

Peer review file

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Reviewer A

Comment 1: In light of the overall very limited number of patients, I understand that it is difficult to expand the depth of statistical analyses. However, I still see possibilities to further analyze the data.

Reply 1: Thank you for raising this important point. We added figure about the Kaplan-Meier curve. (see Page 8, line 10, Figure 2)

Changes in the text:

Over a median follow-up period of 30.2 months in patients who underwent salvage surgery, the five-year overall survival was 72.5%, and the five-year disease-free survival was 70.6%.

To

Over a median follow-up period of 34.8 months in patients who underwent salvage surgery, The 5-year overall survival (OS) and disease-free survival (DFS) was 72.5% and 65.2%, respectively (Figure 2A,B). The 3-year OS in patients with lobectomy and limited resection after SBRT were 84.6% and 0%, respectively ($P=0.039$), and the 3-year DFS were 65.6% and 0%, respectively ($P=0.853$) (Figure 2C,D).

Reviewer B

Comment 1: Since 421/932 of SBRT patients did not even have a confirmed diagnosis, it is incorrect to state that the recurrence rate was 5.2% (48/932). The real recurrence rate could only be calculated with confirmed cases as the denominator.

Reply 1: We agree with the Reviewer's comment and have modified our text as advised (see Page 7, line 5)

Changes in the text: A total of 932 patients underwent SBRT for treatment of primary lung cancer (n = 511) and lung tumors suspected to be cancer (n = 421) during the period from July 2005 to July 2015 (Figure 1).

To

A total of 932 patients underwent SBRT as treatment for primary lung cancer during the period from July 2005 to July 2015 (Figure 1). 511 (54.8%) patients had histological confirmation before SBRT, and the remaining 421 patients were clinically diagnosed with primary lung cancer on radiographic imaging.

Comment 2: It is stated that the median time from SBRT to salvage surgery was 17.3 (7.6–58.3)

changes or mass-like fibrosis can occur over more than two years and is considered to be a normal change following SBRT, possible delaying the recurrence diagnosis'. And 'In this series, two patients underwent incomplete resection, possibly because of delay in recurrence'. It is thus important to suggest that SBRT is not always curative.

Reply 2: We agree with the Reviewer's comment and have modified our text as advised (see Page 11, line 11)

Changes in the text: Some reports have stated that the time period from SBRT to recurrence ranges between 10 and 17 months (6-8), and a similar result of 17.3 (7.6–58.3) months was obtained in the present study. Further, we found that the increase in tumor size ranged from 23 (12–48) mm to 38 (15–55) mm. It has been reported that late fibrotic changes or mass-like fibrosis can occur over more than two years and is considered to be a normal change following SBRT (9,20), possible delaying the recurrence diagnosis. In the present study, two patients underwent incomplete resection, possibly because of delay in recurrence.

To

Some reports have stated that local recurrence during follow-up after SBRT defined as continuous increase of the tumor in size or increase FDG avidity(6-8). But, one of the

issues with recurrent lung cancer after SBRT is the difficulty to correctly diagnose recurrence based on imaging. Fibrotic changes often develop after SBRT and tumor shadow becomes indistinguishable from the fibrotic shadow(21). Ogawa et al.(22) reported positive FDG-PET (SUV max ≥ 5) finding does not necessarily indicate tumor recurrence because they experienced a number of false positive cases. It has been reported that late fibrotic changes or mass-like fibrosis can occur over more than two years and is considered to be a normal change following SBRT (9,23), possible delaying the recurrence diagnosis. Therefore there is no criteria to diagnose recurrence after SBRT in primary lung cancer. We defined local recurrence after SBRT as continuous increase of the tumor in size. Further, we found that the increase in tumor size ranged from 23 (12–48) mm to 38 (15–55) mm. And, we defined the time period from SBRT to salvage surgery as from the start of SBRT to the date of salvage surgery. We found the time period from SBRT to salvage surgery ranges 17.3 (7.6–58.3) months. This result was similar to previous report(range between 10 and 17 months)(6-8). Careful follow-up is important to detect disease progression and to implement timely intervention.

Comment 3: No survival curves are presented in the manuscript. It is not sure how DFS was calculated. Usually DFS should be derived from patients having R0 resection only.

Reply 3: Thank you for raising this important point. We added figure about the Kaplan-Meier curve. DFS was calculated with patients having R0 resection only. (see Page8, Line10,Figure2)

Changes in the text: Over a median follow-up period of 30.2 months in patients who underwent salvage surgery, the five-year overall survival was 72.5%, and the five-year disease-free survival was 70.6%.

To

Over a median follow-up period of 34.8 months in patients who underwent salvage surgery, The 5-year overall survival (OS) and disease-free survival (DFS) was 72.5% and 65.2%, respectively (Figure 2A,B). The 3-year OS in patients with lobectomy and limited resection after SBRT were 84.6% and 0%, respectively (P=0.039), and the 3-year DFS

were 65.6% and 0%, respectively ($P=0.853$) (Figure 2C,D).

Reviewer C

Comment 1: The text contains a few grammatical and syntax errors influencing to some extent the meaning. i.e. P7-Line 21. I suggest to have a thorough grammatical, vocabulary and syntactical check of the manuscript before definitive submission.

Reply 1: Thank you for raising this important point. We had a native person check the manuscript.

Comment 2: Some sentences could be combined, delivering a better flowing text. i.e P2-Line 22 P3-Line 1

Reply 2: We agree with the Reviewer's comment and have modified our text as advised (see Page 3, line 3)

Changes in the text: 932 patients underwent SBRT as treatment for primary lung cancer. 48 patients (5.2%) had local recurrence alone. 19 patients (2.0%) underwent salvage surgery.

To

Of 932 patients underwent SBRT as treatment for primary lung cancer, 48 patients (5.2%) had local recurrence alone and 19 patients (2.0%) underwent salvage surgery.

Comment 3: In many occasions throughout the text, words can be replaced in order to suit better the purposes and meaning of the manuscript i.e. Page 5-Line 7 replace 'diagnosed' with found to be or deemed unsuitable, Page 6-line 4 'examined' with assessed or evaluated.

Reply 3: We agree with the Reviewer's comment and have modified our text as advised (see Page 6, line 6, Page 7, line 9)

Changes in the text: During recurrence, if the patients had no lymph node or distant metastasis, and were diagnosed to be medically operable, surgical treatment was performed with their written consent.

To

During recurrence, if the patients had no lymph node or distant metastasis, and were examined to be medically operable, surgical treatment was performed with their written consent.

Nineteen patients (2.0%) underwent salvage surgery, and none of them were examined by a thoracic surgeon before SBRT.

To

Nineteen patients (2.0%) underwent salvage surgery, and none of them were evaluated by a thoracic surgeon before SBRT.

Comment 4: The five-year overall (72.5%) and disease-free survival (70.6%) rates found in the text, at least for me, do not correlate with the tables provided.

Reply 4: Thank you for raising this important point. We added figure about the Kaplan-Meier curve. (see Page 7,line 8, Figure2)

Changes in the text: Over a median follow-up period of 30.2 months in patients who underwent salvage surgery, the five-year overall survival was 72.5%, and the five-year disease-free survival was 70.6%.

To

Over a median follow-up period of 34.8 months in patients who underwent salvage surgery, The 5-year overall survival (OS) and disease-free survival (DFS) was 72.5% and

65.2%, respectively (Figure 2A,B). The 3-year OS in patients with lobectomy and limited resection after SBRT were 84.6% and 0%, respectively ($P=0.039$), and the 3-year DFS were 65.6% and 0%, respectively ($P=0.853$) (Figure 2C,D).

Comment 5: In page 6, Line 13 and 14 we find details regarding the blood vessels and bronchi of the patients that were operated on after having SBRT. It is stated that there was 'no difference' with those who underwent 'usual' lung surgery. I believe most of thoracic surgeons can understand the meaning here, however this is a personal and subjective remark and it cannot be objectified or quantified. I would therefore suggest to re-phrase this statement.

Reply 5: We agree with the Reviewer's comment and have modified our text as advised (see Page 9, line 22)

Changes in the text: As in the present study, a few instances of adhesion have been previously reported due to the effect of SBRT, with no differences in blood vessels or bronchi compared with usual lung surgery.

To

As in the present study, a few instances of adhesion have been previously reported due to the effect of SBRT.

Comment 6: Some inconsistency in page 7, line 1, stating that 'the postoperative courses were uneventful' after writing that 4 patients developed postoperative complications.

Reply 6: We agree with the Reviewer's comment and have modified our text as advised (see Page 6, line 12, Page 8, line 9, Table3)

Changes in the text: All complications were classified into four grades of postoperative complications as per Clavien-Dindo classification criteria (10) The Clavien-Dindo scores were I or II in all 4 patients. The Clavien-Dindo scores were I or II in all 4 patients.