrease	0	0	19	539	**19**
GTV increase	0	12	2	544	**14**
Baseline shift	13	11	10	524	**34**
Totals	17	30	48	-	**95**
Total as a percentage of all ITACs	**18%**	**32%**	**50%**	-	-

Table 2. Distribution of traffic light Scores (558 CBCTs reviewed from 100 patients)

ITACs	Fraction								
	0	1	2	3	4	5	6	7	8
Atelectasis	1	0	1	1	1	1	0	0	0
Infiltrative change	2	2	2	4	4	4	0	0	0
Pleural effusion	1	1	0	1	1	1	0	0	0
GTV decrease	0	0	2	5	3	5	2	1	1
GTV increase	1	4	3	2	2	2	0	0	0
Baseline shift	7	4	4	6	4	3	2	2	2
Total	**12**	**11**	**12**	**19**	**15**	**16**	**4**	**3**	**3**
Total fractions	48	100	100	101	82	82	15	15	15

Table 3. Distribution of ITACs according to fraction of radiotherapy

Fraction number	0	1	2	3	4	5	6	7	8	Total
Number of fractions delivered	48	100	100	101	82	82	15	15	15	558
Frequency of request for Physics support	5	9	2	4	5	0	2	0	0	27
Physics support as a percentage of fractions	**10%**	**9%**	**2%**	**4%**	**6%**	**0%**	**13%**	**0%**	**0%**	**5%**
Frequency of request for clinician support	5	8	3	8	4	1	0	0	0	29
Clinician support as a percentage of fractions	**10%**	**8%**	**3%**	**8%**	**5%**	**1%**	**0%**	**0%**	**0%**	**5%**

Table 4. The frequency of requests for physics and clinician support distributed across treatment fractions

	Green vs Yellow effect size	Green vs Orange effect size	Green vs Red effect size	Likelihood ratio test
Centre A	60 s	214 s	477 s	$X^2(3)=4.27$ p=0.2
Centre B	-35 s	25 s	288 s	$X^2(3)=11.60$ p=0.01
Pooled	-18 s	80 s	339 s	**$X^2(3)=9.22$ p=0.02**

Table 5. Mixed model analysis of treatment time versus ITAC grade

Illustrations

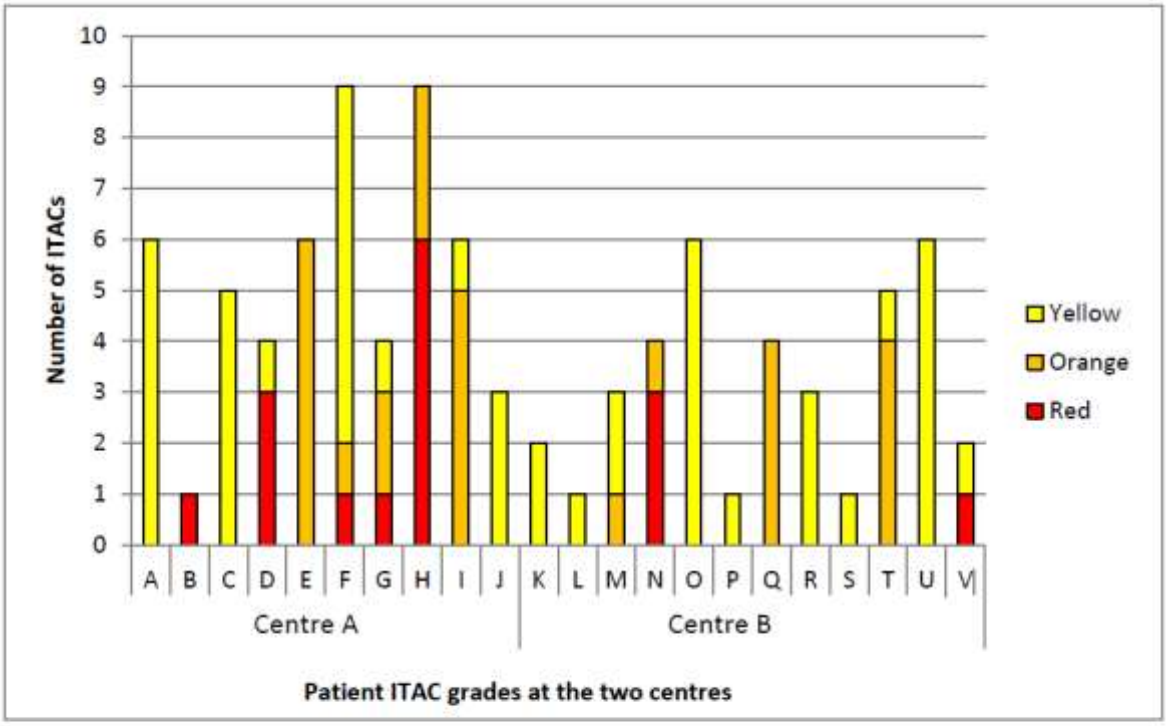

Figure 1. The distribution of ITACs per patient (558 CBCTs reviewed from 100 patients)

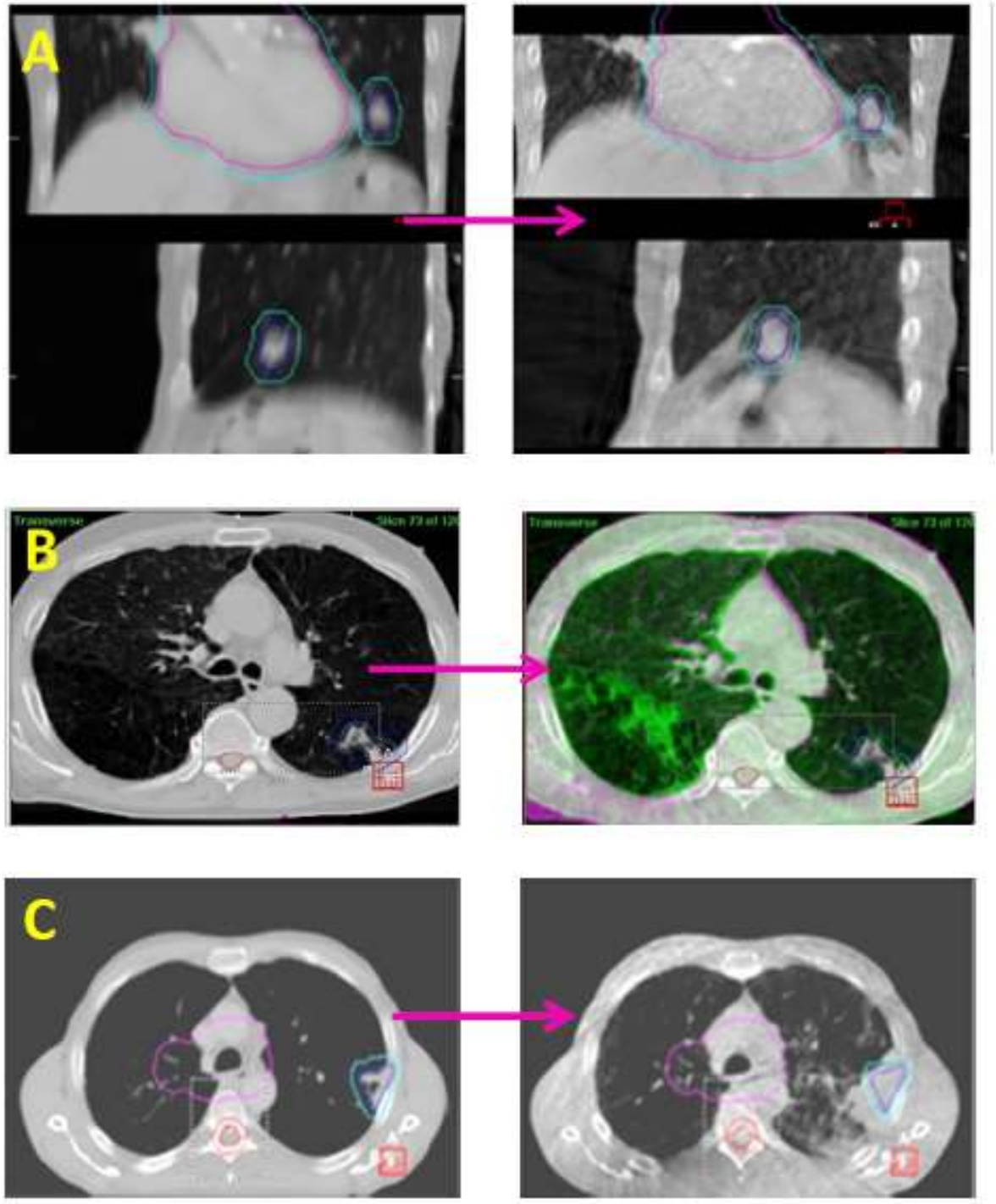

Figure 2. Examples of ITACs, in the left column is the RTP CT depicting the GTV and PTV contour (blue). In the right column is the CBCT. A- Coronal and sagittal projections showing tumour close to the diaphragm. The CBCT demonstrates a baseline shift scored *red* whereby the tumour has moved closer to the diaphragm causing the PTV to overlap with the small bowel. B- Axial images that show the development of infiltrative change in the contralateral lung scored *yellow*. C- Axial images of a tumour that becomes obscured by atelectasis and infiltrative change scored *red*. This ITAC makes it difficult to localise the tumour.

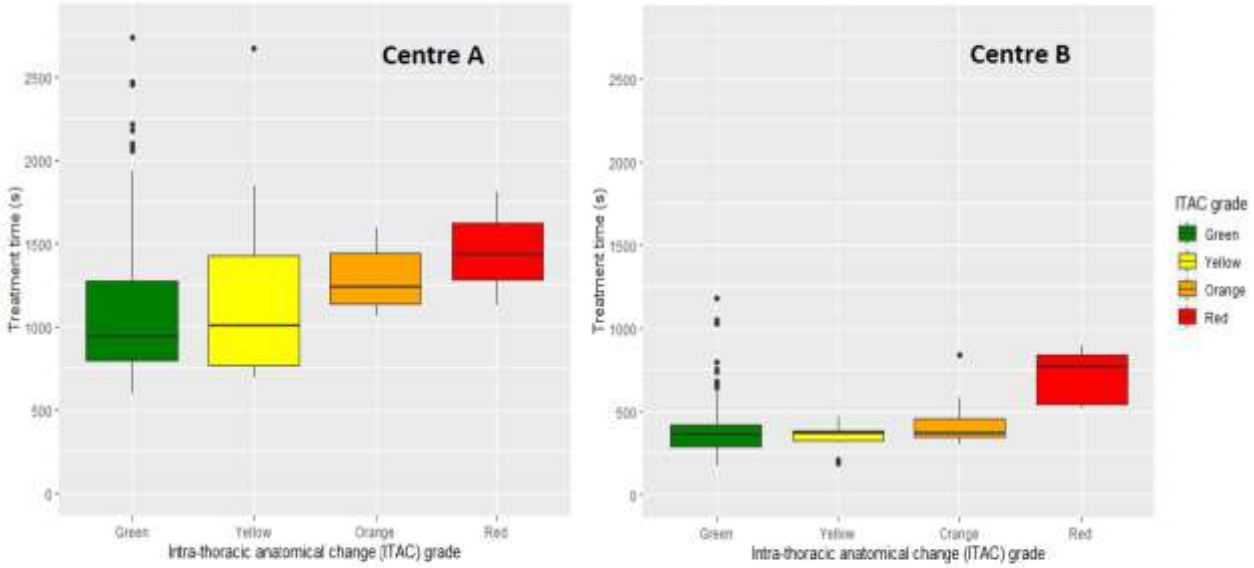

Figure 3. Treatment set-up times according to the grade of ITAC