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FULL PAPER

Lung stereotactic ablative radiotherapy (SABR): dosimetric considerations for chest wall toxicity

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Objective: To investigate chest wall pain in patients with peripheral early stage lung cancer treated with stereotactic ablative radiotherapy (SABR), and to identify factors predictive of Common Terminology Criteria of Adverse Events Grade 2 + chest wall pain.

Methods: Patients who received 55 Gy in five fractions were included. A chest wall structure was retrospectively defined on planning scans, and chest wall dosimetry and tumour-related factors recorded. Logistic regression was performed to identify factors predictive of ≥Grade 2 chest wall pain.

Results: 182 patients and 187 tumours were included. There were 20 (10.9%) episodes of ≥Grade 2 chest wall pain. Multivariate logistic regression demonstrated that the maximum dose received by 1 cm^3 of chest wall (D_{max}1 cm^3) and tumour size were significant predictors of ≥Grade 2 chest wall pain [D_{max}1 cm^3 odds ratio: 1.104, 95% confidence interval: 1.012–1.204, $p = 0.025$; tumour size (mm) odds ratio: 1.080, 95% confidence interval: 1.026–1.136, $p = 0.003$]. This model was an adequate fit to the data (Hosmer and Lemeshow test non-significant) and a fair discriminator for chest wall pain (area under receiver-operating characteristic curve: 0.74). Using the multivariate logistic regression model, parameters for D_{max}1 cm^3 are provided, which predict <10% and <20% risks of ≥Grade 2 chest wall pain for different tumour sizes.

Conclusion: Grade 2+ chest wall pain is an uncommon side effect of lung SABR. Larger tumour size and increasing D_{max}1 cm^3 are significant predictors of ≥Grade 2 chest wall pain. When planning lung SABR, it is prudent to try to avoid hot volumes in the chest wall, particularly for larger tumours.

Advances in knowledge: This article demonstrates that Grade 2 or greater chest wall pain following lung SABR is more common when the tumour is larger in size and the D_{max}1 cm^3 of the chest wall is higher. When planning lung SABR, the risk of chest wall pain may be reduced if maximum doses are minimized, particularly for larger tumours.

INTRODUCTION

Stereotactic ablative radiotherapy (SABR) in patients with early-stage peripheral lung cancer is an increasingly adopted treatment option for patients who are considered unsuitable for surgical intervention.[1] Despite the high dose per fraction, SABR is usually well tolerated.[1–3] Fatigue, pulmonary toxicity, chest wall toxicity and brachial plexopathy are reported side effects.[2–7] Chest wall toxicity includes skin reactions (erythema, ulceration and fibrosis), chest wall pain and rib fracture.[5,8–10] The duration of chest wall pain varies from transient to several weeks or longer and usually occurs more than 6 months after SABR.[5,11]

This report details chest wall pain following lung SABR in a cohort of 182 patients and attempts to identify factors which may contribute to the development of chest wall pain. Patients with tumours adjacent to the chest wall, who therefore received a SABR dose of 55 Gy in five fractions, were included in the analysis.

METHODS AND MATERIALS

This was a retrospective review of clinically gathered data.

Patients, eligibility for stereotactic ablative radiotherapy and treatment

Medically inoperable patients treated with lung SABR at St James's Institute of Oncology between January 2009 and December 2012 were included. Patients were treated using a risk-adapted SABR protocol.

Patients were eligible for SABR provided the tumour was:[12]
(1) peripheral (*i.e.* out with a 2-cm safety zone around the central, lobar and segmental airways)
(2) histologically proven non-small cell lung cancer or considered malignant based on fludeoxyglucose positron emission tomography (PET) positivity and/or growth on sequential CT scans
(3) ≤5 cm
(4) node negative on PET +/− endobronchial ultrasound-guided biopsy
(5) non-metastatic based on fludeoxyglucose PET scanning.

Patients were immobilized with a custom-made Vac-Lok™ bag (Civco Medical Solutions, Coralville, IA) using a standard wing board arm support system in the supine position. If the wing board was unsuitable owing to tumour position, then a thermoplastic shell (Orfit Industries, Wijnegem, Belgium) was used. A multislice, helical, respiration-correlated CT (four-dimensional CT) was performed to determine patient-specific motion margins using a Siemens Somatom® scanner (Siemens AG, Erlangen, Germany) connected to a commercially available respiratory sensor (AZ-733V; Anzai Medical, Tokyo, Japan).

The gross tumour volume (GTV) was contoured on three of the respiratory phases [the mid-ventilation position (typically 40% exhale), 0% exhalation and 100% exhalation], and an ITV (internal target volume) was generated which encompassed all three GTVs. All other four-dimensional CT data sets were reviewed to check that the ITV encompassed the tumour in all respiratory phases, and if necessary, the GTV was adapted to include any inadequately encompassed tumour.[12] The final ITV therefore encompassed the GTV throughout the whole respiratory cycle. No margin was added for the clinical target volume, as is standard in lung SABR practice.[12,13] A 5-mm isotropic margin was added to the ITV to create the planning target volume PTV as is recommended when using daily online image guidance using cone-beam CT,[12,13] and as has been found to be adequate based on local audit. The Advantage Workstation (GE Healthcare, Waukesha, WI) was used for contouring purposes.

Treatment planning was performed using CMS Xio (Eletka AB, Stockholm, Sweden). Coplanar or non-coplanar field arrangements and 6-MV photons were used. In the majority of cases, treatment was prescribed to the 80% isodose. Organ at risk and conformity constraints were as per the UK SABR consortium guidelines.[12] Three dosing schedules were used depending on tumour location: 54 Gy in three fractions (for tumours away from airways and not adjacent to the chest wall), 55 Gy in five fractions (for tumours adjacent to the chest wall) and 60 Gy in eight fractions (for tumours close to the mediastinum and airways or brachial plexus). Although a specific fractionation schedule is used for tumours in close proximity to the chest wall, no specific dosimetric chest wall constraints are employed for SABR planning. As above, daily online image guidance was performed using cone-beam CT and a tolerance of <3 mm.[12]

Only tumours prescribed 55 Gy in five fractions were included in this analysis as this dose fractionation is used for tumours in closest proximity to the chest wall. By including only one dose fractionation schedule, this avoids the need for biologically equivalent dose conversion (and therefore avoids the introduction of uncertainties in the alpha/beta ratios for the different tissues of the chest wall and uncertainties regarding the use of the linear-quadratic model for dose conversions when using high doses per fraction).[14]

Response assessment and follow-up

Patients were routinely assessed during treatment by therapeutic radiographers before each fraction, then by an oncologist (MS, KC, RT or KF) at 6 weeks and 12 weeks following completion of treatment and then 3 monthly for the first 2 years, and 6 monthly for 3–5 years. Chest X-ray was performed at each patient visit and CT scanning was performed every 6 months for 5 years.

Chest wall pain was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 3. Asymptomatic rib fractures were not considered in the analysis.

Definition of the chest wall and dosimetry

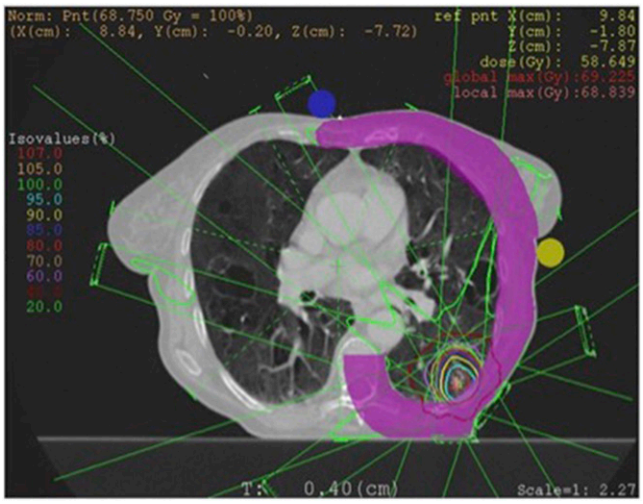
The chest wall, including the bone and soft tissue (parietal pleura and intercostal muscles) in the treated hemithorax, was contoured retrospectively on the original treatment plans.

The chest wall structure was created as follows:

$$\text{Chest wall} = (\text{lung} + 3\ \text{cm isotropic margin}) - [\text{lung} + (\text{pericardium} + \text{margin})]$$

The margin around the pericardium was 0 cm superiorly, anteriorly and laterally, 2 cm inferiorly and 4 cm posteriorly. The resulting contour was then edited to exclude any remaining mediastinum and vertebral bodies (Figure 1).

Figure 1. Example of lung stereotactic ablative radiotherapy plan showing a stage T1 left-sided lung tumour in close proximity to the chest wall. The chest wall structure which was used in the analysis is highlighted in magenta. A dose of 55 Gy is prescribed to the 80% isodose.



For each plan, the chest wall mean dose (D_{mean}), the maximum dose received by 1 cm^3 ($D_{max}1\ cm^3$) of the chest wall and the volume of chest wall receiving 50 Gy or more (V_{50}), 30 Gy or more (V_{30}) and 10 Gy or more (V_{10}) were recorded.

For every patient, the same experienced radiation oncologist (EK) measured the shortest distance between the edge of the tumour and the chest wall (mm) using the lung windows setting. Maximum tumour diameter was recorded from the diagnostic imaging reports, and a radiologist in the multidisciplinary meeting reviewed all imaging prior to SABR.

Data analysis

Overall survival, time to relapse (death not considered an event unless from lung cancer) and ≥Grade 2 chest wall pain-free survival were calculated from the first day of radiotherapy treatment using Kaplan–Meier analysis. In cases of patients with more than one tumour who received sequential SABR treatments, overall survival statistics were calculated from the treatment start date for the first lesion.

Univariate and multivariate binary logistic regression were performed using backwards elimination using likelihood ratios in order to determine which factors predicted ≥Grade 2 chest wall pain. The factors included in the analysis were: patient age, gender, minimum chest wall to tumour distance, tumour size, chest wall D_{mean}, chest wall $D_{max}1\ cm^3$ (to reflect a near maximum dose) and chest wall V_{50}, V_{30} and V_{10} to reflect volumes of chest wall receiving high, medium and low doses.

Since chest wall pain may develop over time, consideration was given to assessing the risk of ≥Grade 2 chest wall pain using a Cox regression model in addition to a logistic regression analysis. As the event of importance was whether or not chest wall pain occurred, and the exact time at which chest wall pain developed was of less importance, it was decided to use a logistic regression analysis alone.

Table 1. Baseline characteristics

Characteristic	
Age [median (interquartile range)] (years)	75 (69–81)
Male : female (%)	57 : 43
Tumour diameter [median (interquartile range)]	20 mm (16–28 mm)
Histological diagnosis (%)	39% ($n = 72$)
Positron emission tomography standardized uptake value [median (interquartile range)]	7.9 (4.8–11.9)
Minimum tumour-to-chest wall distance [median (interquartile range)]	0 (0–5.4 mm)

A p-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS® v. 21 (IBM Corp., New York, NY; formerly SPSS® Inc., Chicago, IL). Goodness of fit was assessed using the Hosmer and Lemeshow test, and the discrimination of the model was assessed using the area under the receiver-operating characteristic (ROC) curve.[15]

The final logistic regression model was used to determine some clinically useful parameters to limit the risk of ≥Grade 2 chest wall pain.

RESULTS

In total, 187 tumours were irradiated using a schedule of 55 Gy in five fractions in 182 patients. 3 patients had 2 lesions treated simultaneously and 2 patients had 2 lesions treated sequentially (thus, 184 treatment episodes in total). Median follow-up was 21.0 months (range: 0.3–45 months). Baseline characteristics are summarized in Table 1. At the time of analysis, there had been 63 deaths and 27 episodes of cancer relapse, including 6 patients who developed new primary lung tumours. In total, there were five episodes of local relapse (2.7%), two of which were cases of isolated local relapse and three of which were associated with

Figure 2. Crude number of episodes of chest wall pain at different time points.

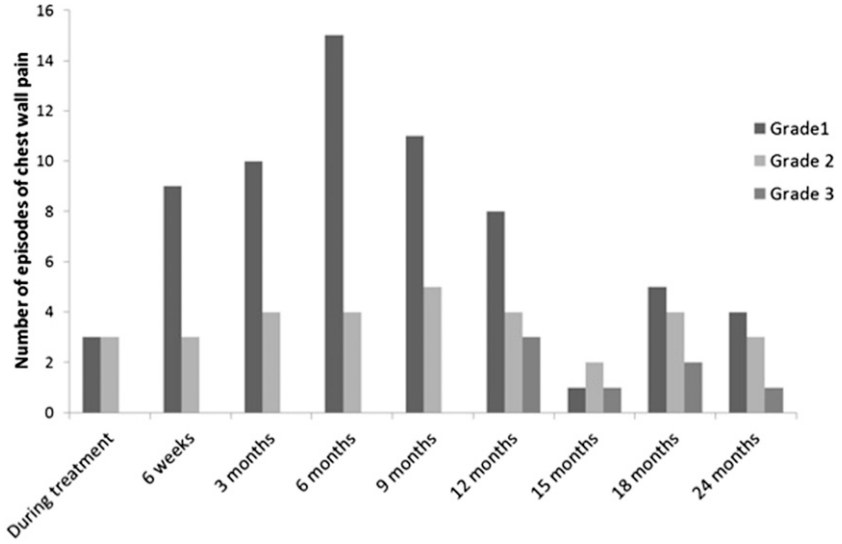


Table 2. Univariate and multivariate logistic regression for ≥Grade 2 chest wall pain

Factor	*p*-value	Odds ratio	95% confidence interval
Univariate analysis			
Minimum tumour-to-chest wall distance (mm)	0.058	0.842	0.704–1.006
Chest wall D_{mean}	0.001	2.104	1.335–3.315
Chest wall $D_{max}1\,cm^3$	0.019	1.103	1.016–1.197
Chest wall V_{50}	0.003	1.063	1.021–1.108
Chest wall V_{30}	< 0.001	1.031	1.015–1.047
Chest wall V_{10}	0.004	1.006	1.002–1.010
Tumour size (mm)	0.002	1.082	1.030–1.136
Age	0.269	0.971	0.920–1.023
Gender	0.867	1.083	0.426–2.754
Multivariate analysis			
Chest wall $D_{max}1\,cm^3$	0.025	1.104	1.012–1.204
Tumour size (mm)	0.003	1.080	1.026–1.136

nodal (two patients) or distant (one patient) relapse. In total, 6 (3.3%) patients developed isolated nodal relapse and 11 patients developed metastatic disease with or without locoregional recurrence (6.0%, and including 1 patient, already mentioned above, who experienced local recurrence). Overall survival was 80.0%, 59.5% and 45.6% at 1, 2 and 3 years, respectively. Median overall survival was 29 months. The disease relapse-free proportion (including patients with new primary tumours) was 90.1%, 77.8% and 69.6% at 1, 2 and 3 years, respectively.

The crude number of chest wall pain episodes at different time points is summarized in Figure 2. For a total of 184 treatment episodes, a total of 49 (26.7%) patients experienced chest wall pain of any grade. Chest pain of any grade was reported at only 1 visit in 26 patients, on 2 consecutive visits (*i.e.* persisting more than 3 months) in 11 patients and on at least 3 consecutive visits (*i.e.* persisting more than 6 months) in 10 patients. Non-consecutive episodes of chest wall pain occured in 12 patients (*i.e.* 2 episodes of pain occurred with at least 1 pain-free visit in between). In total, 20 (10.9%) patients experienced Grade 2 or 3 chest pain. In those patients who experienced ≥Grade 2 chest wall pain, the median time to onset was 9 months (range 0–24 months). Grade 2 or greater chest wall pain-free survival was 92.0% and 89.3% at 1 and 2 years, respectively. Grade 3 chest wall pain occurred in 5 (2.7%) patients only, and there were no Grade 4 pain events. None of the patients who experienced local relapse reported chest wall pain, and so local recurrence with associated ingrowth into the chest wall did not account for any of the episodes of chest wall pain described above.

Univariate analysis identified that the chest wall D_{mean}, $D_{max}1\,cm^3$ and V_{50}, V_{30} and V_{10} were statistically significant predictors of ≥Grade 2 chest wall pain. In addition, tumour size was found to be significant (Table 2). On multivariate analysis, only chest wall $D_{max}1\,cm^3$ and tumour size remained in the final model (Table 2). The final model was non-significant using the Hosmer and Lemeshow test ($p = 0.380$), thus suggesting that the final model is an adequate fit for the data.[15] The area under the ROC curve for the final model was 0.74 (95% confidence interval 0.634–0.845), suggesting that the discrimination of the model was fair.[15]

Using the multivariate logistic regression model, based on different tumour sizes, parameters for $D_{max}1\,cm^3$ were calculated which limit the predicted risk of ≥Grade 2 chest wall pain to < 10% and < 20% (Table 3). For tumours up to 10 mm, despite the dose heterogeneity that accompanies SABR, it is unlikely that the chest wall will receive doses high enough to result in a 10% risk of ≥Grade 2 chest wall pain. For tumours up to 20 mm, it is unlikely that the chest wall will receive doses high enough to result in a 20% risk of ≥Grade 2 chest wall toxicity.

DISCUSSION

Chest wall pain in association with SABR is more common for lesions in close proximity to the chest wall.[11,16] Symptoms may develop without obvious injury or may result from rib fracture,

Table 3. Parameters to limit predicted risk of ≥Grade 2 chest wall toxicity depending on tumour size based on multivariate logistic regression model

Tumour size (mm)	$D_{max}1\,cm^3$ to limit predicted risk to < 10% (Gy)	$D_{max}1\,cm^3$ to limit predicted risk to < 20% (Gy)
≤10 mm	71.5	80.0
11–20 mm	64.0	72.0
21–30 mm	56.0	64.0
31–40 mm	48.0	56.5
41–50 mm	40.0	48.0

D_{max} 1 cm^3 maximum dose received by 1 cm^3 of chest wall.

Table 4. Studies which have examined chest wall pain in patients treated with lung stereotactic ablative radiotherapy

Study	Treatment period (years)	Tumours	Total dose (Gy)/fraction number	Number of patients/lesions	CTC version	Chest wall pain incidence	Comments
Baumann et al[28]	2003–2005	Primary NSCLC, all peripheral	45 Gy/3	57 patients	2.0	All grades: 19% Grade 3 pain events: 2 (3.5%)	Low incidence of chest wall pain, especially Grade 3 events
Dunlap et al[5]	2005–2008	Primary lung + lung metastases, all peripheral (within 2.5 cm of chest wall)	Varied by institution 3–5	60 patients	3.0 (adapted)	Grade 1/2/3: 3.3%/ 1.7%/28.3%	Suggested: $V_{30} < 30\ cm^3$ to reduce the risk of chest wall toxicity
Andolino et al[11]	2000–2008	Lung and liver lesions	54 Gy (18–72)/3 (2–5)	347 lesions; dosimetry for 79 patients	3.0	All grades: 36 (11%)	Suggested: chest wall $D_{max} < 50$ Gy, $V_{40} < 5\ cm^3$ to minimize toxicity
Bongers et al[25]	2003–2009	Early stage lung cancer	60 Gy/3 60 Gy/5 60 Gy/8	500 patients	4.03	All grades: 11.4% Grade 3 in 2%	Patients with chest wall pain had larger treatment volumes and shorter tumour–chest wall distances For Grade 3 chest wall pain, V_{30} to V_{50} larger trend only, not significant on univariate analysis
Nambu et al[17,29]	2001–2009	Primary NSCLC	48 Gy/4 60 Gy/10 70 Gy/10	177 patients; dosimetry for 48 patients	3.0	Grade 1/2/3–4: 6%/4%/0%	Rib fractures frequent (23.2%) but related chest wall pain is less frequent and generally mild
Asai et al[18]	2003-2007	Primary lung + lung metastases	48 Gy/4	116 patients	3.0	Among 28 cases with rib fracture, Grade 1/2/3 chest wall pain in 4/7/1 patients	Rib fractures in 24% 57% of patients with rib fracture were asymptomatic 43% symptomatic but duration of pain short and generally mild
Creach et al[9]	2004–2009	Primary lung + lung metastases	54 Gy/3 50 Gy/5	146 patients	3.0	Grade 1/2/3: 7%/6%/1%	Elevated BMI and presence of CTD significant predictors of chest wall pain suggested: V_{30} threshold $\leq 0.7\%$, $V_{40} \leq 0.19\%$ to limit to 15% risk of chest wall pain
Taremi et al[24]	2004–2008	Early stage NSCLC	54 Gy/3 60 Gy/3	46 patients	3.0	Grade 1/2/3: 20%/20%/6.5%	Maximum point dose to ribs are higher for patients with chest wall pain Age, female gender and $D_{0.5cc}$ of ribs significant predictors of rib fracture

(Continued)

Table 4. (Continued)

Study	Treatment period (years)	Tumours	Total dose (Gy)/fraction number	Number of patients/lesions	CTC version	Chest wall pain incidence	Comments
Stephans et al[10]	2005–2008	Primary NSCLC + lung metastases	60 Gy/3	48 patients	3.0	Grade1/2/3: 8.3%/12.5%/0%	Tumour size significant predictor on univariate analysis only Suggested: $V_{30} < 30\,cm^3$ and $V_{60} < 3\,cm^3$ for ≤10–15% risk of chest wall toxicity
Welsh et al[16]	2004–2008	Primary + lung metastases, all within 2.5 cm of chest wall	50 Gy/4	265 patients	3.0	Acute: 5%, any grade; chronic: 17%, any grade (8.6% Grade 2 + 3)	$V_{30} \geq 31$ ml and BMI ≥ 29 were significant predictors of chest wall pain; DM also important in patients with BMI ≥ 29
Ding et al[27]	-	Primary NSCLC + lung metastases to the lung	60 Gy/5	10 patients	–	Study evaluating VMAT for decreasing chest wall	VMAT technology has potential to limit dose to the chest wall (decreased V_{30} of the chest wall and ribs)
Mutter et al[21]	2006–2009	Early stage NSCLC	60 Gy/3 54 Gy/3 48 Gy/4 45 Gy/5	126 patients	3.0	Grade1/2/3: 15%/13%/15%	$V_{30} \geq 70\,cm^3$ correlated with ≥Grade 2 chest wall pain
Cuaron et al[22]	2007–2011	Stage T2–T4N0 NSCLC, >3 cm		63 patients	4.0	22.8% developed ≥Grade 2	$V_{30} \geq 70\,cm^3$ correlated with ≥Grade 2 chest wall pain
Woody et al[26]	2004–2008	Majority early stage NSCLC	60 Gy/3 50 Gy/5 48 Gy/4 50 Gy/10	102 patients	3.0	Grade1/2/3: 5.7%/ 12.3%/0.9%	mEUD better predictor of chest wall pain than V_{30} (small volume of chest wall receiving high dose is important) mEUD and BMI significant predictors of chest wall pain
Kelly et al[30]	2004–2008	Previously standard EBRT to the thorax for lung cancer	50 Gy/4 40 Gy/4 and other	36 patients	–	Total: 31% Requiring narcotic: 17%	Chest wall pain more common if undergoing SABR for in-field relapse
Coroller et al[31]	2010–2013	Primary + lung metastases, all peripheral	54 Gy/3 if chest wall $V_{30} < 30$ ml or 50–60 Gy/5	69 patients	4.0	Grade 1/2/3: 4.2%/2.8%/ 1.4% Rib fracture:6.9%	Optimization of treatment plans based on chest wall V_{30} resulted in low incidence of chest wall pain; no significant patient-related or dosimetric factors identified for prediction of chest wall pain with this strategy

(Continued)

Table 4. (Continued)

Study	Treatment period (years)	Tumours	Total dose (Gy)/fraction number	Number of patients/lesions	CTC version	Chest wall pain incidence	Comments
Li et al[23]	2006–2013	Early stage or isolated recurrent biopsy confirmed NSCLC	70 Gy/10	82 patients not suitable for 50 Gy/4	Not stated	Grade2/3: 4.9%/1.2%	Suggested: (for 70 Gy/10 fractions) $V_{30} \leq 250\,cm^3$ $V_{40} \leq 120\,cm^3$ and $V_{50} \leq 60\,cm^3$ limits incidence of chest wall pain to <6% $D_{max} \leq 82$ Gy to limit incidence of chest wall pain to 10%
Current study	2009–2012	Early stage peripheral lung cancer	55 Gy/5	182 patients	3.0	Grade 1/2/3: 15.7%/ 8.2%/2.7%	Tumour size and $D_{max}1\,cm^3$ predicted ≥Grade 2 chest wall pain

BMI, body mass index; CTC, Common Terminology Criteria; CTD, connective tissue disease; DM, diabetes mellitus; mEUD, modified equivalent uniform dose; NSCLC, non-small-cell lung cancer; SABR, stereotactic ablative radiotherapy; VMAT, volumetric modulated arc therapy.

nerve damage or skin reaction (erythema, ulceration and fibrosis).[5,8–10] Equally, rib fractures may occur in association with SABR but without symptoms.[17,18] Chest wall pain syndrome is characterized by positional pain that can be pleuritic and is often worsened by activity and can range from mild to severe.[19] The process which underlies SABR-associated chest wall pain is not fully understood. Cortical thinning in association with chest wall pain has been observed,[20] and peripheral intercostal nerve injury[10,21] and osteoblastic remodelling of weakened bone in association with inflammation are proposed mechanisms.[19]

We investigated chest wall pain in patients receiving 55 Gy in five fractions as this dose and fractionation is used specifically for patients with tumours adjacent to the chest wall. Chest wall pain of any grade was observed in 27% of patients, while ≥Grade 2 pain was infrequent, affecting 11% of patients. Although a range of frequencies is reported in the literature, pain of ≥Grade 2 is generally uncommon. We investigated factors which might predict ≥Grade 2 chest wall pain. Univariate analysis identified tumour size, chest wall D_{mean}, $D_{max}1\,cm^3$ and V_{50}, V_{30} and V_{10} as significant predictors of ≥Grade 2 chest wall pain. It is expected that V_{50}, V_{30} and V_{10} are closely correlated and so the significance of all three parameters in the univariate analysis should not be overinterpreted. Multivariate logistic regression identified tumour size and $D_{max}1\,cm^3$ as significant predicators of chest wall pain. Parameters were determined for $D_{max}1\,cm^3$ for different tumour sizes, below which the predicted risk of ≥Grade 2 chest wall pain is < 10% and < 20%. Our final model was an adequate fit to the data and the discrimination of the model was fair (area under the ROC curve: 0.74). Often, little is reported regarding the goodness of fit of logistic regression models for chest wall pain in the existing literature,[9,10,16] and so it is not possible to comment in detail on the fit of our model in comparison with other studies.

A small number of studies have previously defined patient-, tumour- and treatment-related factors associated with chest wall pain after lung SABR (Table 4). A variety of analysis techniques have been employed and a variety factors have been examined, thus making it challenging to draw definitive conclusions regarding the most important factors in predicting chest wall pain. Most studies include patients with primary non-small cell lung cancer as well as oligometastatic disease to the lung or liver. Furthermore, a range of dose and fractionation schedules are often evaluated within the same study. In this present study, we describe outcomes in relation to 187 SABR treatments for primary lung cancer (including histologically unproven disease), all prescribed 55 Gy in five fractions. This is the only study to evaluate this schedule in isolation. By evaluating only one schedule, we have avoided introducing the uncertainties which can result from different fraction sizes and equivalent dose calculations, particularly in the setting of large dose per fraction treatments where the reliability of the linear-quadratic model is debated.[14]

The chest wall was contoured in a similar way to Dunlap et al[5] potentially allowing meaningful comparisons between results. Using a different modelling process to that used in this present study, Dunlap et al[5] found V_{30} to be the most useful predictor of severe chest wall pain or rib fracture. We also found the chest

wall V_{30} to be a significant predictor of ≥Grade 2 chest wall pain on univariate analysis, but found $D_{max}1\,cm^3$ and tumour size to be the only significant factors on multivariate analysis, meaning that the predictive effect of V_{30} is diminished when these factors are taken into account. These factors were not included in the Dunlap et al analysis. V_{30} has also been found to be important in other studies examining SABR-associated chest wall pain, although there is variation in how these analyses were performed.[9,10,21–23]

As above, we observed that the maximum chest wall dose (evaluated as $D_{max}1\,cm^3$) was a significant predictor in the risk of chest wall pain. Similarly, Andolino et al[11] and Taremi et al[24] found maximum doses (point dose and D_{max} $0.5\,cm^3$, respectively) to be important in the development of chest wall pain.

Bongers et al[25] in a study of 500 patients, demonstrated that larger treatment volumes and shorter tumour-to-chest wall distances were related to chest wall pain. Similarly, Stephans et al[10] concluded that tumour size correlated with late chest wall toxicity. This present study also demonstrated that tumour size was a significant predictor of chest wall pain. It may be that tumour-to-chest wall distance was not identified as a significant predictor of chest wall pain since all the tumours in this analysis were close to the chest wall, and more distant tumours (which would have been prescribed 54 Gy in three fractions) were not included.

Some studies have investigated patient-related factors which may contribute to the risk of chest wall pain: body mass index, connective tissues diseases and diabetes mellitus have been shown to be important.[9,16,26] Our study is limited in that we did not have sufficient information to include these in the analysis, and it may be that the addition of these factors would improve the goodness of fit and utility of our model. Indeed, Woody et al[26] produced a multivariate model which included dosimetric information (modified equivalent uniform dose) and body mass index. The area under the ROC curve was 0.83, and so the inclusion of this patient-related factor resulted in a more discriminating model than we describe here.

The median time to the onset of chest wall pain is generally 6 months or more after SABR.[5,11,16] In this present study, 20 patients had chest wall pain of ≥Grade 2 after a median of 9 months (range: 0–24 months). This is in keeping with existing data such as that reported by Andolino et al[11] [median time to chest wall toxicity 9 months (range: 1–50) months] and Welsh et al[16] [median time to chest wall pain 6 months (range: 0–11 months)].

This study has limitations. Firstly, this was a retrospective review and as such there are inherent problems with this method of data collection. In addition, and as mentioned above, we did not have sufficient information to perform detailed analysis regarding patient-related factors (*e.g.* comorbidities) which may contribute to the risk of chest wall pain. Furthermore, the number of patients is relatively small, as was the number of episodes of ≥Grade 2 chest wall pain. Nonetheless, tumour size and the $D_{max}1\,cm^3$ were significant predictors of ≥Grade 2 chest wall pain, and this information is clinically useful in terms of attempting to avoid hot volumes in the chest wall, particularly in patients with larger tumours. Our analysis was based on two-dimensional tumour and target measurements, rather than three-dimensional measurements such as GTV or the volume of overlap between the PTV and the chest wall. The impact of these three-dimensional factors on the development of chest wall pain requires further investigation, although it is likely that maximum tumour diameter (evaluated here) is closely correlated with tumour volume, and that the distance from the tumour to the chest wall (evaluated here) is closely correlated with the volume of PTV overlap with the chest wall. Despite these limitations, this analysis remains worthwhile by contributing to the existing data regarding SABR-associated chest wall pain, and providing a simple practical approach to evaluating the risk of chest wall pain.

The advent of volumetric modulated arc treatment for lung SABR has been shown to reduce chest wall doses,[27] and this may result in lower incidences of chest wall toxicity than have been observed with static beam arrangements. Furthermore, new parameters to limit chest wall toxicity may need to be defined, given the changes in dose distribution that occur with volumetric modulated arc treatment.

CONCLUSION

Grade 2 or greater chest wall pain is an infrequent side effect of SABR treatment. For patients with tumours adjacent to the chest wall who receive five-fraction SABR, increasing tumour size and $D_{max}1\,cm^3$ were significant predictors of ≥Grade 2 chest wall pain. In an effort to reduce the risk of chest wall pain, it is prudent to try to avoid hot volumes in the chest wall region, particularly in patients with large tumours.

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