Interval from simulation imaging to treatment delivery in SABR of lung lesions: How long is too long for the lung?

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Abstract:

Purpose: The purpose of this study was to evaluate the impact of delay, between planning computed tomography (CT) used as a basis for treatment planning and the start of
treatment (delay planning-treatment (DPT)), on local control (LC) for lung lesions treated by stereotactic ablative radiotherapy (SABR).

**Methods and materials:** We pooled two databases from two monocentric retrospective analysis previously published and added planning CT and positron emission tomography (PET)-CT dates. We analyzed LC outcomes based on DPT and reviewed all available confounding factors among demographic data and treatment parameters.

**Results:** A total of 210 patients with 257 lung lesions treated with SABR were evaluated. The median DPT was 14 days. Initial analysis revealed a discrepancy in LC as a function of DPT and a cut-off delay of 24 days (21 days for PET-CT almost systematically done 3 days after planning CT) was determined according to the Youden method. Cox model was applied to several predictors of local recurrence free survival (LRFS). Univariate analysis showed a LRFS decreasing significantly related to DPT ≥24 days (p=0.0063), gross tumor and clinical target volume (p=0.0001 and p=0.0022) but also with the presence of more than one lesion treated with the same planning CT (p=0.024). LRFS increased significantly with higher BED (p<0.0001). On multivariate analysis, LRFS remained significantly lower for lesions with DPT ≥24 days (p = 0.027, hazard ratio: 2.113, 95% confidence interval: 1.097-4.795).

**Conclusions:** DPT to SABR treatment delivery for lung lesions appears to reduce local control. Timing from imaging acquisition to treatment delivery should be systematically reported and tested in future studies. Our experience suggests that the time from planning imaging to treatment should be <21 days.

**Introduction**

Time plays a crucial role in radiation oncology (RO), sometimes in unexpected ways (FLASH-radiotherapy (RT) (1), chrono-RT (2)). In the treatment of cancer, by definition a progressive disease, avoidance of delays is essential (3,4). This was recently challenged during the COVID 19 pandemic (5).

In stereotactic ablative radiotherapy (SABR), it is obvious that the delay between planning computed tomography (CT) used as a basis for treatment planning and the start of treatment (delay planning-treatment DPT) must be as short as possible. This reduces changes in the lesion (size and shape) to be treated and/or the patient's anatomy thus increasing the precision of the delivered treatment. DPT is also a required period for target volume and organs at risk identification, treatment plan preparation and pre-treatment quality control (6).

Causes of long DPT are numerous and not fully discussed in this article such as the complexity of treatment plans, increased demand of SABR (7), treatment machine breakdown and patient's intercurrent pathologies. At the level of the treatment team both oversight or staffing problems can play a role.

Ongoing trials are investigating the efficacy of SABR for oligometastatic disease (OMD) in up to 10 lesions (8). If it is not possible to treat all lesions in the same treatment session, the
choice of the best sequence (simultaneous, alternating, sequential) is still partly unknown (9). In case of sequential treatment, the DPT for the last treated lesion could become too long.

But “how long is too long?” For brain metastases RT, a retrospective analysis addressed this question and suggested a maximal delay of 14 days between the MRI scan and the start of stereotactic radiation surgery (SRS) (10). Moreover, a prospective analysis of 69 lesions (including 15 resection cavities) found that in 46% of cases, an interval of less than 7 days between the planning MRI and a second MRI performed 24 hours before the treatment required a re-planning. This percentage increased to 62% of cases with an interval between 8 and 14 days (11). Although it is reasonable to suppose that re-planning does not always mean better local control (LC), this increase in rates remains questioning.

To the best of our knowledge, there is no specific data on DPT in SABR for pulmonary lesions. Moreover, the study protocols like the RTOG 0915 study for primary lung lesions (12) and the SABR-COMET studies for secondary lesions (8,13,14), do not report these delays. A recent ASTRO white paper on the safety of SRS/SABR reiterates the need to specify these temporal criteria in trials and recommends not to exceed a DPT of 14 days for SRS (15).

In order to assess the impact of DPT on LC for lung lesions, we retrospectively analyzed patients treated by SABR with the CyberKnife® (CK) system. Our hypothesis was that a long DPT will have a negative impact on LC independently of other variables such as volume or prescription dose.

Materials and methods

Patient selection
In 2020, Berkovic et al. published the results of a monocentric retrospective analysis of 104 patients and 132 metastatic lung lesions treated with SABR on CK in the setting of oligorecurrent disease between May 2010 and March 2016 (16).

In 2017, Janvary et al. published a retrospective analysis of 130 patients and 160 lung lesions (primary, recurrent or metastatic) treated consecutively with SABR at the same center and on the same treatment machine between April 2010 and June 2012 (17).

We pooled these two databases, removed duplicates by keeping the lesion with the longest follow-up, and added planning CT and positron emission tomography (PET)-CT dates. For the few identified conflicting data, a review of the institutional records of the patients was performed.

Two patients with lung metastases arising from adenoid cystic carcinoma of the salivary glands were removed because the slow progression of this disease could limit the impact of a large DPT on LC and complicate follow-up.

Ultimately, 210 patients and 257 lung lesions were analyzed.

Statistical analyses
DPT duration was calculated from existing database items. Results were expressed as means, standard deviations (SD) or medians (Q1-Q3) for quantitative variables and as numbers and percentages for categorical variables. To determine the best cut-off value for DPT based on
LC, we used the Youden method. Means between the two groups thus defined were compared with a Student t-test and proportions with a chi-square test. To normalize their distribution, some variables were log-transformed. Local recurrence free survival (LRFS) was examined using Cox regression models. Multivariate model with stepwise selection was also applied. The hazard ratio (HR) and its 95% confidence interval were reported. LRFS was plotted using Kaplan-Meier curves. Results were considered significant at the 5% significance level (P < 0.05). All statistical analyses were carried out by SAS version 9.4 (SAS Institute, Cary, NC, USA) and figures by R version 4.1.1.

Results

Demographic data and treatment parameters

A total of 210 patients and 257 treated lesions were included in the analysis. Key demographic and treatment data are available in the source articles. Initial analysis revealed a discrepancy in LC as a function of DPT. According to the Youden method, a cut-off of 24 days was set. This cut-off shows very good specificity (88.1%) but low sensitivity (25.0%).

Demographic and treatment parameters are reported in Table 1 in each arm: DPT < 24 days (A) and DPT ≥24 days (B). A total of 219 (85.2%) lesions were treated in arm A and 38 in arm B. There was no difference between the two groups in age, gross tumor volume (GTV) and planning target volume (PTV), biological effective dose (BED), number of fractions or percentage of treatment of primary or secondary lesions. However, tracking technique (spine tracking versus real-time tumor tracking) was used more frequently in the short delay group (p=0.042).

Regarding SABR of metastatic lesions, there was no difference in the percentage of pulmonary, digestive or other primary origin. There was no difference in the percentage of use of previous chemotherapy or radiotherapy.

Treatment of multiple lesions with the same planning CT (≥2) is significantly more frequent in arm B (≥24 days) (p=0.0021).

In both arms, the treated volumes were determined using the same margins: 3 mm from GTV to clinical target volume (CTV).

DPT

The median time from planning CT to first day of treatment was 14 days (Q1-Q3: 11-19 days). Figure 1 shows the frequency histogram of DPT expressed in days.

Almost all patients had planning PET-CT 3 days after planning CT and the histogram is simply shifted by 3 days. This excludes the delay “PET to treatment” as a confounding factor and this delay is therefore not considered further.

LC and LRFS by DPT
The median DPT was 13 days (11-18 days) for locally controlled lesions versus 14 days (12-23 days) for LR lesions. Using the Cox model, the risk of LR increased significantly with DPT, with a HR of 2.11 (p=0.029).

Cox model was applied to several predictors of LRFS (Table 2). Univariate regression analysis was performed for different variables of interest such as time course (DPT and cut-off delay), BED, GTV, PTV, presence of tumor real-time tracking or prior cytotoxic treatment (chemotherapy or radiotherapy). LR was found to be significantly related to time delay (DPT (log), HR =2.11, p=0.029; DPT ≥24 days, HR=2.33, p=0.0063), volume (GTV (log), HR=1.49, p=0.0001; PTV (log), HR=1.61, p=0.0022), but also increased with the presence of more than one lesion treated with the same planning CT (HR=2.04, p=0.024). LR decreased with a higher BED (HR=0.99, p <.0001).

The multivariate Cox regression analysis showed that the following parameters were significant: the cut-off time of 24 days (HR =2.29, p=0.027), GTV (log) (HR=1.34, p=0.014), BED (HR=0.99, p=0.001) and the presence of more than one lesion to be treated with a single planning CT (HR=2.13, p=0.033).

### Survival curves for the local recurrence event

Figure 2 shows the Kaplan-Meier curves of LRFS in each arm (A: DPT < 24 days and B: DPT ≥ 24 days). There was a LC dropout in the arm B (HR =2.33, p=0.0063). LRFS at 12 months was 89.7% for arm A and 77.7% for arm B.

### Discussion

DPT is an important period in RO. Obviously this delay should be as short as possible without compromising the quality of the process leading up to the treatment (a principle that could be called "ASASA", as soon as safely achievable). To reduce this period, online adaptive radiotherapy is a promising concept but technical and clinical challenges remain (18).

Currently, little is known about the safe maximal time interval between the planning CT and the start of treatment in SABR of primary and secondary lung lesions. Some guidelines recommend a maximum DPT of 14 days. This cut-off is based on retrospective data from the treatment of brain metastases with SRS (15). There are no clear recommendations for lung lesions, even in study protocols addressing this technique (8,12–14).

Our retrospective analysis confirms the impact of DPT on LC for primary and secondary lung lesions. This impact withstands multivariate analysis including BED and tumor/target volume known to affect LC. Other available variables were also tested but do not significantly affect LC such as a tracking method or previous chemotherapy/radiotherapy treatment. The presence of tracking allows to assess whether the decrease of LC could be due to anatomical changes of the patient that make spinal tracking of CK less efficient. Previous cancer treatment could be a marker of radioresistance and/or rapid repopulation, which would explain lower LC (19).
Determining a cut-off DPT with prospective testing of this delay is undesirable for obvious ethical considerations and has no clinical basis. The only way to investigate this DPT is therefore with retrospective data. In our analysis, a cut-off of 24 days was defined based on the Youden method. This cut-off shows a good specificity but poor sensitivity which is not surprising since a short delay does not provide certainty of LC. It allows us to define two arms and observe a significant decrease in LC for patients in arm B with DPT ≥24-days. This is of course a maximum time frame from which a new simulation should be considered. With the 3 days gap between the planning CT and PET-CT, we recommend a maximum of 21 days between imaging used for treatment planning and the start of treatment. The recommended 14 days seem to be a clinically relevant choice while remaining pragmatic (13).

Several hypotheses can explain the decrease in LC with DPT observed in this study. The main one concerns a geometric miss. Lesions can change both in volume and shape with time explaining decrease in LC. This problem could be exacerbated by the current “2,5D” image guidance during RT by the CK system, which makes volumetric assessment of the lesion difficult. A full soft tissue 3D imaging system, and a medical procedure to inspect these images at each fraction would not solve all problems (because not taking into account microscopic disease), but could already detect (large) macroscopic changes (20). The evolution of neoplastic lesions remains very heterogeneous. It is known that tumor volume/growth plays a role on probability of tumor control (21,22). This raises the question of appropriate DPT depending on the type of lesion, histology or previous treatments. For example, in primary lung tumors, Mural et al. retrospectively analyzed the progression of stage I non-small cell lung cancers treated with SABR between diagnostic CT and planning CT. They showed a 2-fold longer doubling time for adenocarcinomas compared to squamous cell carcinomas (23). Another cause of geometric miss could be an anatomical change around the lesion. Concerning this geometric miss, the systemic CTV margin of 3 mm used for all of our patients could have compensated for some modifications, thus underestimating the effect of the delay. In most of the other series assessing SABR for lung lesions, the principle of GTV = CTV is often used (8,12–14).

Several limitations exist in this study:
First, it is an aggregation of retrospective studies with sometimes limited follow-up period. This can lead to inexact results or lack of robustness. To evaluate this problem, a rapid update of our data from LC based on available institutional imaging and pathology follow-up protocols was made. 10 additional LR in arm A (DPT <24-days) versus 7 in arm B (DPT ≥24-days) were found (unpublished data). Although this information is basically "crude", it seems relevant to us given the relatively short follow-up time of the two source studies (median follow-up time of less than 2 years, 66 lesions less than 1 year). We note that 10 of the 17 identified recurrences occurred in the first year after SABR. This update increases the significance of all tests performed in this study. For example, HR increases from 2.11 (p=0.029) to 2.94 (p=0.0003) with a median DPT of 13 days (11-18 days) and 14 days (12-24 days) depending on LC and LR respectively. To test the robustness of the analysis, we performed an identical analysis with the extreme values of DPT (over 5 weeks) removed. In this scenario, the cut-off delay remains at 24 days and the statistical analysis at this cut-off value remains significant.
A second limitation of this study concerns numerous confounding factors. We have seen that planning PET-CT was almost systematically done 3 days after the simulation CT, so this was not directly considered a factor. Another potential confounding factor could be that the longer DPT is associated to a more complicated treatment plan, which can be associated with a lower BED. A correlation test between the two variables showed a negative correlation but remained non-significant (p=0.11). Furthermore, multivariate analysis accounting for BED and cut-off delay remained significant for the latter.

Regarding the dose, the volume and type of the lesions, the article by Janvary et al. showed a better LC for smaller tumor volume, higher BED and for primary tumors compared to metastases (17). Berkovic et al. showed a better LC for tumor volume, BED and for metastases of digestive origin compared to the "other" groups (16) despite conflicting data in the literature (24). In our study, these different factors were well distributed between both arms.

For metastatic lesions, previous systemic treatments with chemo, immuno or targeted therapies may act as radiomodulator agents and affect LC. Only information about previous chemotherapy was available and well balanced between both arms.

Another possibility would be a greater radiation resistance of lesions with a larger DPT, either acquired during this period (very hypothetical) or related to the fact that more than one lesion is more often treated in the case of a large DPT. Irradiation of multiple lesions is certainly the most important confounding factor. It can be considered as a cause of delay since more frequent in arm B (DPT ≥24 days) (p=0.0021). However, a DPT ≥ 24 days remains significant even after adjusting for irradiation of multiple lesions.

Identification of other causes of delay was not the aim of this article. Some of these can also be considered confounders (e.g. deterioration of patients with change/disruption in breathing pattern).

Finally, let’s mention two more arguments to illustrate the complexity of the situation and the importance of DPT. These aspects are not discussed in this paper but support our conclusions.

First, cancer treatment care delay is a well-known problem (4). Delay may have an impact on the progression of the disease at distance, especially if RT requires the therapeutic window of systemic treatments. It may also necessitate re-staging and a different therapeutic approach.

Second, it should be pointed out that in addition to macroscopic geometric miss, tumor change during the delay may result in a lower and less uniform dose outside the (true) GTV and under-dosage of microscopic disease with the risk of local and distant recurrence (25,26).

Conclusions

SABR of lung lesions is now part of routine clinical practice in many radiotherapy centers. The maximum DPT to avoid compromising LC is not known and limited data is available. Our experience reflects the time period of the introduction of SABR in our department with some longer delays and thus provides a unique opportunity to assess this issue. This monocentric retrospective study shows that a cut-off of 24 days allows to define 2 groups of
patients with different outcomes in terms of LC. New planning CT should be considered after a maximum period of 3 weeks (ideally 2 weeks) between the planning CT and the start of the treatment. Until adaptive online radiotherapy becomes fully integrated in daily practice, the DPT should be systematically reported and tested in the different studies.

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Table 1: Demographics and treatment parameters. Abbreviations: BED = biological equivalent dose; CT = computed tomography; GTV = gross tumor volume; PTV = planning target volume. BED with α/β = 10 Gy

| Patients / Lesions | Arm A DPT< 24 days | Arm B DPT≥ 24 days | P-value |
|--------------------|--------------------|--------------------|---------|
|                    |                    |                    |         |
### Table 2: Univariate and multivariate analysis in Cox model for different explanatory variables of local recurrence.

| Parameters                                                                 | HR    | 95%CI       | p-value |
|---------------------------------------------------------------------------|-------|-------------|---------|
| **Univariate Cox regression analysis**                                     |       |             |         |
| DPT (days. log)                                                           | 2.113 | 1.081       | 4.129   | 0.029   |
| Arm B (≥ 24 days) vs. arm A (<24 days)                                     | 2.328 | 1.269       | 4.271   | 0.0063  |
| BED (with α/β = 10 Gy)                                                    | 0.986 | 0.980       | 0.992   | <0.0001 |
| GTV (cm³, log)                                                            | 1.490 | 1.214       | 1.828   | 0.0001  |
| PTV (cm³, log)                                                            | 1.608 | 1.187       | 2.178   | 0.0022  |
| ≥ 2 lesions treated with the same planning CT                              | 2.044 | 1.098       | 3.806   | 0.024   |
| ≥ 2 lines of chemotherapy before current treatment                        | 1.738 | 0.873       | 3.460   | 0.12    |
| Presence of real time tumor tracking: yes vs. no                          | 1.061 | 0.628       | 1.793   | 0.82    |
| Primary vs. Secondary lesions                                             | 0.732 | 0.399       | 1.341   | 0.31    |
| Radiotherapy for previous treated secondary lesions                       | 1.628 | 0.865       | 3.064   | 0.13    |
Chemotherapy for previous treated secondary lesions 1.005 0.542 1.862 0.99

Multivariate Cox regression analysis

| Factor                                      | Hazard Ratio | 95% CI       | p-value |
|---------------------------------------------|--------------|--------------|---------|
| Arm B (≥ 24 days) vs. arm A (<24 days)      | 2.293        | 1.097 - 4.795| 0.027   |
| BED (Gy)                                    | 0.987        | 0.979 - 0.995| 0.001   |
| GTV (cm³, log)                              | 1.363        | 1.065 - 1.746| 0.014   |
| ≥ 2 lesions treated with the same planning CT| 2.127        | 1.061 - 4.263| 0.033   |

Figure 1: Frequency histogram of DPT expressed in days. Abbreviations: DPT = delay planning-treatment

Figure 2: Kaplan-Meier curves for local recurrence free survival with significantly greater local control for lesions with DPT < 24 days (p=0.0063). Abbreviations: DPT = delay planning-treatment.
