

Peer Review File

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Reviewer A

For Major comments:

Comment 1: Although the authors discuss the good points of RSI-BT throughout, it is also true that its high effectiveness leads to improved OS and that late complications need to be considered. Therefore, it should be necessary to control the irradiation dose precisely. Because the authors have entered the main discussion without sufficiently mentioning this point, the readers have a somewhat difficult time understanding the contents regarding the different settings of irradiation doses and the contribution of the planning systems.

Please revise the introduction and the technical background so that these points are adequately conveyed to the readers.

Reply 1: Thank you for your great comment. We are extremely grateful to the editor's valuable comment. According to your suggestion, we added some details our manuscript. Thank you for your valuable suggestions.

Changes in the text: Line 54-64 & Line 101-119 & Line 508 Table 2 Outcome (positive & negative)

Line 54-64: "External beam radiotherapy (EBRT), as a conventional radiation therapy, has been one of the optional therapies for the treatment of NSCLC. Although EBRT has some advantages, such as mature technology, and more convenient. However, due to the limitation of therapeutic mechanism, EBRT needs to pass the accelerated photon or electron beam through normal tissues before it can reach the tumour tissues. On the one hand, this causes additional damage to normal tissues; on the other hand, in order to achieve the therapeutic dose, EBRT needs to increase the irradiation dose, which in turn exacerbates the damage to the tissues in the irradiation path(3). However, brachytherapy has some advantages in the above problems. Since the irradiation comes from inside the tumour, the irradiation to the surrounding tissues can be effectively reduced."

Line 101-119: "As an example, Ir-192, which is commonly used as a source for HDR-BT, typically delivers at a rate of ≥ 12 Gy/h, compared to 0.4-2.0 Gy/h of LDR-BT. The linear quadratic (LQ) equation can be used to calculate the total biologically effective dose (BED), which can be used to assess the frequency that HDR-BT/LDR-BT is received(13). At the same time, more precise treatment planning systems and the use of high-resolution Computed Tomography (CT) have made dose control easier.

The standard treatment planning procedure for 3D volumetric image-based brachytherapy involves 3 main steps: (1) anatomic contouring, (2) applicator digitization, and (3) dosimetric planning and optimization, using a dedicated treatment planning system (TPS)(14). Step(1) and (2) would be accomplished by using TPS, but step (3) usually need more BT teams' effort and time. Accurate delineation of the clinical target volume (CTV) and organ at risk (OAR) is a crucial step in radiotherapy treatment planning(15,16). However, it is still a labor-intensive

process to manually contour the CTV and OARs in a 3D image volume with some guidelines exist to help define the contours. Deep-learning-based image processing has demonstrated tremendous potential to help this(17). Additionally, dose calculations based on the AAPM Task Group 43 formalism are currently the mainstream(18). Some model-based calculation methods are increasing being used to improve efficiency, such as Monte Carlo simulation or solving the Boltzmann transport equation(19).

”

Comment 2: In the introduction, it is true that radiotherapy is an alternative to surgery in local treatment, but the standard method is external radiation. Even though the authors understand this point, it is difficult to understand the content of their argument because it is based on brachytherapy. Please rewrite the article so that the problems with external irradiation are mentioned first, and then the differences caused by brachytherapy in contrast to the problems with external irradiation are understood.

Reply 2: Thank you for your great comment. We are extremely grateful to the editor’s valuable comment. According to your suggestion, we added some details our manuscript. Thank you for your valuable suggestions.

Changes in the text:

Line 54-64: “External beam radiotherapy (EBRT), as a conventional radiation therapy, has been one of the optional therapies for the treatment of NSCLC. Although EBRT has some advantages, such as mature technology, and more convenient. However, due to the limitation of therapeutic mechanism, EBRT needs to pass the accelerated photon or electron beam through normal tissues before it can reach the tumour tissues. On the one hand, this causes additional damage to normal tissues; on the other hand, in order to achieve the therapeutic dose, EBRT needs to increase the irradiation dose, which in turn exacerbates the damage to the tissues in the irradiation path(3). However, brachytherapy has some advantages in the above problems. Since the irradiation comes from inside the tumour, the irradiation to the surrounding tissues can be effectively reduced.”

Comment 3: The abstract's conclusion states, “more research is needed on the combination of RSI-BT with immunotherapy”, but the text concludes in a similar manner for many combination therapies, which is disconcerting. The relevant sentence should be changed to “more research is needed on the combination of RSI-BT with them”, instead of focusing only on immunotherapy.

Reply 3: Thank you for your great comment. We are extremely grateful to the editor’s valuable comment. According to your suggestion, we have changed part of our manuscript. Thank you for your valuable suggestions.

Changes in the text:

Line 46-47: “but more research is needed on the combination of RSI-BT with them.”

Comment 4: Lines 113–114: The authors assert that RSI-BT is less invasive than traditional surgery and radiotherapy, but as I mentioned in my first comment, there is a lack of description of late complications in this manuscript. Also, in the absence of studies directly comparing them in RCTs, it is not possible to make this statement. For this statement, sufficient evidence must

be given or the wording must be weakened based on cited references and other information.

Reply 4: Thank you for your great comment. We are extremely grateful to the editor's valuable comment. According to your suggestion, we have deleted part of our manuscript. Thank you for your valuable suggestions.

Changes in the text:

Line157-158: ~~“RSI-BT also has its own advantages over traditional surgery and radiotherapy: it is less invasive.”~~

Comment 5: Throughout, it is not clear whether abbreviations are listed and used without spelling them out, or whether they are spelled out the first time they appear. In addition, there are some places where abbreviations are unnecessarily used for words that appear only once. The authors themselves should carefully review and correct these errors.

Reply 5: Thank you for your great comment. We are extremely grateful to the editor's valuable comment. According to your suggestion, we have checked the whole manuscript and change some places.

For minor comments

Comment 1: Line 123: “controlled side effects” should be “controllable side effects”?

Reply 1: Thank you for your great comment. We are extremely grateful to the editor's valuable comment. According to your suggestion, we changed the part of our manuscript.

Changes in the text: Line 168: controllable side effects

Comment 2: Line 139: “tracheal stenosis” should be “tracheal restenosis”?

Reply 2: Thank you for your great comment. We are extremely grateful to the editor's valuable comment. According to your suggestion, we changed the part of our manuscript.

Changes in the text: Line 184: tracheal restenosis

Comment 3: Line 163: “as a specific type of radiotherapy” has already been explained and is not needed here?

Reply 3: Thank you for your great comment. We are extremely grateful to the editor's valuable comment. According to your suggestion, we changed the part of our manuscript.

Changes in the text: Line 209: ~~as a specific type of radiotherapy,~~

Comment 4: Line 206: “However” should be deleted.

Reply 4: Thank you for your great comment. We are extremely grateful to the editor's valuable comment. According to your suggestion, we changed the part of our manuscript.

Changes in the text: Line 256: ~~However,~~

Comment 5: Line 216: “Conclusion” should be “Conclusions”.

Reply 5: Thank you for your great comment. We are extremely grateful to the editor's valuable comment. According to your suggestion, we changed the part of our manuscript.

Changes in the text: Line 267: Conclusions

Reviewer B

1. Please check if the date of search should be changed to “03/02/2023 till 03/05/2023” in Table 1.

■ **Table 1. Brachytherapy and Lung Neoplasms literature research**

Items	Specification
Date of search	03/02/2023

Reply 1: Thank you for your great comment. We are extremely grateful to the valuable comment. According to your suggestion, we have changed the date of search to “03/02/2023 till 03/05/2023” in Table 1 in our manuscript. Thank you for your valuable suggestions.

2. Ref. 67-73 have been cited in **Table 2**, yet in the main text Table 2 was cited after Ref. 6. Please check.

Reply 2: Thank you for your great comment. We are extremely grateful to the valuable comment. According to your suggestion, we have deleted Table 2 citation in Line 74 in our manuscript. Thank you for your valuable suggestions.

3. And Table 2 should be cited **after** Table 1 in text, please check and revise.

Reply 3: Thank you for your great comment. We are extremely grateful to the valuable comment. According to your suggestion, we have deleted Table 2 citation in Line 74 in our manuscript. Thank you for your valuable suggestions.