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Research Article

Normal Tissue Dose Constraints for Multiple Lung Stereotactic Radiotherapy Treatments

B. Allos[1*], J. Bhogal[1], R. Stevenson[1], S. Watkins[1], S. Yahya[1], D. Stange[2], H. Howard[2], M. Brennan[2] and Q. Ghafoor[1]

[1]Department of Clinical Oncology, Cancer Centre, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, UK
[2]Department of Medical Physics, Cancer Centre, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, UK

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ABSTRACT

Introduction: The role and use of stereotactic radiotherapy (SABR) is evolving rapidly. A key article by Hanna *et al.* (2017) provides an excellent overview of current evidence and suggestion of sensible dose constraints. Given the topical nature of this discussion we present a short retrospective analysis of treating multiple lung SABR patients at our centre.

Method: We retrospectively analysed toxicity, both early (within 3 months of SABR) and late, and normal tissue dose constraints on all patients who had multiple lung lesions treated with SABR (using volumetric modulated arc therapy (VMAT) technique) at our tertiary centre over a 25-month period from April 2016 until May 2018.

Results: We have treated 78 lung lesions in 37 patients with a combination of synchronous lung cancer primaries and lung metastases diagnoses. Median follow-up was 9 months. Almost all patients received treatment on the same day for multiple lesions. We report no grade 3 toxicities in any patient nor any unexpected side effects. 5 patients (14.7%) developed grade 2 pneumonitis. In all 5 patients, lung V12.5 was >20% (range 20.8-32.2%), yet only 1 patient exceeded acceptable lung V20 constraints. Regarding long-term toxicity, 66.6% of patients reported no treatment-related effects. Of 9 patients with long-term toxicity, 8 exceeded V12.5 constraint of <15%, indeed of these 5 were >20%. Lung V20 levels were acceptable for the majority of these. Local control of treated lesions at median follow-up in all comers was 86.2%.

Discussion: Our findings show that multiple lung SABR is tolerable, safe with minimal long-term toxicity and acceptable early toxicity. Defining normal lung V12.5 of <15% (optimal) and <20% (acceptable) will significantly reduce the risk of pneumonitis and longer-term toxicity, proving itself more predictive than lung V20 levels for toxicity. Additionally, treating multiple lesions concurrently appears to bare no extra risk to patients.

Introduction

The role and use of stereotactic radiotherapy (SABR) is evolving rapidly, with the UK radiotherapy community providing significant data through the commissioning through evaluation (CtE) programme, and trials such as CORE, HALT and SARON [1-4]. A key article by Hanna *et al.* provides an excellent overview of current evidence and suggestion of sensible dose constraints for the UK community [5]. With regards to treating 2-3 lung lesions simultaneously using SABR it recommends using conservative fractionation schedules where possible and aiming for an optimal V20 (percentage volume of lung receiving 20 Gray (Gy)) of <12.5% and an acceptable V20 of <15%. With regards to treating multiple lung volumes, we have significant experience in Birmingham which has created healthy debate as to constraints that may be used [6, 7]. Given the topical nature of this discussion we present a short

Correspondence to: B. Allos, Department of Clinical Oncology, Cancer Centre, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW; E-mail: Beshar.allos@uhb.nhs.uk

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retrospective analysis of the first 37 multiple lung SABR patients treated at University Hospital Birmingham.

Method

We retrospectively analysed toxicity, both early and late, and normal tissue dose constraints on all patients who had multiple lung lesions treated with SABR (using volumetric modulated arc therapy (VMAT) technique) at our tertiary centre over a 25-month period from April 2016 until May 2018. Our patients are formally routinely reviewed for toxicity whilst on treatment, at 6 weeks and at 3 months post-treatment. Early toxicity is thus defined as any toxicity within that period of time. We have classified late toxicity to be any ongoing or new adverse effects from 3 months onwards post-treatment. Data on normal lung dose constraints for each patient has been collected looking at V5, V10, V12.5 and V20 specifically. Maximum heart dose (0.1cc and 0.5cc) and maximum planning risk volume (PRV) cord dose (0.1cc) data is also included.

Results

In total we have treated 37 patients with a combination of synchronous lung cancer primaries and lung metastases diagnoses. Median follow-up was 9 months (range 1.5 months to 20 months). Demographic data is presented in (Table 1). Tumor demographics and radiotherapy data is presented in (Table 2). Within our cohort, 78 lung lesions were treated and almost all patients received treatment on the same day for multiple lesions. A more conservative dose/fractionation schedule of 60Gy/8# was used only in 14 lesions with the most common schedule being 55Gy/5# (53 lesions). Size of lesions ranged from 5 to 49milimetres (mm) with the majority measuring between 10-29mm.

Table 1: Patient demographics, diagnosis and FEV1.

SEX	Male – 15 Female – 22
AGE	Median – 71 Range – 36-87
PERFORMANCE STATUS (PS)	PS 0 – 5 PS 1 – 13 PS 2 – 12 Not recorded – 7
DIAGNOSIS	Synchronous lung cancers – 22 Lung metastases – 15 Colorectal – 7 Head & Neck SCC – 2 Renal cell – 2 Bladder SCC – 1 Upper GI – 1 Gynaecology – 1 Sarcoma - 1
FEV1 PRE-TREATMENT	Yes – 14 No – 23 Range – 0.77-2.85L (26%-100%)

Normal lung V20 exceeded the suggested optimal level of <12.5% in 10 patients, with 4 of these exceeding the acceptable level of <15%. V12.5 is commonly recorded for SABR plans in our centre and for single treated lung lesions should not exceed 15% at all dose/fractionations. Within our multiple lung SABR cohort, only 9 patients have met this constraint with 15 patients having a V12.5 of >20%. There are no suggested constraints when treating multiple lung lesions for maximum heart dose to 0.5cc (D0.5cc). All of our patients SABR plans met existing heart constraints as defined for single lung SABR, which differs depending on dose/fractionation schedule. For example, all patients treated with 60Gy/8# to multiple lung lesions simultaneously had met normal heart D0.5cc for a single lung lesion being treated. The same can also be said for maximum dose to PRV cord to 0.1cc (D0.1cc) which was within standard single lung SABR constraints for all patients.

Table 2: Tumor demographics and Radiotherapy data.

NO. OF LUNG LESIONS TREATED	2 lesions – 33 3 lesions – 4 Total number of treated lesions – 78
LESIONS TREATED AT SAME TIME	Yes – 34 No – 3
SIZE OF LESIONS	< 10mm – 10 10-19mm – 31 20-29mm – 17 30-39mm – 3 >40mm – 2 Not recorded – 15
DOSE/FRACTIONATION PER LESION (Gy = Gray)	54Gy/3# – 9 55Gy/5# – 53 60Gy/8# – 14 30Gy/5# – 2
V20 Lung	<12.5% - 24 12.5-15% - 6 >15% - 4
V12.5 Lung	<15% - 9 15-20% - 10 >20% - 15
MAX HEART DOSE 0.5CC	All within normal dose constraints for single lung SABR
MAX PRV CORD 0.1CC	All within normal dose constraints for single lung SABR

Regarding toxicity and outcome data, 3 patients were excluded from analysis due to a lack of follow-up data. From the remaining 34 patients, all were analysed for early toxicity whilst longer term toxicity data was available for 27 patients. Local control rates, although not the focus of this paper, were available for 29 patients. Toxicity and outcomes are presented in (Table 3). We report no grade 3 toxicities in any patient throughout follow-up. The commonest acute toxicity was fatigue (18/34 patients) and other reported toxicities were in keeping of what is commonly seen in lung SABR in general, such as cough, increased breathlessness and upper GI symptoms. We noted 7 patients (20.1%) had no toxicity at all acutely, whilst 11 patients (32.4%) reported three or more side effects. No patient presented with any unexpected or unusual side effects.

5 patients (14.7%) developed pneumonitis, all symptomatic and grade 2, none requiring hospital admission. These patients all had two lung

lesions treated simultaneously with a range of the common dose/fractionation schedules used. No pattern was seen with regards to size of lesions treated in these cases either, ranging from 7mm to 45mm. However, all 5 patients had a lung V12.5 of > 20% (range 20.8-32.2%), yet only 1 of these exceeded acceptable lung V20 constraints. 3 of these patients have fully recovered during the follow-up period, 1 has long-term evidence of lung fibrosis likely to be a sequelae of their pneumonitis, and 1 is recovering but remains mildly symptomatic.

Table 3: Toxicities and Outcomes.

ACUTE TOXICITY RATES – all grade 1-2 (N=34)	Fatigue – 18 Cough – 13 Increased breathlessness – 11 Pneumonitis – 5 Decreased appetite – 4 Dysphagia – 4 Chest pain – 3 Nausea – 3 Oesophagitis – 2 Skin reaction – 1
LONG-TERM TOXICITY RATES – all grade 1-2 (N=27)	Increased breathlessness – 6 Lung fibrosis – 2 Chest pain – 2 Worsened angina symptoms – 1
LOCAL CONTROL RATES - at median follow-up (N=29)	All patients – 86.2% Synchronous lung cancers – 94.4% Oligometastatic lung disease – 72.3%

Regarding long-term toxicity, 18 of 27 patients (66.6%) report no treatment-related effects at median follow-up. Increased breathlessness was seen in 6 patients and felt to be linked to their SABR treatment with 2 of these having suffered pneumonitis previously and 1 having new lung fibrosis, unrelated to pneumonitis, on scans. 1 patient reported worsening of their angina symptoms post-SABR, but max heart D0.5cc was 14.2 Gy in this case and thus comfortably met single lung SABR constraints for that dose/fractionation.

Interestingly, of the 9 patients who reported long-term toxicity, 8 exceeded V12.5 constraint of <15%, indeed 5 of those 8 cases recorded V12.5 of >20%. Analysis of the 4 patients who recorded a V20 of >15% did not reveal any confirmed pattern of increased toxicity; indeed 1 patient had no toxicity throughout follow-up. 2 patients did develop longer term toxicity reported as increased breathlessness, one of which was related to pneumonitis. This small group, however, did not exhibit any significant increase in side-effects compared to rest of our cohort.

Furthermore, there was an even distribution of expected acute toxicity throughout all performance statuses, although no patient with confirmed performance status 0 displayed long-term toxicity at median follow-up. The majority of those who did were evenly spread between performance status 1 and 2. FEV1 data was restricted to a small number of patients within the cohort, but again no increased rates of toxicity were observed in patients with poor lung function and equally we did not see reduced toxicity in those with good lung function.

In terms of local control rates at median follow-up, in all comers local control of treated lesions was 86.2%. Patients with oligometastatic lung lesions did worse than those with synchronous lung primaries but still retained a high level of control (72.3% vs 94.4%).

Discussion

This retrospective analysis presents our experience of treating multiple lung lesions simultaneously over the last two years. Within the context of multiple lung SABR we have treated a significant number of patients and have garnered substantial experience into the safety aspects of treating these patients. We have developed a good understanding of acceptable OAR dose constraints in clinical practice.

Our data suggests treating multiple lung lesions, whether synchronous primaries or oligometastases, is safe and as tolerable to patients as treating single lesions. We have reported no grade 3 toxicities either in the acute or longer-term setting. This is despite exceeding suggested optimal or acceptable normal lung V20 constraints (5) in 29.4% of patients, exceeding locally suggested normal lung V12.5 constraints (8) in 73.5% (for single lesion lung SABR) and not using the most conservative dose fractionation schedule in 82.1% of lesions treated.

It has been suggested that any normal lung V20 between 15-20%, whilst not desirable, could be acceptable in patients with good lung function. Of our 4 patients whose normal lung V20 was >15%, only two had perceived good lung function in terms FEV1 (2.85L (92% pred) and 1.80L (97% pred)) but transfer factor was poor in one of these at 51% of predicted and not recorded in another. No extra significant toxicity was noted in any of these patients and, indeed, it did not predict development of pneumonitis in particular, thus suggesting normal lung V20 constraints in multiple lung SABR may not be the best predictive tool for safety and toxicity. It also suggests that, unlike conventional fractionated lung radiotherapy using intensity modulated radiotherapy (IMRT), lung function is a less important factor in deciding suitability for treatment in lung SABR.

A more interesting finding was that the normal lung V12.5 was more predictive for more significant toxicity than any other normal lung constraint. 5 patients developed grade 2 pneumonitis post-SABR. All 5 had a V12.5 of >20% (range 20.8-32.2%), thus significantly exceeding suggested single lung SABR constraints of <15%. In total, 33% of patients whose V12.5 was >20% developed pneumonitis. As mentioned previously, only 1 of these patients had a V20 of >15%. In addition to this we note that V12.5 of >15% predicted a higher chance of longer-term toxicity, with 8 of the 9 patients reporting long-term toxicity falling in this category. Again, a V20 above acceptable limits was not consistently associated with this pattern of toxicity.

These results advocate a potential shift in acceptable normal lung dose constraints. We can propose that the normal lung V12.5 be considered as a standardised constraint in treating multiple lung SABR as our cohort has shown this to be more predictive of both acute toxicity with pneumonitis and longer-term toxicity when compared to V20 constraints. As no patient with a V12.5 of <15% developed pneumonitis and only 1 patient reported longer-term toxicity (in this case increased breathlessness) then this figure would be a sensible constraint as an optimal target. Again, this could be pushed to <20% as an acceptable

target given it was above this level that pneumonitis risk sharply increased to 1 in 3.

Accepting these suggested normal lung V12.5 constraints ensures V20 constraints will almost certainly be within current accepted levels. Of all our patients with V12.5 of <20%, the highest V20 we recorded was 12.7%, within acceptable limits for multiple lung SABR. Of those SABR plans where V12.5 was <15%, the highest recorded V20 was 8.4%, within optimal limits for multiple lung SABR. In any case, V20 levels were much less predictive than V12.5 levels for acute and long-term toxicity, thus, altering our focus to recording normal lung V12.5 readings seems a reasonable approach.

Single lung SABR maximum heart D0.5cc and PRV cord D0.1cc constraints were met for all patients in this cohort. Subsequently we did not see any unexpected rates of toxicity with these organs, suggesting such constraints can be acceptable for multiple as well as for single lung SABR.

All patients received radiotherapy on alternate days. 34 of 37 patients had lesions treated concurrently rather than one after another. These 34 patients were not selected for concurrent treatment based on specific factors, such as meeting optimal V20 constraints, treating small sized lesions, having a good performance status or having two lesions encompassable in one planning treatment volume (PTV). This was more of a blanket treatment policy to treat multiple lesions concurrently if possible. By treating this way, we have not reported declining tolerability for treatment in our cohort and again toxicity was generally comparable to single lung SABR. Thus, we can make the case that in most instances it is safe and tolerable for patients to have multiple lung lesions treated at the same time.

A conservative dose/fractionation, although not defined, has also been thought to reduce toxicity in multiple lung SABR. 14 lesions were treated in 7 patients with a dose of 60Gy in 8 fractions. Of these only one patient had no toxicity at all and interestingly two patients developed pneumonitis. This is comparable to those who received 54Gy in 3 fractions, which occurred with 9 lesions in 5 patients, where one patient had no toxicity at all, one patient developed pneumonitis and the remaining three had tolerable acute toxicity but no, as of yet, long-term toxicity. The size of lesions treated in these groups are also comparable as all, but 2 lesions were over 20mm in the two groups combined. By far the commonest dose/fractionation was 55Gy in 5 fractions and this was also eminently tolerable. A conservative dose/fractionation is therefore not necessarily a good indicator of treatment durability for patients and actually should not be considered an important factor in ensuring multiple lung SABR is safe. It remains a factor to consider of course.

Conclusion

Our findings show that multiple lung SABR is tolerable, safe with minimal long-term toxicity and acceptable early toxicity. At this point we can say that defining an optimal lung V12.5 of <15% and an acceptable V12.5 of <20% will likely significantly reduce the risk of pneumonitis and longer-term toxicity. Doing so ensures existing lung V20 constraints are met in any case, although we found this constraint to be far less predictive of toxicity and suggest introducing V12.5 as a standard constraint to plan to. We can also suggest treating multiple lesions concurrently bares no extra risk to patients and that more conservative dose/fractionations do not necessarily mean lower risk of toxicity. It will be prudent to continue to collect data on these patients to ensure the ongoing development and understanding of normal organ dose constraints in this relatively new area of SABR.

In future, CtE will report on value of SABR in oligometastatic disease [1]. This data will hopefully add to the fact that ablative radiotherapy should be available as part of our treatment paradigm in managing oligometastatic cancer in the modern era.

Conflicts of Interest

None.

Competing Interests

None.

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