Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: Thank you for contributing to the body of literature on Phyllodes Tumors (PTs). As a rare disease, it is exceptionally challenging to make clinical decisions and the more we study and publish, the more we learn as a group.

Regarding your study, there are a few concerns. It is an exceptionally small sample size. With 14 patients, and them being heterogeneous (about 1/3 from each of benign, borderline and malignant) it is really hard to draw any conclusions regarding the use of radiation. I would also advocate that most modern data suggest that even with positive margins, radiation should not be used on benign PT and including them in this study, while increasing the size, decreases the value of the results. Does the group have an understanding or comparison of PTs treated at the center who did not receive adjuvant RT and their outcomes?

Reply 1: Thank you very much for your comments. We are in complete agreement regarding the distinct variations in behavior and risk exhibited by different variants of phyllodes tumors, and we acknowledge the ongoing debate surrounding the consideration of adjuvant radiotherapy for benign phyllodes tumors. Several authors do not advocate for adjuvant irradiation in such cases.

In our clinical practice, we consider phyllodes tumors more alike soft tissue sarcomas of the breast than breast adenocarcinomas. Similar to the former, we firmly believe that the presence of involved margins increases the risk of local recurrence, justifying the use of adjuvant radiotherapy. Nevertheless, we are fully aware that this approach is a subject of intense debate, and we recognize that the ideal course of action, as rightly pointed out by the reviewer, would involve a comparative analysis against benign phyllodes tumors treated exclusively with surgery. Unfortunately, we have been unable to carry out this analysis with patients from our institution as the multidisciplinary committee has consistently considered affected margins as an indication for adjuvant radiotherapy. However, we find great value in pursuing such an analysis, even if conducted on patients treated at another institution. This avenue of research holds significant promise for future investigations and deserves careful consideration.

Comment 2: Additionally, while the median follow up was long, there were patients included with only 3 months follow-up, which seems inadequate for locoregional or

distant recurrence.

Reply 2: Thank you for your suggestion. We agree with the acknowledgment of the limitations posed by the short follow-up period and the challenges in obtaining consistent data on tumor control and survival at 3 months. However, we firmly believe that in the case of these patients, an analysis of the acute tolerance to treatment can be conducted, which serves to bolster the safety of its utilization when deemed appropriate.

Comment 3: One of the interesting parts of the paper is the higher dose of radiation employed- and this may be one novel feature. Depending on the treatment centre, sarcoma radiation oncology expertise may or may not be available, and traditional breast dosing may be used frequently. Presenting this more as a safety paper of higher dose radiation may be an angle that is more valuable in presenting as the oncologic outcomes are hard to interpret

Reply 3: Thanks a lot for your wise recommendation. We find this perspective to be truly original and have made the decision to accept it. Consequently, we have made modifications to both the manuscript's content and its title, placing a prominent focus on the (moderate) dose escalation approach we employ in the radiotherapy of the PTs included in our series.

The title and paragraph would look like this:

"REAL-WORLD EFFICACY OF POSTOPERATIVE RADIOTHERAPY WITH A MODERATE DOSE-ESCALATION FOR PHYLLODES TUMORS OF THE BREAST."

"The standard radiation treatment schedules for breast cancer involve the use of conventional fractionation at 1.8-2 Gy, reaching a total dose of 50.4-50 Gy in 28-25 fractions, or moderate hypofractionation with 15 fractions of 2.7 Gy, resulting in a total dose of 40.5 Gy. The linear-quadratic (L-Q) formalism allows for different radiotherapy regimens comparison by calculating the Biologically Effective Dose (BED = $n \times d \times [1 + d (\alpha / \beta]$), where n is the number of fractions, d is the fraction size of the applied regimen, and α/β is the ratio of radiation fractionation sensitivity (which has been assumed to be equal to 4 Gy for soft-tissue sarcomas and for phyllodes tumors (11)). Corresponding BED values would be e of 73.1-75 Gy and 67.8 Gy for the conventional and moderate hypofractionated schedules used for breast cancer, respectively. The patients with PTs attended in our institution underwent whole breast/chest wall irradiation with different schedules at physician discretion but always trying to reach a BED value above 90 Gy, representing a slight increase over the dose usually used in the postoperative setting for breast cancer and is closer to the dose used for soft tissue sarcomas. Regional lymph nodes were not irradiated in any of the included patients."

Reviewer B

Comment 1: It's a well-written review of the different types of phyllodes tumors and their management. Unfortunately, more robust data with a much larger number has already been published and I don't feel any new data or recommendations are gleaned from your data. Moreover, the patient characteristics of who received radiation and why weren't really discussed.

Reply 1: Thank you for your valuable feedback. We fully acknowledge the limitations of our series, stemming from the small number of patients and the relatively short follow-up period, particularly when compared to published studies featuring larger cohorts and longer observation periods. Nevertheless, we firmly believe that even small series can hold significance, particularly in the context of low-prevalence pathologies like phyllodes tumors of the breast. Such studies can still make valuable contributions to advancing our understanding of this condition, while also highlighting the feasibility and tolerability of a moderate dose escalation approach. While we recognize the importance of larger and longer-term studies, we trust that our findings can add valuable insights to the existing knowledge base regarding this disease.

Reviewer C

Comment 1: What about indication for radiotherapy?

Reply 1: Thank you for your pertinent question. As we describe in then Material and Methods section, we included borderline and malignant PTs, but also some benign tumors with close/affected surgical margins not amenable for re-excision albeit we acknowledge the ongoing debate surrounding the consideration of adjuvant radiotherapy for benign phyllodes tumors, and that some authors do not advocate for adjuvant irradiation in such cases. However, in our clinical practice, we consider phyllodes tumors more alike soft tissue sarcomas of the breast than breast adenocarcinomas. Similar to the former, we firmly believe that the presence of involved margins increases the risk of local recurrence, justifying the use of adjuvant radiotherapy.

Comment 2: Define correlation patient factors including BMI and age with acute/late toxicity.

Reply 2: Thank you for your recommendation. We include age in pergformed analysis. Unfortunately, data of height and weight were not available for most of patients and correlation with BMI could not be analyzed.

Comment 3: There are many manuscripts that margin width is not related with local recurrence of PTs. Wider margin you mentioned in this manuscript should be revised with appropriate reference.

Reply 3: We agree with your comment that this is a debatable issue. As we mention in the manuscript, several risk factors can contribute to the occurrence of local recurrence after surgery, including the presence of high number of mitoses as well as the presence of infiltrative margins, stromal cellularity with atypia and overgrowth, or presence tumor necrosis. These factors have been identified by different authors as related to recurrence risk (Chaney AW, et al.; Lu Y, et al., Yogi V et al.)

Comment 4: Follow up period should exceed at least 12 months.
Reply 4: We fully agree with your suggestion, mainly regarding local and distant control. The median follow-up in our series is 48 months and only 1 patient has a follow-up of less than 12 months. However, we are also convinced that the sometimes shorter follow-up could be useful for the tolerance analysis

Comment 5: There are several spacing errors in your manuscript.
Reply 5: Thank you for your comment. Typos have been corrected throughout the manuscript.