Peer Review File

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Review Comemnts

Intensity-modulated radiotherapy is now widely implemented and has replaced classical 3D radiotherapy in many tumor sites, as it allows a better target dose conformity and a better sparing of organs a risk, at the expense, however, of increasing the volume of low dose to normal tissues. Clinical data on toxicities using volumetric arctherapy (VMAT) in lung cancer remain scarce. In the manuscript "Toxicity after Volumetric Modulated Arc Therapy for lung cancer", authors reported acute and late pulmonary (APT, LPT) and oesophageal toxicities (AET, LET) in such setting.

Couple questions are required to be answered before accepted.

(1) There was similar report (Radiat Oncol. 2014 Nov 11;9:243) in the PubMed. What is the novel idea in the paper? Please elucidate in the introduction.

The referred report (Radiat Oncol. 2014 Nov 11;9:243) focuses on patients with lung cancers treated with Stereotactic Radiation Therapy. Prescription doses were significantly different (50Gy or 55Gy in 4 fractions compared to our cohort irradiated with normally fractionated regimens). Furthermore, the stereotactic setting implies tighter margins with smaller volumes and lower doses to the organs at risk and thus does not reflect the concern raised by volumetric arctherapy (VMAT) and the "low dose bath".

(2) In the introduction, please enrich the progress of the treatment for lung cancer?

The manuscript was modified accordingly (page 3, lines 65-67).

(3) What is the meaning of "APT, LPT, AET and LET"?

The meaning of these abbreviations is stated in page 5 but was added in the abstract (page 1, lines 38-39:

- APT: acute pulmonary toxicity
- LPT: late pulmonary toxicity
- AET: acute oesophageal toxicity
- LET: late oesophageal toxicity

(4) In the paper, the case samples were small. How to handle with the issues?

With 167 patients included, this report is, to our knowledge, one of the largest cohort of patients with lung cancer treated by VMAT.

(5) In the introduction, are there any complications after IMRT?

A precision regarding toxicities after IMRT has been added (page 3, lines 72-76). As reported, the higher conformation using IMRT is possible at the expense of a volume increase in adjacent organs receiving doses in the lowest range. This « low-dose bath » may theoretically increase toxicity in the adjacent healthy tissues, especially in the lungs, despite being not really clinically reported. In a retrospective cohort of 73 patients treated with hypofractionnated IMRT (2.2-2.75Gy/fraction), severe pneumonitis and esophagitis (grade ≥ 3) occurred in only 7% and 1% of the population, respectively. For volumetric arctherapy (VMAT), this low dose bath, reflected by the V5% to the lungs,

has raised some concern with the rate of radiological pneumonitis being possibly higher in patients treated with VMAT compared with conformal 3D-RT. However, reported results are contradictory in terms of occurrence of lung complications following IMRT or VMAT, thus the need of reports such as ours.

批注 [01]: J'ai modifié cette réponse ainsi que le paragraphe dans le texte en essayant de plus insister sur la diminution des tox après IMRT

(6) In the assessment of toxicity, how to identify the adverse events induced by RT, but not ChT?

A precision regarding the distinction between Cht and RT toxicities has been added (page 5, lines 134-140):
"To distinguish between Cht and RT toxicities, toxicities specifically due to Cht were also collected during and after the radiation delivery. Here, we only report toxicities due to RT. Indeed, the Cht toxicity profile is significantly different with, mainly and depending on the Cht regimen, systemic toxicities such as gastro-intestinal (nausea, …), haematological (neutropenia, anemia, …), renal and neurologic (neuropathy). In the cChRT setting, Cht is used as a radio-sensibilization agent. Therefore, toxicities are often due to the RT but increased by the Cht" .

(7) How many cases enrolled in the paper? Please illustrate clearly in the methods.

As explained in the Methods Paragraph, all consecutive patients treated with (chemo-) RT using VMAT delivered with curative intent for lung cancer between November 2015 and January 2018 at the University Hospital of Brest were included (Methods, Page 4, Lines 89-91). Consequently, and as stated in the Results (Population, Page 6, Line 166), 167 patients were included.

(8) What are the criteria of inclusion and exclusion for enrolled patients? How to overcome the noted limitations?

As explained in the Methods Paragraph, all consecutive patients treated with (chemo-) RT using VMAT delivered with curative intent for lung cancer between November 2015 and January 2018 at the University Hospital of Brest were included (Methods, Page 4, Lines 89-91).
Therefore, no criteria of inclusion or exclusion were retained.

(9) Whether or not, the toxicity after VMAT is different for different kind of lung cancer?

Toxicity after VMAT does not depend on lung cancer histology as toxicities are correlated with the prescribed dose and the doses to the OARs.