Peer Review File

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Reviewer A

Comment 1: Leiomyosarcoma are aggressive tumors with high rates of recurrence, they require larger margins than ductal carcinoma. Please include the margins taken in the resection of the leiomyosarcoma in the case report section.

Reply 1: We fully agree with your comments. After consulting the pathology center, we confirmed that the margin of the tumor was approximately 3 cm. The patient underwent simple mastectomy, including the nipple, areola and fascia of the pectoralis major muscle, so the range of excision was standard, reliable and safe (see line 116-119).

Changes in the text: The patient was then submitted to simple mastectomy of the right breast with approximately 3-cm margins, including the nipple, areola, breast gland and fascia of the pectoralis major muscle. Postoperative pathology showed that all margins were negative.

Comment 2: What are the suggested margins for each tumor type? I suggest that you include these details in your paper in the (Please refer to Horton et. al "Rare case of primary leiomyosarcoma of the breast treated with wide local excision and planned cosmetic breast reduction surgery" for details as to the recommendations for breast leiomyosarcoma follow up and treatment).

Reply 2: Thank you for your kind reminder. Moreover, we sincerely thank you for providing us the excellent reference [6], which helps us a lot in the revision of this manuscript and will certainly bring great help in our future work. In the revision, we added the suggested margin status for ductal carcinoma in situ, invasive breast cancer and leiomyosarcoma (see line 195-201).

Changes in the text: The main treatment of RAS is complete excision of the tumour. The National Comprehensive Cancer Network (NCCN) recommends a resection margin of 2 mm for ductal carcinoma in situ and no ink on tumours for invasive breast cancer. However, considering the recurrence pathology and the malignant characteristics of leiomyosarcoma, wider tumour margins of at least 2 cm are needed

for conservative breast treatment, and a resection margin of 3 cm is preferred.[6]

Comment 3: Radiation is a known risk factor for leiomyosarcoma development. The authors state that this is the first case of recurrent radiation associated leiomyosarcoma following ductal carcinoma. This is not the first case of radiation associated leiomyosarcoma following ductal carcinoma. A brief literature search found another example published this year entitled "Postoperative radiotherapy induced leiomyosarcoma in breast cancer: a case report and literature review" by Liu et. al. published in Breast Cancer. There are very likely other cases of radiation associated leiomyosarcoma in the literature as well. If the authors mean that the leiomyosarcoma is recurrent – and it is the first case of recurrent disease –then the question becomes were adequate tumor margins taken in the mastectomy, as residual disease due to inadequate resection is a reasonable cause for the patient disease recurrence. This needs to be addressed and discussed, as the "disease recurrence" may be a result of an inadequate resection and thereby not a unique phenomenon.

Reply 3: Thank you for your kind reminder and we have modified the manuscript to make it more sufficient and reasonable. We fully agree with your comments that this is not the first case of radiation associated leiomyosarcoma following ductal carcinoma. Fewer than 20 cases about radiation-associated leiomyosarcoma of the breast have been reported in the literature to date. In our case report, the first time the patient suffered from radiation-associated leiomyosarcoma was located at 6 o'clock direction of the right breast, approximately 2.5 cm from the nipple. The patient was then submitted to simple mastectomy of the right breast with approximately 3 cm margins, including the nipple, areola, breast gland and fascia of the pectoralis major muscle. Postoperative pathology showed all margins were negative. Therefore, adequate tumor margins were taken in the mastectomy. After 13 months of follow-up, the second time the patient suffered radiation-associated leiomyosarcoma was subcutaneously located in the right chest wall of the radiation region and axillary levels. According to the above, this is the first case report of recurrent radiation associated leiomyosarcoma following invasive ductal carcinoma (see line 104, 116-119, 122-123).

Changes in the text: 1) …and speculation at 6 o'clock direction of the right breast, approximately 2.5 cm from the nipple…

2) The patient was then submitted to simple mastectomy of the right breast with approximately 3-cm margins, including the nipple, areola, breast gland and fascia of the pectoralis major muscle. Postoperative pathology showed that all margins were negative.
3) …a painless lump was found located in the right chest wall of the radiation region and axillary levels.

Comment 4: Line 26: ill-borders should read ill-defined borders.
Reply 4: Thank you for your criticism. We have modified our text as advised (see line 26, 102-103. see *Figure 1* caption).
Changes in the text: 1) Ultrasonography revealed an oval mass, with ill-defined borders, irregular margins…
2) Ultrasonography (*Figure 1*A) found an oval, hypoechoic mass, 1.0 × 0.7 cm in size, with ill-defined borders and irregular margins
3) **Figure 1** (A) Ultrasound image showing an oval, hypoechoic mass, 1.0 × 0.7 cm in size, with ill-defined borders and irregular margins…

Comment 5: Line 27: are these power doppler findings relevant? And why?
Reply 5: Thank you for your comments. Power Doppler US showing arterial blood flow inside the tumor, suggesting that the tumor was likely to be malignant, for the richer the blood flow inside the tumor, the higher the possibility of malignancy (see line 28-29).
Changes in the text: We delete the power doppler findings in the abstract.

Comment 6: Line 42: replace was with the present tense "is".
Reply 6: Thank you for your criticism. We have modified our text as advised (see line 44).
Changes in the text: Although postoperative RT is well recognized to increase the overall survival (OS) rate of cancer patients…

Comment 7: Line 43: replace might with may.
Reply 7: Thank you for your criticism. We have modified our text as advised (see line 45).

Changes in the text: … it may also lead to secondary malignancies due to the carcinogenic effect of ionizing radiation.

Comment 8: Line 45-46: Please keep plurality. If using sarcomas the appropriate verb would be "are" not "is". Replace "malignancies" with "malignancy". Replace "after" with "following". These are a few of several examples by which this manuscript could benefit from editing for the English language writing. The manuscript holds merit, but it is not the place of this reviewer to provide type editing services at this time and it is not acceptable for publication in The Annals of Palliative Medicine in its current state.

Reply 8: Thank you for your criticism. We have invited a native English-speaking expert to check the article and made overall modifications. We have modified our text as advised (see line 48).

Changes in the text: Radiation-associated sarcomas (RAS), also known as radiation-induced sarcomas (RIS), are a rare type of secondary malignancy following RT…

Comment 9: Line 46: probably less than 1% of what?

Reply 9: We are sorry for the confusion. We explain the 'probably less than 1%' as follows: Radiation-associated sarcomas (RAS) occur in <1% of patients treated with radiotherapy (see line 48-49).

Changes in the text: Radiation-associated sarcomas (RAS), also known as radiation-induced sarcomas (RIS), are a rare type of secondary malignancy following RT, and occur in <1% of patients treated with RT.

Comment 10: Line 48: should read "… period between RT and RAS development, ranging from 3 to…"

Reply 10: Thank you for your comments. We have modified our text as advised (see line 50).

Changes in the text: There is a long period between RT and RAS development, ranging from 3 to 20.3 years.

Comment 11: Line 60: delete "were" in were proved to be. replace "so" with "as".

Reply 11: Thank you for your comments. We have modified our text as advised (see line 70).

Changes in the text: The 18 axillary lymph nodes proved to be tumour free, as were the resection margins.

Comment 12: Line 61: What margins were taken?

Reply 12: Thank you for your comments. We added the margins of the resection (see line 69).

Changes in the text: …with approximately 1-cm margins…

Comment 13: Line 61-63: this sentence is awkward – please revisit.

Reply 13: We are sorry for the confusion and we have modified the sentence. (see line 75-78).

Changes in the text: Based on the above characteristics, the patient received adjuvant chemotherapy with fluorouracil-epirubicin-cyclophosphamide followed by docetaxel (FEC-T) plus human HER2-targeted therapy with trastuzumab for one year.

Comment 14: Line 65: perhaps instead of target volume you mean target area of radiation? Please make sure this is the correct term.

Reply 14: Thank you for your kind reminder. We are sorry for the confusion. We changed "The target volume" to "The clinical target volumes (CTVs)" (see line 82).

Changes in the text: The clinical target volumes (CTVs) of the patient included…

Comment 15: Line 75-76: should read "There was no nipple dimpling" or "no nipple dimpling was present".

Reply 15: Thank you for your criticism. We have modified our text as advised (see line 99-101).

Changes in the text: There was no nipple dimpling and no palpable axillary lymph node to indicate metastasis.

Comment 16: Line 90: the size of the tumor free margins must be included here. It is very important for your paper due to the claims made about being the first recurrent radiation associated leiomyosarcoma.

Reply 16: Thank you for your kind reminder. We have modified our text as advised (see line 116-119).

Changes in the text: The patient was then submitted to simple mastectomy of the right breast with approximately 3-cm margins, including the nipple, areola, breast gland and fascia of the pectoralis major muscle. Postoperative pathology showed that all margins were negative.

Comment 17: Case report section: was any screening imaging done prior to the physical exam findings revealed the tumors? Or was physical exam the main method of post-resection cancer screening?

Reply 17: Thank you for your comments. After the breast surgery, the patient came regularly for postoperative screening. We added the postoperative follow-up rule to make the Case report section more sufficient and reasonable (see line 91-95).

Changes in the text: After breast surgery, the patient came regularly for postoperative screening. Physical examination, blood biochemistry, tumour markers, and colour ultrasound of the breast and lymph nodes were performed every 3 months. Mammography, chest computed tomography (CT), abdominal CT, bone scan and brain magnetic resonance imaging (MRI) were performed every 12 months.

Comment 18: Line 105: increases should read increased.

Reply 18: Thank you for your criticism. We have modified our text as advised (see line 152-153).

Changes in the text: With the increased use of RT…

Comment 19: Line 106-107: should read "… the incidence of RAS is increasing."

Reply 19: Thank you for your kind reminder. We have modified our text as advised (see line 152-154).

Changes in the text: With the increased use of RT and multidisciplinary therapy to improve the OS of patients with malignant tumours, the incidence of RAS is increasing.

Comment 20: Discussion section: it is mentioned often how rare the tumor type is. How rare is it? What is the incidence? How many cases have been reported in the literature?

Reply 20: Thank you for your comments. We have developed the discussion section

as advised (see line 139-150).

Changes in the text: Primary leiomyosarcoma of the breast accounts for < 0.0006% of all breast malignancies, and fewer than 80 cases have been reported in the literature to date.[6] Additionally, fewer than 20 cases of radiation-associated leiomyosarcoma of the breast have been reported in the literature to date. Here we report the first case of recurrent radiation-associated leiomyosarcoma following invasive ductal carcinoma. Radiation-associated leiomyosarcoma is a rare type of RAS that accounts for 8% of RAS patients.[2] RAS originates from mesenchymal tissue. It accounts for up to 5% of sarcomas but occurs in less than 1% of patients treated with RT.[2, 7]

Comment 21: Discussion: what are the follow up recommendations for this tumor type? Please refer to Horton et. al. above.

Reply 21: Thank you for your comments. In the revision, the follow up recommendations of this tumor type has been added (see line 237-239).

Changes in the text: It is necessary for the patient to come regularly for postoperative screening. Horton et al.[6] recommended follow-up examinations with mammogram and chest CT to be performed every 6 months in years 1-7 and annually thereafter.

Comment 22: Line 182: the patient was a he?

Reply 22: Thank you for your kind reminder. We are very sorry for the mistake and it has been corrected in the revised version (see line 262).

Changes in the text: We would like to thank the patient and her family for the consent of the publication.

Comment 23: Figure 1 caption: replace showed with showing and ill-borders with ill-defined borders. Replace flowing with flow, delete signals and replace were with was.

Reply 23: Thank you for your comments. We have modified our text as advised (see Figure 1 caption).

Changes in the text: Figure 1 (A) Ultrasound image showing an oval, hypoechoic mass, 1.0 × 0.7 cm in size, with ill-defined borders and irregular margins, and speculation at 6 o'clock direction of the right breast; (B) Power Doppler US showing rich blood flow inside the tumour, and arterial blood flow was detected.

Comment 24: Figure 2 caption: delete “the tumor with” and “particular”. Instead of binucleation and multinucleation, use binucleated and multinucleated.

Reply 24: Thank you for your comments. We have modified our text as advised (see Figure 2 caption).

Changes in the text: Histopathology revealed typical spindle cells arranged as long fascicles in a collagenous background. The tumour was well defined, well encapsulated, and composed of a pack of binucleated and multinucleated cells.

Comment 25: Please edit entire manuscript including figure caption for English language writing.

Reply 25: Thank you for your criticism. We have modified our text as advised and invited a native English-speaking expert to check the article and made overall modifications. We would like to express our sincere appreciation to you again for the valuable comments and suggestions that have significantly enhanced the quality of this paper. Thank you very much!

Reviewer B

Comment 1: This is a good paper and should be published with revisions. Radiation-induced leiomyosarcomas of the breast have been reported by: Olcina M, Merck B, Giménez-Climent MJ, et al. Radiation-induced leiomyosarcoma after breast cancer treatment and TRAM flap reconstruction. Sarcoma 2008; 2008:456950 and Yap J, Chuba PJ, Thomas R, et al. Sarcoma as a second malignancy after treatment for breast cancer. Int J Radiat Oncology Biol Phys 2002; 52:1231-7.

Reply 1: Thank you for your kind reminder. We fully agree with your comments that this is not the first case of radiation associated leiomyosarcoma following ductal carcinoma. In 2008, Olcina et al. reported a case of leiomyosarcoma in a patient who underwent mastectomy followed by radiotherapy for invasive ductal carcinoma. In 2002, Yap et al. searched SEER Cancer Incidence Public-Use Database 1973–1997 and found 82,296 breast cancer patients received radiation therapy. After radiation therapy, 2 patients within or adjacent to the radiation area developed leiomyosarcoma. Fewer than 20 cases about radiation-associated leiomyosarcoma of the breast have

been report in the literature to date. However, in our case report, the first time the patient suffered from radiation-associated leiomyosarcoma was located at 6 o'clock direction of the right breast, approximately 2.5 cm from the nipple. The patient was then submitted to simple mastectomy of the right breast with approximately 3 cm margins, including the nipple, areola, breast gland and fascia of the pectoralis major muscle. Postoperative pathology showed all margins were negative. Therefore, adequate tumor margins were taken in the mastectomy. After 13 months of follow-up, the second time the patient suffered radiation-associated leiomyosarcoma was subcutaneously located in the right chest wall of the radiation region and axillary levels. According to the above, this is the first case report of recurrent radiation associated leiomyosarcoma following invasive ductal carcinoma (see line 104, 116-119, 122-123).

Changes in the text: 1) …and speculation at 6 o'clock direction of the right breast, approximately 2.5 cm from the nipple…

2) The patient was then submitted to simple mastectomy of the right breast with approximately 3-cm margins, including the nipple, areola, breast gland and fascia of the pectoralis major muscle. Postoperative pathology showed that all margins were negative.

3) …a painless lump was found located in the right chest wall of the radiation region and axillary levels.

Reviewer C

Comment 1: Authors state that this is the first case of recurrent radiation-associated leiomyosarcoma. It appears that Kirova et al (Ref No: 4) have reported recurrence before.

Reply 1: Thank you for your kind reminder. We fully agree with your comments that this is not the first case of radiation associated leiomyosarcoma following ductal carcinoma. In 2005, Kirova et al reported 2 patients developed radiation associated leiomyosarcoma after radiotherapy for breast cancer. Fewer than 20 cases about radiation-associated leiomyosarcoma of the breast have been detailed report in the literature to date. However, in our case report, the first time the patient suffered from radiation-associated leiomyosarcoma was located at 6 o'clock direction of the right

breast, approximately 2.5 cm from the nipple. The patient was then submitted to simple mastectomy of the right breast with approximately 3 cm margins, including the nipple, areola, breast gland and fascia of the pectoralis major muscle. Postoperative pathology showed all margins were negative. Therefore, adequate tumor margins were taken in the mastectomy. After 13 months of follow-up, the second time the patient suffered radiation-associated leiomyosarcoma was subcutaneously located in the right chest wall of the radiation region and axillary levels. According to the above, this is the first case report of recurrent radiation associated leiomyosarcoma following invasive ductal carcinoma (see line 104, 116-119, 122-123).

Changes in the text: 1) …and speculation at 6 o'clock direction of the right breast, approximately 2.5 cm from the nipple…

2) The patient was then submitted to simple mastectomy of the right breast with approximately 3-cm margins, including the nipple, areola, breast gland and fascia of the pectoralis major muscle. Postoperative pathology showed that all margins were negative.

3) …a painless lump was found located in the right chest wall of the radiation region and axillary levels.

Comment 2: They concluded that "simple mastectomy seemed to be inadequate". I would encourage authors to suggest an alternate to the inadequate treatment or how the treatment of radiation-associated leiomyosarcoma could have been different in their patient.

Reply 2: Thank you for your comments. Because of the recurrence of this patient after simple mastectomy, it seems that simple mastectomy is inadequate. We suggsted the patient to undergo a second extended surgical resection (see line 210-217).

Changes in the text: Mito et al.[2] shared their experiences in preventing the local recurrence of radiation-associated breast angiosarcoma by removing the irradiated tissue as much as possible, including all or nearly all previously irradiated breast skin, with a resection field that extends from the clavicle to at least 1 cm below the inframammary crease and from midsternum to the anterior border of the latissimus dorsi muscle. After a second recurrence, the patient refused to undergo a second extended surgical resection because the radical surgical protocol was too aggressive. She insisted on continuous observation and regular follow-up.

Comment 3: Why did the patient undergo axillary dissection and not sentinel node biopsy?

Reply 3: Thank you for pointing out this important issue. In 2014, we were only able to use methylene blue staining for sentinel lymph node biopsy rather than radiotracerapproach. We don't do sentinel node biopsy very often due to the limitations of technology at that time.

Changes in the text: None

Comment 4: Do authors have capability/considered to perform sequencing to possibly identify tumor mutational burden (Ref No: 2; Mito et al)

Reply 4: Thank you for your comments. We are very sorry that our laboratory does not have the experimental equipment to perform for genetic testing to possibly identify tumor mutational burden at present.

Changes in the text: None

Comment 5: What was the original breast tumor's receptor status?

Reply 5: Thank you for your kind reminder. We added the immunohistochemistry results of the patients and endocrine therapy regimen in the revision. Figure 5 has been replaced with a modified figure in which endocrine therapy was added. Meanwhile, we modified Figure 5 to make it richer and clearer (see line 71-74, 88-90, Figure 5).

Changes in the text: 1) Immunohistochemistry demonstrated that estrogen and progesterone receptors were positive (ER+/PR+), HER2 receptor was positive (HER2 3+), and the Ki67 staining positive rates were approximately 80%. Therefore, the patient was classified as having luminal B subtype breast cancer.

2) Endocrine therapy began at the same time after chemotherapy, initially with tamoxifen for 2 years followed by conversion to letrozole untill now due to bilateral oophorectomy for increased ovarian cysts in 2017.

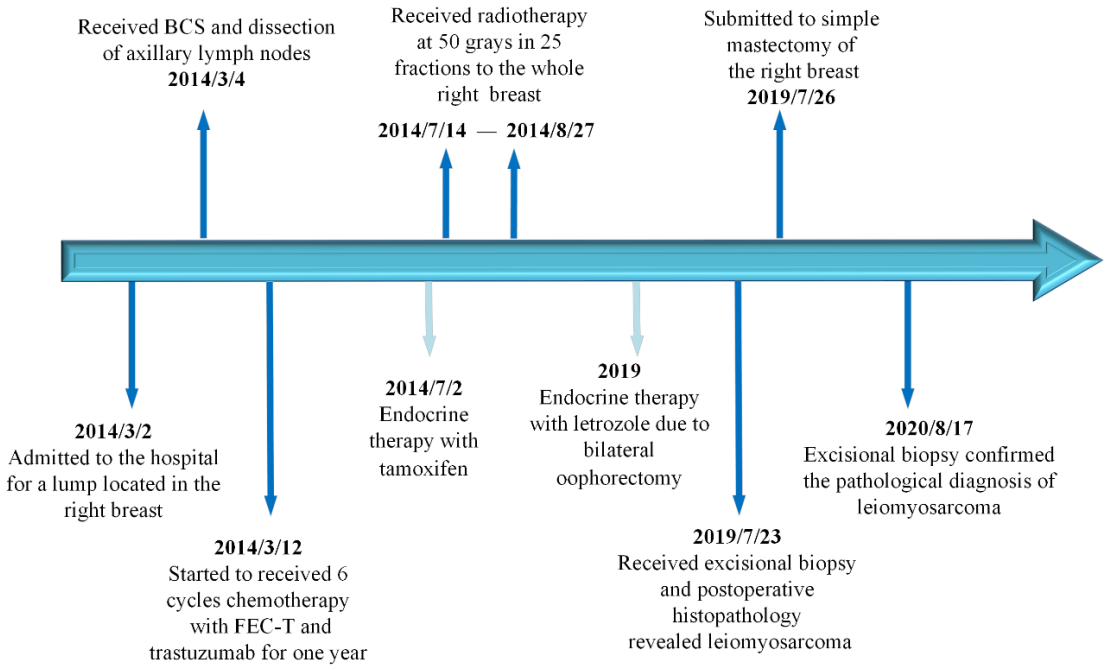

Figure 5 Timeline. The information of the patient with secondary leiomyosarcoma after breast cancer radiotherapy. FEC-T, fluorouracil-epirubicin-cyclophosphamide followed by docetaxel; BCS, breast-conserving surgery.

Reviewer D

Comment 1: In the section: case presentation, please describe the patient's familial history of cancer. Has this patient been indicated for genetic testing at the moment of the first diagnosis? I suggest viewing who patients should be indicated for genetic testing, please see it at testing criteria for high-penetrance Breast cancer in American Society of clinical Oncology, NCCN.versdion 1.2021.

Reply 1: We fully agree with your comments and have modified the case presentation section to make it more sufficient and reasonable (see line 66).

The patient's familial history of cancer has been added in the revised paper. Immunohistochemistry demonstrated that estrogen and progesterone receptors were positive (ER+/PR+), HER2 receptor was positive (HER2 3+). Therefore, the patient was classified as luminal B subtype breast cancer. NCCN guidelines do not strongly recommend genetic testing for luminal B subtype breast cancer patient with no familial history of cancer. The patient was diagnosed with breast cancer at age 45. According to NCCN.versdion 1.2021, the 45-year-old patient should be advised to undergo genetic testing. However, the patient did not undergo genetic testing for the

following reasons:

a) In 2014, NCCN guidelines (NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2014) recommended early-age-onset breast cancer patients for genetic testing. However, at that time, the early age defined as either ≤40 or ≤50 y. In China, Physicians usually define young patients as under 40 y in 2014 and even now.
b) In China, genetic testing is self-paid. The acceptance of genetic testing among Chinese patients is not high, and it is not a regular tool for patients undergo genetic testing to assess the risk of recurrence or RAS.

Changes in the text: (1) A 45-year-old female patient with no familial history of cancer underwent…

Comment 2: In the section: case presentation, I suggest viewing publication about radiotherapy-induced malignancies in the Breast Cancer patients with TP53 pathogenic gremlin varmints: Heymann S et al (2010) DOI 10.1186/1748-717X-5-104 and Petry V et al (2020) DOI 10.1007/s10689-019-00153-5.

Reply 2: We fully agree with your comments. Moreover, we sincerely thank you for providing us the excellent reference, which helps us a lot in the revision of this manuscript and will certainly bring great help in our future work.

Changes in the text: Case presentation

Comment 3: I the introduction "There is a long period between RT to RAS, ranged from 3 to 20.3 years. Please describe the difference of latency between patient with pathogenic variants of TP53, and the patients with no pathogenic variants.

Reply 3: Thank you for your comments. We have described the difference of latency between patient with pathogenic variants of TP53, and the patients with no pathogenic variants in the revision (see line 51-55).

Changes in the text: RT is the main cause of RAS, and TP53 gene mutations are another risk factor. Breast cancer patients with pathogenic variants of TP53 have shorter intervals of RAS after radiotherapy (occasionally 2–3 years) than patients with no pathogenic variants (usually approximately 9-15 years).[5]

Comment 4: In line 57, please describe details of this surgery. "breast-conserving

surgery (BCS) and dissection of axillary lymph nodes, How many lymph nodes, describe the staging, if you know the genetic testing of this patients, would you think about change the surgical approach?

Reply 4: Thank you for your comments. We have modified our text as advised. Postoperative histopathology revealed an invasive ductal carcinoma of 2.5 × 2.0 cm in size. Eighteen axillary lymph nodes dissected during the operation proved to be tumor-free. The clinic-pathological class was Stage IIA. In our institution, If I know the genetic testing of this patients, we would recommend the patient undergo total mastectomy with sentinel node biopsy + immediate breast reconstruction (see line 70-71, 74-75).

Changes in the text: The 18 axillary lymph nodes proved to be tumour free, as were the resection margins.

According to the UICC-pTNM classification, the clinicopathological class was stage IIA.

Comment 5: In line 60, please describe the immunohistochemistry of breast cancer

Reply 5: We fully agree with your comments. Thank you for your kind reminder. We added the immunohistochemistry results of the patients and endocrine therapy regimen in the revision. Figure 5 has been replaced with a modified figure in which endocrine therapy was added. Meanwhile, we modified Figure 5 to make it richer and clearer (see line 71-74, 88-90, Figure 5).

Changes in the text: 1) Immunohistochemistry demonstrated that estrogen and progesterone receptors were positive (ER+/PR+), HER2 receptor was positive (HER2 3+), and the Ki67 staining positive rates were approximately 80%. Therefore, the patient was classified as having luminal B subtype breast cancer.

2) Endocrine therapy began at the same time after chemotherapy, initially with tamoxifen for 2 years followed by conversion to letrozole untill now due to bilateral oophorectomy for increased ovarian cysts in 2017.

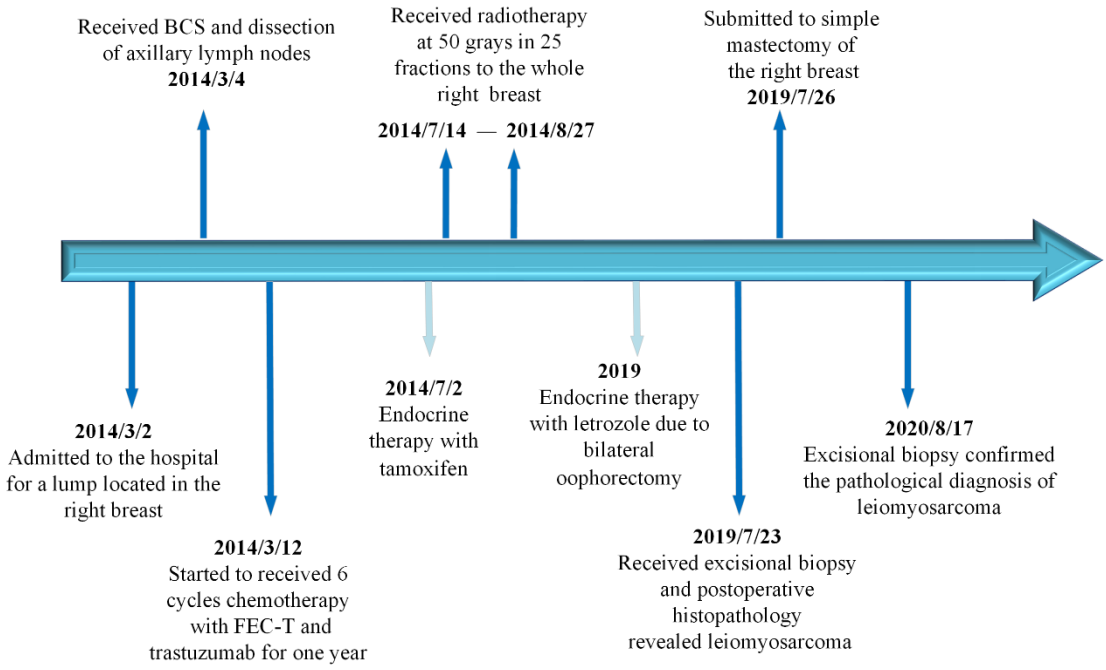

Figure 5 Timeline. The information of the patient with secondary leiomyosarcoma after breast cancer radiotherapy. FEC-T, fluorouracil-epirubicin-cyclophosphamide followed by docetaxel; BCS, breast-conserving surgery.

Comment 6: In Line 105, can you describe the incidence of RAS in patients with pathogenic germline pathogenic of TP53?

Reply 6: Thank you for your kind reminder. We have added the incidence of RAS in patients with pathogenic germline pathogenic of TP53 (see line 150-152).

Changes in the text: Radiation exposure among TP53 mutation carriers seems to increase the rate of second cancers. Studies have reported that the incidence of RAS in patients with pathogenic germline pathogenicity of TP53 is 16%-33%.[5]

Comment 7: In Line 161, " and the second RT may lead to more treatment-related toxicities, such as rib fracture, radiation pneumonia, soft tissue necrosis"and radiotherapy-induced malignancies? I think this is a very important problem for this patient, describe it.

Reply 7: Thank you for your suggestion. We described the influence of re-irradiation after radical adjuvant radiotherapy for our patient (see line 218-235).

Changes in the text: Although RT and chemotherapy are effective in select cases, their association with improved a prognosis of RAS has not been validated. In addition, breast re-irradiation may increase the toxicity for higher cumulative lifetime

doses to critical organs, such as the lungs and heart. Re-irradiation after radical adjuvant radiotherapy can be considered only for selected patients after careful informed consent. In our case report, the patient developed RAS after radical adjuvant radiotherapy, suggesting possible TP53 gene mutations. Re-irradiation not only increases radiation-related toxicities, such as rib fracture, radiation pneumonia and soft tissue necrosis, but also increases the risk of developing RAS again. In view of the patient in our case report with R0 resection and the lack of sufficient strong evidence to support the effectiveness of chemotherapy and RT for RAS patients, she received no radiation or chemotherapy after simple mastectomy in our institution.

Comment 8: In the conclusion I suggest to describe why this patient didn't acess the genetic testing, and please review the management of hereditary breast cancer: American Society of clinical Oncology, American Society of radiation, and Society of Surgical Oncology. Guideline 2020. JCO 38:2080-2106.

Reply 8: Thank you for your suggestion. We described why this patient didn't acess the genetic testing in the conclusion section (see line 248-251).

Changes in the text: Unfortunately, genetic testing was not performed because the patient’s tumour molecular type was luminal B, the patient had no familial history of cancer, the patient was 45 years old at the time of the initial diagnosis, and there were high self-paid expenses.