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Round 1

Reviewer A

Comment 1A: This is the article that presents a case report of practical implementation of lattice radiotherapy (LRT) to manage an unresectable metastatic sarcomatoid lung cancer.
I kindly suggest that the paper in its present form should not be approved for publication, and I recommend minor revision.
Reply 1A: Thank you for your opinion.

……

Comment 2A: My impression of this manuscript is positive. The topic is fairly interesting and important. The quality of English is acceptable for a non-native English-speaker. However, the presentation of the text (punctuation, typos) should be corrected (for example, X-ray, chemo agents without capital letters, etc.)

Reply 2A: Thank you for your assessment. Our manuscript has undergone an extensive English revision by a native speaker of a professional translation and interpreting service.

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Comment 3A
In my opinion, some issues should be solved before it will be acceptable for publication:
INTRODUCTION:
You stated that sarcomatoid lung cancer is "a very radioresistant tumor". Please provide any references to support your statement.
Reply 3A: Thank you for the advice. We agree with the Reviewer. We added an adequate reference in the “Introduction”, to support that the sarcomatoid lung cancer is a very radioresistant tumor, with poor response to systemic therapy. We report the reference below.
(Please see line 62-63)

“Li X, Wu D, Liu H, Chen J. Pulmonary sarcomatoid carcinoma: progress, treatment and expectations. Ther Adv Med Oncol. 2020;12:1758835920950207. Published 2020 Aug 25. doi:10.1177/1758835920950207”

……..

Comment 4A

- I recommend mentioning two available ways to plan LTR, namely simultaneous integrated boost LTR (as you did - concomitant increase of the dose to verticles) and conventional (you named it "hybrid" in the discussion; one large fraction and then conventionally fractionated radiotherapy).

Reply 4A

We understand Reviewer point. Due to the novelty of the technique, literature on LTR is limited and further studies are mandatory. LTR is considered a RT with a heterogeneous dose delivery. More precisely, there is a common agreement that, in LTR plans, high and ablative radiation doses are administered to discrete sub volumes inside a large tumor target (vertices or hotspots), while a safer lower dose is delivered to the remainder of the target. This is practically based on a group of simultaneous integrated boosts which are delivered concurrently on a discrete lesion volume, according to an opportunely created framework, to generate the maximum number of vertices with a favorable geometry (i.e., vertices are supposed to be positioned not too adjacent to OARs in order not to overdose them). Considering LTR definition, it appears to us that what the Review defines as "simultaneous integrated boost LTR" coincides with LTR. Thus, it seems reasonable to refer as a hybrid or not-exclusive LTR approach to a treatment where a conventionally fractionated RT palliative regimens is delivered after one or two upfront LTR fraction (Please see reference below). However, we added that a hybrid LTR is a non-exclusive LTR to try to clarify this difference (Please see line 164). We would like also to underline that no data are available on which strategy should be preferable (exclusive LTR (LTR) or LTR + conventionally that we define as hybrid LTR), therefore, all LTR approach should be positively welcome and investigated. (We added this information in the conclusion of the revised manuscript, Please see line 206-208).

1. *Duriseti S, Kavanaugh J, Goddu S, Price A, Knutson N, Reynoso F, Michalski J, Mutic S, Robinson C, Spraker MB. Spatially fractionated stereotactic body radiation therapy (Lattice) for large tumors. Adv Radiat Oncol. 2021 Jan 8;6(3):100639. doi: 10.1016/j.adro.2020.100639. PMID: 34195486; PMCID: PMC8233471*
2. *Ferini G, Valenti V, Tripoli A, Illari SI, Molino L, Parisi S, Cacciola A, Lillo S, Giuffrida D, Pergolizzi S. Lattice or Oxygen-Guided Radiotherapy: What If They Converge? Possible Future Directions in the Era of Immunotherapy. Cancers (Basel). 2021 Jun 30;13(13):3290. doi: 10.3390/cancers13133290. PMID: 34209192; PMCID: PMC8268715.*

……

Comment 5A

CASE PRESENTATION:

- "quickly relieved with prompt treatment" --> describe what kind of treatment was used.

Reply 5A

Thank you for highlighting this lacking point, we added in "Case presentation" the therapy administered, describing the drugs and their dosages. Please see line 93-94 "Case presentation"

……..

Comment 6A

- Was the improvement of QoL measured using objective tools?

Reply 6A

Thank you for your point. Even though no objective tools was used to assess patient's QoL evolution, the patient himself reported an "important improvement" in his subjective well-being, in his autonomy, and in his daily activities after LTR. The same improvement was also reported by patient's caregivers. Considering this, we thought it might have been reasonable to affirm at the end of "Case presentation", that the patient experimented an improvement in his QoL after LTR. However, since no objective tool was adopted we decided to modify the sentence as follows "*…improvement in subjective well-being (ECOG 1) and, as the patient said, in his daily life".*
Please see line 84 and line 99.

……

Comment 7A

- " From the 10th to 22sd of September" --> 2020? 2021?

Reply 7A

Thank you for the feedback, we provided to add the year (i.e.,2021). Please see line 90.

……

Comment 8A

LATTICE RADIATION TREATMENT PLANNING:

- Please provide more details regarding planning: did you use any supportive imaging (MR, PET), did you use IMRT or VMAT, what kind of RT equipment you used, doses received by organs at risk (sum of lungs' volume, heart, great vessels, skin, ribs, esophagus, etc.). That may be extremely useful for further attempts of LTR.

Reply 8A

Thank you for your feedback. We agree with the Reviewer that more details on LTR planning may be extremely useful for further attempts of LTR. We added the information about treatment planning, treatment delivery, dosimetry and DVH parameters in the sections "Treatment Planning and Delivery", and "Lattice Framework" (Please see lines 108-115 and 117-135). In addition, we added a Table 1 in the revised

manuscript showing dose volume endpoints. (Please see Table 1 in revised manuscript. We also report the table below).

OAR	Dose Volume Endpoints
Total lung	*V5 = 77.6 %* *V10 = 18.7%* *V20 = 1.3 %* *Dmean = 9.1 Gy*
Heart	*V5 = 99.8%* *V10 =77.9 %* *V20 = 12.6 %* *Dmean = 14 Gy*
Spinal Cord	*Dmax = 16.9 Gy*
Esophagus	*Dmean = 10.6 Gy* *Dmax = 24.9 Gy*
Ventricle L	*V5 = 100%* *Dmean = 13 Gy*
LAD	*Dmax = 23.7 Gy* *Dmean= 16.3 Gy*
LCA	*Dmax = 23.7 Gy*
Left Atrium	*Dmean = 14.5 Gy*
Right Atrium	*Dmean 9.0 Gy*

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Comment 9A

DISCUSSION:

- Another issue that may be worth discussing is the application of LTR in the treatment of nonmetastatic but unresectable disease (for example, bulky soft tissue sarcomas). It has been shown in several trials that larger doses per fraction even delivered to extensive volumes is a safe and effective treatment (see: 10.1158/1078-0432.CCR-19-3524 /10.1016/j.ijrobp.2021.02.019), so LTR may be a very interesting option for such patients.

Reply 8A

Thank you for your suggestion. We agree that it may be worth further analyze LTR

application in non-metastatic patients affected by an unresectable lesion. The paper you kindly suggested is a valid example. Considering the case report word limit (2,500 words max), we added a statement on this point. (Please see lines 194-195 at the end of the conclusions). In light of the relevance of the argument, it should be worth analyzing and discussing the application of LTR in the treatment of nonmetastatic but unresectable disease in a further paper.

……

Comment 9A

- Please discuss the limitations of the study (for example, too short follow-up to assess late toxicity.)

Reply 9A

We want to thank the reviewer for the advice and for highlighting the lack of this important point. We provided to add our study main limitations at the end of the "Discussion": Please see lines 196-201.

……

Comment 10A

FIGURES:

- Please consider adding LTR dose (used regimen) to "Lattice RT" field in Figure 1.

Reply 10A

Thank you for your suggestion, we added LTR dose to "Lattice RT" field in Figure 1.

……

Comment 11A

- Explanation of used abbreviations under figures is highly recommended, like LTR, RT, CT, PD, XR, PET/CT, GTV, PTV

Reply 11A

Thank you for your feedbacks; we added an explanation of all abbreviations used under the figures to improve the understanding of the figures. (Please see Figure 1, Figure 2 and Table 1)

Reviewer B

Comment 1B

Line 15a: Add "the" between "in" and "palliative"

Line 15b: Add "a" between "Since" and "surgical"

Line 16a: Add "commonly" between "are" and "referred"
Line 16b: Replace " to a" for "for"
Line 17a: Add "of" between "doses" and "palliative"
Line 17b: Replace "is" for "are" at end of the line
Line 25: Remove "allowed to" and add "ed" at the end of "confirm"
Line 26: Replace "upfront" with "initial"
Line 28: Correct spelling is "dyspnea"
Line 31: Add "we have" between "treatment" and "delivered"
Line 42a: Replace "of" with "the"
Line 42b: Replace "neoplastic lesions" with "tumors"
Line 44: Replace "neoplastic" with "tumor"
Line 53: Remove "Thus" and capitalize "T" for "the"
Line 62: Add "favorable" at the end of "the persistence of the"
Line 75a: Replace "The X ray (XR) performed in the emergency department" with "The plain pelvic radiograph in the ER"
Line 75b: Replace "displaced a big" for "displayed a large"
Line 76: Add "large mass" between "a" and "mass"
Line 79: Replace "one lesion" with "another"
Line 80: Replace "another" with "other"
Line 105: Add hyphens (-) to "center to center" (center-to-center)
Line 113: Add a "d" at the end of "replace"
Line 131: Add an "a" between "keeping" and "lower"
Line 224: Reference #7 should be reference #1

Reply 1B

Thank you for your assessment and your suggestions. We modified our paper in agreement with Reviewer's suggestions and correction relating to grammar and style, with the following exceptions.

- Add "we have" between "treatment" and "delivered": This was the first patient we treated with LTR, but this is also one of the firsts LTR exclusive treatment delivered with follow up. Hence, to convey both messages, we thought to change the sentence as follows: *"This is our first LTR treatment. It provides new evidence on LTR planning and it shows". Line 30*
- Replace "The X ray (XR) performed in the emergency department" with "The plain pelvic radiograph in the ER": It was not performed a pelvic radiograph but a chest X ray. However, to render more concise the sentence we decided to modify as follows: *"The emergency department radiograph displayed a large opacity…".Please see line 69.*
- Reference #7 should be reference #1. We understand reviewer feedback; however, we decided to write down reference sequences according to their position in the manuscript and not according to their importance or clinical relevance.

Comment 2B

Recommendation 1: We would like to include and report the V5 Gy per fraction (which needs to be included in the paper)

Reply 2B:

We thank the reviewer for the feedback. Since the journal is not specifically focused on the topic of radiation oncology but on palliative medicine, we thought it would have been more adequate not to precisely describe treatment planning and delivery as well as patient dosimetry. However, considered the feedbacks on this point, we provided to add the requested information (Please see Table 1 in the revised manuscript and "Treatment Planning and Delivery" lines 108-115).

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Comment 3B

Recommendation 2: We recommend including PET-CT images before and after treatment.

Reply 3B:

We understand Reviewer's suggestion and it would have been interesting to compare the PET-CT images before and after treatment. However, no PET-CT has been performed after LTR and, consequently, this data is not available. In our center, the PET-CT is performed in agreement with current guidelines and recommendation. We acknowledge that PET-CT would be very useful in a clinical trial on LTR.

Reviewer C

Comment 1C

1) Please discuss briefly about the response of the sacral lesion that was treated at diagnosis. My understanding is that the lesion was treated to the "same" dose of 20Gy in 5 fractions. What was the radiological and clinical response? Did the patient still require analgesia? This may help the reader compare and contrast this to the response of the primary tumour to LRT.

Reply 1C

We thank the reviewer for these feedbacks. The sacral lesion was a 3.8x3.8 cm lesion, and it was treated with a standard palliative RT regimen of 20 Gy in 5 fractions of 4 Gy/die, with a good antalgic response. The patient did not require additional analgesia. In this case, also a SBRT could have been feasible, however, a palliative RT schedule was preferred since available diagnostic imagines revealed a metastatic condition.

In standard palliative RT treatment, the dose delivered is homogeneous and no hotspots

of dose escalation are created. Thus, the RT schedule adopted on pelvic lesion (3.8 x 3.8 cm) was completely different from LTR delivered on the lung mass (19 cm x 16 cm).

Notwithstanding this, we acknowledge that how we had reported this information was misleading, consequently, we modified the sentence as follows: *"After an antalgic standard radiotherapy on the sacrum to relieve the back pain (4 Gy x 5 fractions a 38x38 mm lesion with positive antalgic response)…"*.

Please see lines 79-81.

……

Comment 2C

2) With respect to LRT, please discuss the consideration for using lattice radiotherapy. Is this the first case to be done at your Centre? Is it considered experimental? What was communicated with the patient during the consent taking process? Do you need to clear any ethics board/ tumour board? This would help readers in the radiation oncology field in considering implementing this treatment technique in their centres.

Reply 2C

Thank you for your request because we do believe it will help to implement this treatment in other center. This was the first case we have done in our center and we provided to add this information in the abstract (Please see the abstract conclusion: line 30).

With reference to LTR, we discussed deeply with the patient and his caregivers about the pros and cons of LTR considering available evidence and patient condition. We explained that a Phase I study was ongoing at the Washington University (Saint Luis) [1] and that positive different LTR experiences were reported in literature. Notwithstanding this, we made clear that we had no data on LTR predictable outcome and toxicity in acute and chronic setting. We also explained to the patient and his caregivers, the probable treatment result of standard palliative RT or chemotherapy [2]. We added this information in "Case presentation" (Please see lines 87-89). At that time, the patient had a disabling burden of symptoms due to bulky mass in the lung and he expressed the will to undertake a treatment as quick as possible, as a result, we shared with the patient and his caregiver the decision of LTR with consecutive fractions. The ethical committee authorization was not necessary.

[1] Duriseti S, Kavanaugh JA, Szymanski J, Huang Y, Basarabescu F, Chaudhuri A, Henke L, Samson P, Lin A, Robinson C, Spraker MB. LITE SABR M1: A phase I trial of Lattice stereotactic body radiotherapy for large tumors. Radiother Oncol. 2021 Dec 4:S0167-8140(21)09018-6. doi: 10.1016/j.radonc.2021.11.023. Epub ahead of print. PMID: 34875286

[2] Li X, Wu D, Liu H, Chen J. Pulmonary sarcomatoid carcinoma: progress, treatment and expectations. Ther Adv Med Oncol. 2020;12:1758835920950207. Published 2020

Aug 25. doi:10.1177/1758835920950207

……

Comment 3C

3) Besides the sacral lesion, were there other sites of metastases? It seems like this is a de novo oligometastatic disease at diagnosis and despite multiple lines of systemic therapy, there is only progression of disease in the primary. Thus further bolstering the use of LRT for the primary.

Reply 3D

Thank you for your assessment. The patient was a de novo metastatic sarcomatoid lung cancer since he had mediastinal node lesions, one lesion close to the left sacroiliac muscles, a formed lesion close to the gastro-splenic space, and a sacral metastasis at diagnosis. There was a progression of the primary disease and of mediastinal nodes. It is also important to underline that the patient was never off-therapy from diagnosis to LTR delivery.

Considering the intrinsic limitation of a case report, we agree with the Reviewer that a possible LTR use on the primary tumor in an oligometastatic patient should be further investigated, however, LTR evidence are limited, and further studies are mandatory.

……

Comment 4C

4) Please clarify the time sequence of lattice radiotherapy with respect to vinorelbine. What was the dose and route of administration of vinorelbine? Was it concurrent administration, or was vinorelbine stopped temporarily for the administration of lattice RT? Vinorelbine is a known radiosensitiser, though not routinely used clinically with radiotherapy. Thus, there is a need to address the possibility that the response may be enhanced by vinorelbine as well.

Reply 4C

We thank the reviewer for having underlined this important point. Since Vinorelbine is a well-known radiosensitizer and no data are currently available on the interaction between LTR and Vinorelbine, Vinorelbine administration was suspended during LTR and restarted at the end of the LTR (one week before and one week after). We added a sentence to clarify that Vinorelbine was suspended during treatment and restarted at the end of it: *"Since Vinorelbine is a known radiosensitizer, its administration was suspended during LTR". (Please see lines 91-92)*

……

Comment 5C

5) Is there a record of the patient's functional status? Is it possible to report in terms of ECOG/ KPS/ PPS? Also in terms of dyspnea, did the patient require oxygen supplementation?

Reply 5C

Thank you for your feedback. With reference to patient's performance status, we agree with the Reviewer, and we provided to add the ECOG before and after LTR. Please see line 84 and line 99. With reference to oxygen, the patient did not required any oxygen supplementation; otherwise, it would have been our care to report it.

……

Comment 6C

6) Please provide details on the radiotherapy simulation process. Did you use 4DCT and immobilization?

Reply 6C

We thank the reviewer for his request. We added a new paragraph (namely, "*Treatment planning and delivery*") where we reported all details about LTR simulation process and its delivery. Please see lines 108-115.

……

Comment 7C

7) In the placement of the vertices, did you follow the lattice framework strictly? Did you shift individual vertices when it is too close to the OAR for e.g. the bronchus/ trachea/ esophagus/ heart?

Reply 7C

Thank you for your feedback. With reference to Duriseti et al. [1], during lattice framework creation, vertices must not be located within a distance less than 1.5 cm of any OARs. We added this information in the section *"Lattice Framework*". Please see lines 117-135

[1] Duriseti S, Kavanaugh J, Goddu S, Price A, Knutson N, Reynoso F, Michalski J, Mutic S, Robinson C, Spraker MB. Spatially fractionated stereotactic body radiation therapy (Lattice) for large tumors. Adv Radiat Oncol. 2021 Jan 8;6(3):100639. doi: 10.1016/j.adro.2020.100639. PMID: 34195486; PMCID: PMC8233471.

……

Comment 8C

8) Please provide more details of the treatment planning process? For example the treatment planning software, and the script written. What is the field arrangement and beam energy used?

Reply 8C

We thank the reviewer for his feedback. We provided to add the requested information in detail in the new section: "Treatment Planning and Delivery". Please see lines 108-115.

……

Comment 9C

9) You mentioned the dose was limited to 55Gy out of prudence, but is there a reasoning for selecting this dose? I.e., why not 50Gy or 60Gy? Similarly, it was mentioned you wanted to reach 250% of the PTV prescribed dose? But is there a reason for 250% as opposed to 200% or 300%?

Reply 9C

Thank you for your question. When we decided to treat the patient, the results of "LITE SABR M1 phase I trial" were not available. Literature about dosimetry and treatment planning was limited, however, there was a general agreement around hot spots dose escalation of at least 250% prescribed dose (PTV dose – periphery dose). Generally, the standard palliative dose in 5 fraction is 20 Gy (4 Gy/die: with a good balance between efficacy and toxicity) and in "LITE SABR M1 phase I trial" the dose escalation was up to 66.70 Gy in the hotspots. Due to sarcomatoid lung cancer radioresistence, we estimated that reaching a 200% of the PTV prescribed dose would have been too low. After our analysis of dosimetry, we decided to limit the dose escalation up to 55 Gy to obtain an adequate heterogeneous dose distribution – which is considered essential to completely exploit LTR activity on cancer lesion –, preserve plan quality, not to overdose OARs, and to preserve dose conformity.

……

Comment 10 C

10) What was the LINAC used to deliver the treatment? Did you use CBCT? How long was the treatment time/ time on couch?

Reply 10 C

Thank you for your feedback. We added detailed information in the new section: "Treatment Planning and delivery". Please see lines 108-115.

……

Comment 11 C

11) Did you order for a lung function test prior to treatment?

Reply 11C

Thank you for the question. We did not request any a lung function test prior to LTR treatment.

……

Comment 12 C

12) In figure 1, please add in the coronal view for the "before and after" CT scan corresponding to the treatment planning view

Reply 12

Thank you for your suggestion. We modified Figure 1 adding below the axial view also

the coronal view for the "before and after" CT scan. (Please see Figure 1)

……

Comment 13 C

13) In figure 2, The DVH view is not informative as there is no corresponding legend. The reader is unlikely able to discern the values. Suggest reporting the OAR values of selected structures in table format instead.

Reply 13 C

Thank you for your feedback, we agree with the Reviewer and we added more information on dosimetry and on dose-volume endpoints in Table 1. Please see Table 1.

……

Comment 14 C

14) The paper is generally comprehensible but the writing can be more engaging and concise. There are also spelling and grammatical mistakes.

Reply 14 C

Thank you for your assessment. Our manuscript has undergone an extensive English revision by a native speaker of a professional translation and interpreting service.

Reviewer D

Comment 1D

The idea of spacially fractionated radiotherapy (GRID) by 2D or 3D cerrobend blocks has been developed for decades. However, the use of volumetric modulated arc therapy by MLC to perform stereotactic body irradiation for large tumors that deliver 20Gy in 5 fractions to the periphery while simultaneously boosting quite a few small high dose regions with 50-67Gy in 5 fractions with acceptable dose to organ at risks is relatively new (Lattice Radiation Treatment, LTR). The case reported here received LTR and chemotherapy and resulted in a good palliative effect, although interesting, is not surprising. There were cases series reported with LTR alone.

Reply 1D

We thank the Reviewer for the suggestion. We agree with Reviewer that the use of MLC to perform LTR is relatively new, and that the idea of spatially fractionated radiotherapy has been developed for decades, however, we would like to focus on some point.

- We would like to underline that Vinorelbine administration was suspended during LTR, and restarted after treatment end, since Vinorelbine is a well-known radiosensitizer, and no data are currently available on the interaction

between LTR and Vinorelbine. This information was not clearly reported in the first version of our manuscript (we provided to make this point clearer in the "*Case presentation*"; Please see line 91-92). The lesion we treated did not respond to III lines of systemic therapies because it continued to grow. Thus, it seems reasonable to assume that LTR played the key role in the large lesion response. It is commonly accepted that radioresistant tumors require higher doses to be controlled; however, these doses with standard RT would imply a higher risk of toxicity, which is not justified in a palliative setting.
In addition, since the sarcomatoid lung cancer presents limited response rates to traditional treatments such as chemotherapy, radiotherapy (radioresistant tumor), and neoadjuvant therapy, [1] we think that the large lesion shrink due to LTR should be carefully evaluated and not considered as a commonly predictable response, especially considering the limited treatment toxicity.

- We agree with the reviewer that different LTR case series are present in literature. Notwithstanding this, LTR regimens are characterized by a fractions delivery every other day or by a combination between one or more LTR fractions followed by conventional RT regimens (Hybrid LTR or not-exclusive LTR) (Please see the Manuscript bibliography for the references). This implies that palliative treatments require at least 2 weeks to be delivered, and the treatment length is important in a palliative setting. Even in LITE SABR M1 phase I trial, LTR fractions were not delivered consecutively but every other day to limit the risk of excessive toxicity. In addition, the same "LITE SABR M1" group has been carrying out a phase II clinical trial (*NCT 04553471*) to evaluate the efficacy and the late toxicity of LRT with fractions delivered every other day. Conversely, our LTR exclusive regimen is delivered in 5 consecutive days (1 week), and, considering the intrinsic limitations of a case report, it allowed to reach a satisfying tumor response with a limited toxicity in a short amount of time, which can be supposed to minimize the treatment influence on patients' daily activities.

[1] Li X, Wu D, Liu H, Chen J. Pulmonary sarcomatoid carcinoma: progress, treatment and expectations. Ther Adv Med Oncol. 2020;12:1758835920950207. Published 2020 Aug 25. doi:10.1177/1758835920950207

……

Comment 2D

(1) Please change the conclusion in the abstract "this is one of the first LTR treatment." to a modest way.

Reply 2D

Thank you for your feedback. We changed the conclusion in the abstract in a more modest way (Please see abstract conclusion, line 30).

……

Comment 3D

(2) The dose-volume histogram in figure 2 should be well labeled, such as which curve represents vertice, valley, lung, esophagus, heart, spinal cord, etc. The treatment machine, mean lung dose, V5, V10, V20, and the peak to valley dose distribution should be expressed.

Reply 3D

Thank you for your suggestion. Since the journal does not focus on the topic of radiation oncology but on palliative medicine and due to the case report word limit (2,500 words max), we thought it would have been more adequate not to precisely describe treatment planning and delivery, as well as the patient's dosimetry. However, we strongly agree with the Reviewer, and we added the requested information in the new section ""Lattice Radiation Treatment Planning" and in Table 1. (Please see Table 1 and lines 108-115)

……

Comment 4D

(3) The description of " a software script, opportunity created," in line 108, a section of Lattice Radiation Treatment Planning is not clear. A more detailed description with a reference (Kavanaugh JA) should be put.

Reply 4D

Thank you for you feedback. We acknowledge that our sentence was a bit misleading since it suggested that we used an available script designed for LTR planning. Conversely, the script we used was instead original, homemade, and developed in MATLAB.

We provided to change the sentence as follows: *"…a homemade software script, developed in MATLAB, suggested…" Please see lines 124-125.*

……

Comment 5D

(4) The immunological changes have not been described in the manuscript. Please add the trend of neurophil/lymphocyte ratio change, the CRP changes before and after therapy

Reply 5D

Thank you for the suggestion. Although evidence is still quite limited in clinical setting, we agree with the Reviewer that the immunological changes induced by RT are an interesting, actual and important topic (i.e., abscopal effect and bystander effect) which could entail a revolution of RT use in the oncological therapy. Notwithstanding this, the effects of RT doses on immune system innate and adaptive response as well as on tumor vascularization remain unclear.

Our manuscript focuses on the use of LTR to shrink a bulky and symptomatic

sarcomatoid lung cancer. Even though we acknowledge that one of the hypothesized LTR mechanism of actions is the radiomodulation of host immune system to increase immune cells response against cancer, however, we did no investigated the evaluation of immunological changes since our first aim was to provide a quick relief to a palliative patient without other debulking options. We will investigate LTR immune-changes in another study since a comprehensive analysis should encompass at least a characterization of immune cells modification, through cell immunophenotyping, and a quantification of immune-related circulating factors possibly associated with LRT. In addition, the blood sample timing respect to LTR administration (i.e., how much time before and how much time after LTR), is another fundamental variable to consider. We tried to discuss better this topic in the discussion section but we did not execute exams to assess immune system changes due to LTR and we added a statement to clarify this point (Please see lines 198-199). We acknowledge that assessing immune system modification due to LRT would be very useful in a clinical trial and it should be encouraged.

Reviewer E

Comment 1E

General comments:

This is a case report of a 69-year-old man with advanced (cT4N3M1c, stage IV) sarcomatoid lung cancer that was successfully treated with lattice radiation therapy with palliative intent. He received radiation therapy with the inhomogeneous dose distribution, namely 55 Gy in 5 fractions at the intratumor area and 20 Gy in 5 fractions at the peripheral area of the bulky intrathoracic tumor, using lattice radiation technique. His symptom (dyspnea) was relieved, and the tumor was controlled about 5 months after irradiation. This report is interesting but is lacking in impact. Prior to irradiation to the intrathoracic tumor, a total dose of 20 Gy in 5 fractions with the conventional technique was delivered to the metastatic tumor in the sacroiliac muscles and then it was also controlled at the last follow up. This may mean that it was not so radioresistant. Indeed, lattice radiation therapy is the novel and promising radiation technique but unfortunately does not prove to have been the limited treatment option for this patient, although his immunomodulatory activation might be induced by high-dose irradiation to the tumor. In addition, there are some problems that the authors need to clarify and revise as mentioned in the specific comments below.

Reply 1E

We would like to thank the Reviewer for his assessment. We see Reviewer point, since we had not report that the sacral lesion was 3.8 x 3.8 cm, and the lack of this information could have misleadingly suggested that the tumor was not so radioresistant.

Considering this possible element of confusion, we added the information about the sacral lesion dimension: *" After an antalgic standard radiotherapy on the sacrum to relieve the back pain (4Gy x 5 fractions to a 3.8 x 3.8 cm lesion with positive antalgic response"*. Please see lines 80-81.
However, we believe that:

- Sarcomatoid lung cancer presents limited response rates to traditional treatments such as chemotherapy, radiotherapy, and neoadjuvant therapy; and it is commonly considered a radioresistant tumor. [Please see reference 1 below]
  The sacral lesion had a dimension of 3.8 x 3.8 cm, whereas the lesion treated with LTR was 19 cm x 16 cm. Smaller neoplastic lesion tend to have a more preserved vascular matrix which render them keener to respond to chemotherapy, since drugs can more easily reach adequate concentration in neoplastic niches. With reference to RT, large lesions tend to be more radioresistant, because they are commonly more hypoxic, and they have usually necrotic areas inside [Please see 2-3-4 below].
  In addition, we cannot overlook that after the palliative RT on sacral lesion, the patient underwent four chemotherapy lines. Thus, considered the limited dimension of sacral lesion, the palliative RT and the continuative systemic therapy with different lines, as well as the limited time from diagnosis to last follow up, we agree that this stability is not surprising; however, it cannot be considered as a suggestion of sarcomatoid lung cancer radioresistence and it should not lead to overlook LTR impact on large radioresistant lesion.

[1] Li X, Wu D, Liu H, Chen J. Pulmonary sarcomatoid carcinoma: progress, treatment and expectations. Ther Adv Med Oncol. 2020;12:1758835920950207. Published 2020 Aug 25. doi:10.1177/1758835920950207
[2] Li Y, Zhao L, Li XF. Hypoxia and the Tumor Microenvironment. Technol Cancer Res Treat. 2021 Jan-Dec;20:15330338211036304. doi: 10.1177/15330338211036304. PMID: 34350796; PMCID: PMC8358492.
[3] Jarosz-Biej M, Smolarczyk R, Cichoń T, Kułach N. Tumor Microenvironment as A "Game Changer" in Cancer Radiotherapy. Int J Mol Sci. 2019 Jun 29;20(13):3212. doi: 10.3390/ijms20133212. PMID: 31261963; PMCID: PMC6650939.
[4] Forster JC, Harriss-Phillips WM, Douglass MJ, Bezak E. A review of the development of tumor vasculature and its effects on the tumor microenvironment. Hypoxia (Auckl). 2017 Apr 11;5:21-32. doi: 10.2147/HP.S133231. PMID: 28443291; PMCID: PMC5395278.

- We performed a focused palliative treatment with the main aim to relieve symptoms and to possibly shrink the large tumor mass. Radioresistant tumor require higher doses to be controlled, but these doses would imply an unacceptable risk of toxicity with standard RT palliative regimens (with homogeneous dose delivery). This risk is not justified in a palliative setting.

Hence, it could be valuable, and with a clinical impact, the possibility to deliver high doses without increasing treatment toxicity to palliative patients, affected by a radioresistant voluminous tumor mass, unresponsive to systemic therapy and unresectable.

In addition, we performed a local treatment without the main aim of a systemic response (i.e., abscopal effect). Although an eventual role played by the activation of the host immune system against cancer cells due to LTR cannot be excluded (one of LTR possible action is bound to host immune system modulation), literature is very limited and further study are required to clarify LTR heterogeneous dose interaction with immune system.

Notwithstanding this, we would like also to underline that no data are available on which strategy should be preferable; therefore, all LTR approach should be positively welcome and investigated, due to their potential impact on clinical practice. We added this information in the "Conclusion". Please see lines 207-208

……

Comment 2E

Specific comments:

1. Case presentation, page 2, lines 80–84

This patient was pathologically diagnosed with sarcomatoid lung carcinoma by aspiration biopsy. I suggest adding photomicrographs of specimens because definitive diagnosis is important to a case report.

Reply 2E

Thank you for your suggestion. We agree with the Reviewer about diagnosis importance; however, the diagnosis was reached thank to a cytological analysis and immunohistochemistry and, consequently, photomicrographs might be little informative. To be more precise, the cytology highlighted numerous cells, markedly atypical, with evident nucleolus, and solid growth. The immunohistochemistry resulted as follows: CK CAM5.2 +/-, VIMENTINA +, AML -/+, ERG -/+,
TTF1 -, P63 -, CD56 -, LCA -, CDX2 -, S100 -, CD31 -, PAX8 -, GATA3 -, c-MYC -, chromogranin -, sinaptofisine -, pancytokeratin -.

Notwithstanding this, we agree with the suggestion to be more precise about how we reached the definitive diagnosis. Hence, to be clearer, we added how we reached this information in the "*Case presentation*": *"allowed to obtain a sample for cytological analysis, immunohistochemistry, and the tumor proportion score (TPS). These confirmed the diagnosis of a sarcomatoid lung carcinoma PD-L1 TPS >50%, a very aggressive and radioresistant cancer." Please see lines 76-79.*

……

Comment 3E

2. Lattice radiation treatment planning, page 3

Were the metastatic intrathoracic lymph nodes included in the gross tumor volume for lattice radiation therapy?

Reply 3E

Thank you for your point. Only metastatic intrathoracic lymph nodes adjacent to the large mass were included in the gross tumor volume, since they could be reasonably considered as a single bulky target with the T. Considered patient condition and palliative setting, our main aim was to palliate symptoms and to shrink the bulky mass, without exceeding organ at risk tolerance levels. We added this information as follows: "*In addition to the large mass (T), the GTV included the metastatic intrathoracic lymph nodes adjacent to large mass, since they could be reasonably considered with the T as a single bulky target.*" Please see lines 122-124.

……

Comment 4E

Information about radiation therapy is insufficient. Please give treatment and treatment planning machines, energy of X-rays, immobilization of patient body, verification of tumor position, breath situation, etc.

Reply 4E

Thank you for your feedback. Since the journal does not focus on the topic of radiation oncology but on palliative medicine and due to case report words limit, we thought it would have been more adequate not to precisely describe treatment planning and delivery as well as patient dosimetry. Considered the positive and interested feedbacks on this point, we agree with the Reviewer and we provided to add the requested information in the new section "Treatment Planning and delivery" and in Table 1. Please see Table 1 and lines 108-115.

……

Comment 5E

3. Figure 2

The dose distribution of 20 Gy and higher is shown in this figure. The lower-dose distribution should be shown because it may cause readers a misunderstanding that the non-colored area of the lungs was not irradiated at all.

Please denote DVH parameters, such as V5, V10, and V20 of the total lung, in the text.

Reply 5E

Thank you for your feedback. We agree that the lower-dose distribution should be shown because it could be misleading and it may cause to readers a misunderstanding, especially to a person who is not familiar with radiation treatment dosimetry. We corrected Figure 2 adding the 20 Gy isodose and 10 Gy isodose. In addition, and we reported in Table 1 the information about our dose volume endpoints. (Please see Figure 2 and Table 1 in the revised manuscript).

Round 2

Reviewer A:

Comment 1A

Thank you for applying my suggestions. The only remaining issues are punctuation and some editorial changes - why do you use capital letters in the names of procedures or chemo agents (like EndoBronchial UltraSound-guided TransBronchial Needle Aspiration, Carboplatin + Paclitaxel, Radiation Oncology Unit, Radiation Oncology Unit)?

Reply 1A

Thank you for your feedback. We used the capital letter in the names of procedures to easy the understanding of the abbreviations (e.g., EndoBronchial UltraSound-guided TransBronchial Needle Aspiration –> EBUS-TBNA). However, we understand your point and we modified as suggested. Please see the revised manuscript.

……

Comment 2A

Moreover, some abbreviations were introduced more than once (like LTR).

Reply 2A

Thank you for your observation, we modified it in the revised version of our manuscript. Please, see the revised manuscript.

……

Comment 3A

What is Esifal stick? Please use the international name/description if feasible (or add a manufacturer and country).

Reply 3A

Thank you for your feedback. We added this information in the revised manuscript. Please see lines 95-96.

Reviewer B:

Comment 1B

Please see the attached file, corrections in green.

Reply 1B

Thank you for your precise feedbacks. We incorporated your corrections in the revised

version of our manuscript, in which they are marked in red. Please, see the revised manuscript.

Reviewer C:

Comment 1C

Thank you for revising the manuscript. My comments are as follow:

1. Line 24: the term "allowed to" is awkward. Perhaps just saying "confirmed" is adequate.

Reply 1C

Thank you for your feedback we modified as suggested. Please see line 24.

……

Comment 2C

2. Line 26: patient not patients

Reply 2C

Thanks, we changed as suggested. Please see line 26.

……

Comment 3C

3. Line 28: improvement in symptoms

Reply 3C

Thank you for your feedback we modified as suggested. Please see line 28.

……

Comment 4C

4. Line 30: It provides new evidence on the feasibility of LTR planning

Reply 4C

Thanks, we changed as suggested. Please see line 30.

……

Comment 5C

5. Line 42: would avoid words in " "

Reply 5C

Thank you for your feedback we modified as suggested. Please see line 43.

……

Comment 6C

6. Line 43: drop "much"

Reply 6C

Thanks, we changed as suggested. Please see line 44.

……

Comment 7C

7. Line 48: not acceptable-> unacceptable

Reply 7C

Thank you for your suggestion, we modified as indicated. Please see line 49.

……

Comment 8C

8. Line 50: contest-> context

Reply 8C

Thanks, we changed as suggested. Please see line 51.

……

Comment 9C

9. Line 51-52: large lesions… bulky lesions-> repetitive

Repy 9C

Thank you for your suggestion, we modified as indicated. Please see lines 51-52.

……

Comment 10C

10. Line 55: spearing-> sparing

Reply 10C

Thank you for your suggestion, we modified as indicated. Please see line 56.

……

Comment 11C

11. Line 59: persistence of the favorable-> achieving durable

Reply 11C

Thanks, we changed as suggested. Please see line 60.

……

Comment 12C

12. Line 61: not-> non

Reply 12C

Thank you for your suggestion, we modified as indicated. Please see line 62.

……

Comment 13C

13. Line 62: treatment of a patient with symptomatic…

Reply 13C

Thank you for your suggestion, we modified as indicated. Please see lines 63-64.

……

Comment 14C

14. Line 70: can consider putting in ECOG here. I presume ECOG 1. The sacral pain is mild/moderate/severe?

Reply 14C

Thank you for your point. The sacral pain was severe; we added these data as suggested. Please see line 70.

……

Comment 15C

15. Line 71-75: please confirm if the chest CT showed lesions in the sacroiliac masses and sacrum or were they detected on PET/CT

Reply 15C

Thank you for your feedback, we added this information. Please see line 72.

……

Comment 16

16. Line 80: can you please share what happened to the 3.8cm sacral lesion after radiotherapy? Was it stable or did it respond?

Reply 16

Thank you for your comment. After the palliative RT and chemotherapy begin, the sacral lesion remained stable. Please see line 82.

……

Comment 17

17. Line 87-89: thank you for sharing the discussion with the patient. Was he given both options of LTR and standard palliative RT? Is there any difference in terms of payment?

Reply 17

Thank you for highlighting this point. He received both the options with their pros and cons. The patient finally decided to undergo the LTR. Oncological patients do not pay for their treatments in Italy, since the National Health Service, which is public, covers the expenses. Hence, there was not any difference in terms of payment for the patient.

……

Comment 18

18. Line 98: given the interval for manuscript review, would it be possible to share further patient followup? Alive? Symptoms?

Reply 18C

Thank you for your request we update the follow up of the patients. Please see lines 103-105.

……

Comment 19

19. Line 98: patients-> patient

Reply 19

Thank you for your feedback, we added this information. Please see line 101.

……

Comment 20

20. Line 98-99: patient reported… and, as the patient said, -> repetitive

Reply 20

Thank you for your comment. We modified the sentence and we eliminated the repetition. Please see lines 101-102.

……

Comment 21

21. Figure 1: you used “pz” only once, is it necessary?

Reply 21

Thank you for your comment. We modified the Fig.1 erasing the abbreviation. Please see line 107 (Fig 1).

……

Comment 22

22. Line 111: suggest in five daily fractions over one week

Reply 22

Thank you for your comment. We modified the sentence as suggested. Please see lines

118-119.

……

Comment 23

23. Line 113: what is photon x?

Reply 23

Thank you for your point. We see that writing photon x could be misunderstanding. We changed it in the revised manuscript writing: “photon beams”. Please see line 120.

……

Comment 24

24. Line 115: thank you for the time on couch. How about the time from planning CT to first fraction? I presume doing the planning may take a longer time than conventional palliative RT. Also am I right to assume that the usual QA procedures were followed?

Reply 24

Thank you for your comment. As always, all QA procedures were strictly followed. The time from planning CT to first fraction was of 8 days. We added this information in the revised manuscript. Please see lines 116-117.

……

Comment 25

25. Line 118: Can I clarify that the description on the placement of the vertices is the same as that of the LITE SABR M1 trial group? If yes please mention as such. If no, please highlight the difference between your method and that of the LITE SABR M1 group.

Reply 25

Thank you for your comment. For the placement of the vertices was the same as that of the LITE SABR M1 trial group. We clarify this information in the text. Please see lines 128-129.

……

Comment 26C

26. Line 120: suggest drop “phase I”

Reply 26C

Thank you for your comment. We modified the sentence as suggested. Please see line 129.

……

Comment 27C

27. Line 124: a homemade-> an in-house

Reply 28C

Thanks for your feedback. We modified the text. Please see lines 132-133.

……

Comment 28C

28. Line 127: suggest drop "within a distance"

Reply 28 C

Thanks for your feedback. We modified the text. Please see line 135.

……

Comment 29C

29. Line 129: missing punctuation after PTV

Reply 29C

Thank you. We added it. Please see line 137.

……

Comment 30C

30. Line 129: prescribe->prescribed

Reply 30C

Thanks for your feedback. We modified the text. Please see line 137.

……

Comment 31C

31. Line 131-132: The dose reached in the vertices allowed to maintain almost the same dose bath, external to PTV, of a uniform IMRT plan-> this line is unclear, please rephrase.

Reply 32C

Thank you for your observation. We wanted to say that the dose fall-off outside of the PTV was the same of a uniform IMRT plan. As suggested, we modified the phrase to easy its understanding. Please see lines 139-140.

……

Comment 32C

32. Line 138: Figure 2: "In the Figure 2" is repetitive

Reply 32C

Thanks for your feedback. We modified the text. Please see line 145.

……

Comment 33C

33. Line 164-165: drop everything "where the firsts…. Fractionated RT (12-13)" as you are already explaining it after.

Reply 33C

Thanks for your feedback. We modified the text as suggested. Please see lines 160-170.

……

Comment 34C

34. Line 183: "well-feeling"

Reply 35C

Thanks for your feedback. We modified the text as suggested. Please see line 188.

……

Comment 35C

35. Line 198: I am of the opinion that we cannot rule out the effect of vinorelbine possibly enhancing the effect of RT. Even though it was suspended during LTR, one cannot rule out a possibility of LTR changing the tumour microenvironment such that the chemo can work better subsequently

Reply 35C

We understand your point and we agree that we cannot exclude a possible synergy between LTR and vinorelbine, since TME immunomodulation is one of the hypothesized LTR activities in addition to the ablative one. However, we did not performed basal tests to monitor TME evolution due to LTR (e.g., immune-phenotypes modification) and we have not enough data to investigate a possible. This is an interesting field, which urgently requires further research.

……

Comment 36C

36. Line 216: Physics

Reply 36C

Thanks for your feedback but we refer to the Medical Physic Unit and not to Physics.

……

Comment 37C

KEEP ALL TRACES of changes this time and in the future.

Reply 37C

Thank you for your advice. We highlighted in red all the changes we made in the revised manuscript. The erased parts are strikethrough in red.