Author’s response to reviews

Title: Breast Magnetic Resonance Imaging for Surveillance of Women with a Personal History of Breast Cancer: Outcomes stratified by interval between definitive surgery and surveillance MR imaging

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Author’s response to reviews:

Responses to Reviewer’s Comments

Editor Comments:

Thank you for the submission. Some additional clarification and revision is needed prior to making a final decision on publication. I think reviewer #2 comments are most pertinent. More information is needed about regarding to what affect supplemental screening with breast US altered the results of the study, especially as that is not a typical regimen. How many cancers were detected and removed from the pool by screening US in patients with negative or benign mammography? I also agree that some statistical measures beyond what is currently reported are required to support the conclusion. Please address reviewer #2’s concerns in your revision. Reviewer #1’s comments are more stylistic and likely do not all require individual point by point responses aside from the questions regarding methods.

: Response – Thank you for your comment. We acknowledge that our study population has undergone routine supplemental surveillance with US, and this would have affected the outcome measures of surveillance breast MRI. As this is a retrospective study, we were unable to control for the actual intervals between imaging examinations. The routine surveillance protocol at our institution during the study period was surveillance breast US every 6 months and annual mammography for 5 years, and the median interval between prior surveillance US and MR examinations was 6.1 months. Although we were not able to provide information on how many
cancers were removed from the pool by screening US, we have looked through the excluded 55 cases that underwent MR imaging for contralateral breast cancer/recurrence. We found that 21 (38.2%) first presented with symptoms (palpability, bloody nipple discharge, pain) and 34 (61.8%) were detected at surveillance imaging. Among the 34 examinations, 11 (32.4%) were detected on mammography and 23 (67.6%) were detected on US with negative mammograms. To accurately determine the effect of supplemental breast US on the performance of surveillance breast MRI, a prospective study would be required. In the revised manuscript, we have included additional information regarding supplemental surveillance US and have addressed the comments from reviewer #2. In addition, we have performed additional statistical analysis to compare outcome measures between patients stratified by intervals between definitive surgery and implementation of MRI surveillance (MR examinations performed ≤ 36-month interval vs. > 36-month interval following initial surgery).

The comments of the reviewers were insightful and helped us improve our manuscript. We tried to respond to every issue raised and revised the manuscript accordingly. We hope that our changes are satisfactory and that our paper will be considered for publication in BMC Cancer.

Reviewer #1:

Jaclynn Powell, M.D. (Reviewer 1): TITLE: Consider rephrasing "...Results according to different intervals after treatment" to "...Outcomes stratified by interval between definitive surgery and surveillance initiation"

: Response – Thank you for your helpful suggestion. In our revised manuscript, we have changed the title to “Breast Magnetic Resonance Imaging for Surveillance of Women with a Personal History of Breast Cancer: Outcomes stratified by interval between definitive surgery and surveillance MR imaging”.

ABSTRACT:

Background: 1st sentence: Consider deleting the words "an" and "experiencing" and change "would benefit" to "may benefit". Last sentence: consider deleting "consecutive".

: Response – Thank you for your helpful comment. We have revised the corresponding sentence in the Abstract accordingly.
Background: Women with a personal history of breast cancer are at increased risk of future breast cancer events, and may benefit from supplemental screening methods that could enhance early detection of subclinical disease.

We investigated outcomes of surveillance breast magnetic resonance (MR) imaging in women with a personal history of breast cancer.

Methods: 3rd sentence: Delete "CDR and abnormal interpretation rate" (redundant from preceding sentence). Last sentence: consider rephrasing "...statistics were also assessed according to interval..." to "...statistics were stratified by interval..."

Results: For clarity, consider rephrasing "breast lesions" to "intramammary lesions" and contrast this by stating that the "overall abnormal interpretation rate" and "overall CDR" include both intramammary and extramammary lesions.
“We also calculated the PPV1, PPV3, sensitivity and specificity for MR-detected intramammary lesions”, Abstract Page 1 Line 12-13/

“Results: The CDR for MR-detected cancers was 6.7 per 1000 examinations (7 of 1053) and was 3.8 per 1000 examinations (4 of 1053) for intramammary cancers. The overall abnormal interpretation rate was 8.0%, and the abnormal interpretation rate for intramammary lesions was 7.2%. The PPV1, PPV3, sensitivity and specificity for intramammary lesions was 5.3% (4 of 76), 15.8% (3 of 19), 75.0% (3 of 4) and 98.3% (1,031 of 1,049), respectively”, Abstract Page 1 Line 15-19/

“The overall cancer detection rate for MRI was defined as the total number of intramammary and extramammary cancers detected at MR imaging per 1000 examinations. The overall abnormal interpretation rate for MRI was defined as the percentage of MR examinations that were given BI-RADS categories 0, 3, 4, 5 or those with findings suspicious for extramammary cancer detected at MR imaging”, Methods Statistical Analysis section Page 7 Line 4-7/

“We also calculated outcome measures for MR-detected intramammary lesions. The cancer detection rate for intramammary lesions was defined as the total number of intramammary cancers detected at MR imaging per 1000 examinations. The abnormal interpretation rate for intramammary lesions was defined as the percentage of MR examinations that were given BI-RADS categories 0, 3, 4, or 5.”, Methods Statistical Analysis section Page 7 Line 11-15/

“The overall abnormal interpretation rate for MRI was 8.0% (84 of 1,053) and biopsy…”,

Results section Page 8 Line 23/

“Therefore, the overall cancer detection rate for MRI was 6.7 per 1000 examinations (7 of 1,053)”, Results section Page 9 Line 21-22/

“Cancer Detection Yield for Intramammary Lesions

The abnormal interpretation rate for intramammary lesions was 7.2% (76 of 1053) and the cancer detection rate for intramammary lesions was 3.8 per 1000 examinations (4 of 1053)”, Results section Page 9 Line 24-Page 10 Line 2/
“In addition, the PPV3 in our study for intramammary lesions, 15.8% (3 of 19), was higher than…”, Discussion section Page 12 Line 8-9/

Expressions in Table 2, Table 3, Table 4 Page 22 were also rephrased)

BACKGROUND:

1ST paragraph: 1st sentence: consider deleting "experiencing"

: Response – Thank you for your comment. We have deleted the word “experiencing” from the corresponding sentence.

(Amended Text:

“Although women previously treated for breast cancer are at a statistically significant increased risk of future breast cancer events..”, Background section Page3 Line 1-2)

2nd paragraph: 1st sentence: consider deleting "In contrast". 2nd sentence: consider deleting "generally". Last sentence: consider rephrasing to "Due to sparse data on surveillance breast MR imaging…"

: Response – Thank you for your comment. We have rephrased the corresponding sentences accordingly.

(Amended Text:

“There has been limited information on breast magnetic resonance (MR) imaging surveillance in this specific patient population. Previous screening trials using MR imaging have focused on high-risk women without a personal history of breast….”, Background section Page 3 Line 7-19

“However, due to sparse data on surveillance breast MR imaging, the appropriate interval following surgery for initiation of MRI surveillance has not yet been investigated”, Background section Page 3 Line 20-22
3rd paragraph: 2nd sentence: consider rephrasing to "…from a large group of patients regarding its performance stratified by interval between definitive surgery and implementation of MRI surveillance".

: Response – Thank you for your comment. We have rephrased the corresponding sentence.

(Amended Text:

“…we were able to obtain data from a large group of patients regarding its performance stratified by interval between definitive surgery and implementation of MRI surveillance”, Background section Page 4 Line 1-4)

Last sentence: Delete "Therefore"

: Response – Thank you for your comment. We have deleted the word “therefore” from the last sentence, as suggested.

(Amended Text:

“The purpose of this study…”, Page 4 Line 3)

METHODS

Study population:

Need to explain why 232 MRs performed during the specified period weren't included in analysis (1053 included, out of 1285), as in Figure 1. Could say something like "MRs performed for reasons other than surveillance were excluded from analysis"

: Response – Thank you for your comment. Originally, we did not describe the reasons for exclusion in the initial manuscript as they were specified in Figure 1. In the revised manuscript, we have included a short explanation to avoid confusion.
“Among them, 222 women were excluded either because they underwent MR imaging for reasons other than postoperative surveillance (n=70); they had BRCA genetic mutations (n=20); they had undergone screening breast MR imaging prior to the study period (n=4); or their 12-month imaging follow-up information was unavailable (n=128) (Figure 1).”

Post-treatment surveillance:

1st sentence: change to "After definitive breast cancer surgery…” (to distinguish from excisional biopsy)

Since MR was added to the surveillance protocol in 2013, in what year was the original surveillance protocol started?

Response – Thank you for your comment. Although we are not aware of the specific date, the original surveillance protocol in our institution has been implemented for at least 10 years.
Therefore, all of the patients in our study underwent the same surveillance protocol prior to MR imaging.

MR Imaging technique:

2nd sentence: probably meant "…axial T1-weighted non-fat-suppressed AND fat-suppressed", rather than "or". Last sentence: Bilateral exams were performed for all patients EXCEPT mastectomy patients.

: Response – Thank you for your comment. In our study, MR imaging was performed using two 3-Teslar MR Scanners. With one scanner (Discover 750, GE Medical Systems), axial T1-weighted non-fat-suppressed images were obtained before contrast administration. With the other scanner (Ingenia, Philips Medical Systems), axial T1-weighted fat-suppressed images were obtained. In addition, at our institution bilateral exams are performed for all patients, including mastectomy patients.

MR Imaging Evaluation:

2nd sentence: Delete "routinely" (unless not used universally).

: Response – Thank you for your comment. We have revised the manuscript as suggested.

(Amended text:

“Computer aided evaluation software (CADstream, Confirma, Kirkland, WA) was used.,” Page 6 Line 7-8)

Statistical Analysis:

Delete the word "recurrence" from Ipsilateral breast tumor and Locoregional disease. Ipsilateral disease or locoregional disease could reflect residual/recurrent disease, but could also reflect metachronous cancer.

: Response – Thank you for your comment. In our revised manuscript, we have deleted the word “recurrence” and have changed this to “cancer” or “malignancy” throughout the manuscript. In addition, to avoid confusion, we have removed the terms “ipsilateral breast tumor recurrence” or
“locoregional recurrence” and instead, have defined “intramammary cancer” and “extramammary cancer”, which seem to be more relevant with our results.

(Amended text:

“Intramammary cancer was defined as cancer in the ipsilateral breast following BCS or cancer in the contralateral breast. Extramammary cancer was defined as locoregional disease (cancer in the ipsilateral axilla, internal mammary or supraclavicular lymph nodes or in the mastectomy bed) and distant metastasis.”, Page 6 Line 23-Page 7 Line 1)

Paragraph 2, sentence 1: add "biopsy-proven cancers", and delete the word "correctly" (redundant)

: Response – Thank you for your comment. As suggested, we have deleted the word “correctly” from the corresponding sentence. Among distant metastasis cases, one patient was diagnosed with sternum metastasis based on imaging alone, which was initially detected on breast MRI and subsequently confirmed by whole body bone scan and PET-CT. Therefore, we did not add “biopsy-proven cancers” to the sentence, as this single case did not undergo biopsy.

(Amended text:

“The overall cancer detection rate for MRI was defined as the total number of intramammary and extramammary cancers detected at MR imaging per 1000 examinations.”, Statistical Analysis section Page 7 Line 2-4)

Paragraph 3:

1st sentence: delete "cancer detection rate, abnormal interpretation rate" (redundant from 1st sentence of preceding paragraph), change "breast lesions" to "intramammary lesions" (for clarity and to distinguish from extramammary lesions), 2nd sentence: delete "correctly"

3rd sentence: delete sentence (repeated from 2nd sentence of preceding paragraph) Last sentence: Consider rephrasing "calculated" to "stratified"
Response – Thank you for your comment. We have revised the corresponding paragraph as you have suggested. However in our revised manuscript, we did not delete the 3rd sentence. As the outcome measures described in the 3rd paragraph are for intramammary lesions, the definition for the abnormal interpretation rate slightly differs from the 2nd paragraph, and we felt that a detailed description could prevent possible confusion.

(Amended text:
“We also calculated outcome measures for MR-detected intramammary lesions. The cancer detection rate for intramammary lesions was defined as the total number of intramammary cancers detected at MR imaging per 1000 examinations. The abnormal interpretation rate for intramammary lesions was defined as the percentage of MR examinations that were given BI-RADS categories 0, 3, 4, or 5”, Statistical Analysis section Page 7 Line 11-15)

RESULTS:

1ST paragraph, last sentence: again, would remove the word "recurrence" and replace with "malignancy" to include both recurrent and metachronous disease.

: Response – Thank you for your comment. We have revised the corresponding sentence as you have suggested.

Cancer Detection Yield For MRI:

1st paragraph, 1st sentence: could rephrase "…with lesions that were BI-RADS category 4…” as "with 21 of the 29 exams classified as BI-RADS category 4 and the other 8 exams demonstrating extramammary lesions suspicious for malignancy (Table 2).

: Response – Thank you for your comment. We have rephrased the 1st sentence accordingly.

(Amended text:
“…with 21 of the 29 exams classified as BI-RADS category 4 and the other 8 exams demonstrating extramammary lesions suspicious for malignancy (Table 2)”, Page 8 Line 24-Page 9 Line 1)
2nd paragraph, 1st sentence: change "…and further imaging" to "…OR further imaging"

: Response – Thank you for your comment. We have changed the corresponding sentence accordingly.

(Amended text:
“…considered negative based on image-guided biopsy (n=3) or further imaging evaluation”, Page 9 Line 15)

Cancer Detection Yield For Breast Lesions:
1st sentence: change "…for breast lesions…" to "…for breast MRIs…", and change "breast lesions" to "intramammary lesions"

: Response – Thank you for your comment. We agree that “..for breast MRI” sounds more natural. However in this paragraph, we would like to emphasize that the abnormal interpretation rate was based only on intramammary lesions. Therefore, we have changed the “breast lesions” to “MR-detected intramammary lesions”. If needed, we are willing to accept any better suggestions in the next revision.

(Amended text:
“The abnormal interpretation rate for MR-detected intramammary lesions was 7.2% (76 of 1053) and the cancer detection rate for intramammary lesions was…”, Page 9 Line 25-Page 10 Line 1)

DISCUSSION:
1st paragraph, sentence 4: Consider rephrasing "had previously underwent" to "had previously undergone"

: Response – Thank you for your comment. We have revised the corresponding sentence accordingly.
“.. had previously undergone preoperative breast MR imaging, whereas only 38.9%...”, Page 11 Line 4)

2nd paragraph:

1st sentence: Consider rephrasing to "...was GREATER than that for examinations performed within 3 years (1.41 per 1000) provides a basis for establishing guidelines regarding timing of surveillance MR imaging initiation following definitive breast cancer surgery."

: Response – Thank you for your comment. We have revised the corresponding sentence accordingly.

(The amended text:

“The fact that the cancer detection rate for MR imaging performed at more than 3 years after surgery (17.4 per 1000) was greater than that for examinations performed within 3 years (1.41 per 1000) may provide a basis for establishing guidelines regarding timing of surveillance MR imaging initiation following definitive breast cancer surgery”, Discussion section Page 11 Line 13-16)

2nd sentence: rephrase "...similar with the incidence screening cancer detection rate..." to "similar to the cancer detection rate of screening breast MRIs in average risk women in a recent study (7.5 per 1000 examinations, 13 of 1,741) [23]."

: Response – Thank you for your comment. We have revised the corresponding sentence.

(The amended text:

“Our overall cancer detection rate was similar to the incidence cancer detection rate of screening breast MR imaging in average risk women in a recent study (7.5 per 1000 examinations, 13 of 1,741) [24]”, Discussion section Page 11 Line 16-19)

3rd sentence: Add comma after "therapy"

: Response – Thank you for your comment. We have revised the corresponding sentence.
“In another study on women with a history of breast conservation therapy, of whom 91.8%..”

4th sentence: consider rephrasing "…with no incidence screening diagnosis of breast cancer made until almost 3 years after a negative MR imaging study" to " with no screen-detected breast cancer diagnoses made within 24 months after a negative MR study [23]."

: Response – Thank you for your comment. We have revised the corresponding sentence as shown below.

“… no screening-detected breast cancer diagnoses made until almost 3 years after a negative MR study [24]”, Discussion section Page 11 Line 24-25)

3rd paragraph: change each instance of "ranges" to "ranged". Change "breast lesions" to "intramammary lesions". Need a space after sentence 4

: Response – Thank you for your comment. We have revised the corresponding paragraph as suggested.

“…which ranged from 10.7 % to 19.3% [15, 20, 22, 25]”, Discussion section Page 12 Line 5/

“..which ranged from 9.4% to 52.6% [27-30]”, Discussion section Page 12 Line 10-11/

“..[27-30]. Furthermore, surveillance MR imaging…”, Discussion section Page 12 Line 13)

4th paragraph:

2nd sentence: change "interval" to "intervals"

3rd sentence: delete the last word "itself"
Last sentence: Would be nice to give median intervals of other studies for comparison, since it is stated that the interval in this study was "relatively short". Also, what are the potential implications of this fact for the study?

Response – Thank you for your comment. We have revised the 2nd and 3rd sentence, as suggested. In addition, we have re-reviewed prior studies on surveillance MR imaging in patients with a personal history of breast cancer, and have found that our median interval is not particularly short when compared with prior studies that present this information. The intervals in previous studies are as follows: median of 15 months (range, 12-61 months) for Gweon et al. [1] and mean interval 17.8 months (range, 6-41 months) for Cho et al. [2], although the latter is the mean time from the initial surgery to the detection of a second breast cancer. Although the median intervals were not clearly presented, a prior study did mention that 21% of the second cancer diagnoses occurred after 10 years of initial diagnosis [3]. In our revised manuscript, we have deleted the phrase “compared with prior studies” from the last sentence.

(Amended text:
“…therefore, the intervals between surgery and MR imaging were variable”, Discussion section Page 12 Line 21-22/

“…which could have affected the true cancer yield of MRI”, Discussion section Page 12 Line 23-24)/

“Third, the median interval between initial breast cancer surgery and first-time surveillance MR examination (30.1 months, range, 12.1–240.2 months) was relatively short”, Discussion section Page 12 Line 24-25)
Reference)


CONCLUSIONS

What additional studies would be helpful to confirm your findings? (prospective study, multicenter study, standardized intervals of surveillance after surgery? Etc)

: Response – Thank you for your comment. Indeed, a prospective study with standardized intervals of MRI surveillance after surgery, more favorably a multicenter study, would be helpful to confirm our findings. However, as data stratified by different intervals of surveillance breast MRI initiation is sparse, retrospective studies from other institutions with a large number of patients would also aid in providing basis for the appropriate timing of surveillance breast MRI implementation. We have included the following sentence to the Conclusions section.

(Amended text”

“Further research on the appropriate timing for surveillance breast MR imaging initiation is required, especially in patients who have undergone preoperative breast MR imaging and supplemental surveillance US”, Page 13 Line 6-8)
Reviewer #2:

1. The overall discussion and conclusions of the paper are clouded by the fact that routine ultrasound screening was performed in conjunction with mammography. While you mention this as a limitation at the end of the paper, I believe that it should be stated more explicitly in the introduction. Essentially you are assessing MR surveillance in a group of women who already receive supplemental surveillance with ultrasound. This presumably affects your cancer detection rate, abnormal interpretation rate etc. of supplemental MR. I think a more full disclosure of this in the introduction (and abstract) is warranted, and interpretation of the results with this in mind should be discussed. Rather than waiting to the limitations section of the report to discuss this item. This also makes your comparison with results from other studies murky, did these other studies also have supplemental US surveillance? Additionally, you mention every 6 month US surveillance for 5 years? Does this play into your results regarding different time intervals (ie if patients's are getting US every 6 months, MR may be superfluous, and MR may become more useful when patients switch to yearly screening?). Again all of these issues with the supplemental US screening need to be addressed up front, and throughout the paper. Therefore your conclusions apply to patients who are already screened with Mammo+ultrasound, and discussion of how this extrapolates to the patient population only screening with Mammo is also warranted.

: Response – Thank you for your thoughtful comment. We acknowledge that our study population has undergone supplemental surveillance with ultrasound, and this would have affected the outcome measures of surveillance breast MRI. The routine surveillance protocol at our institution during the study period was surveillance breast US every 6 months and annual mammography for 5 years, and the routine protocol was not changed during the study period. Therefore, it is unlikely that this would have affected our results regarding different time intervals. Following the inclusion of surveillance breast MRI in our routine post-treatment surveillance protocol, the routine protocol was changed to perform breast MRI instead of surveillance US at approximately two and five years after surgery. Therefore, the majority of patients did not receive concurrent surveillance MRI and US.

When comparing the intervals between MR imaging and last prior US, we found that patients with an initial surgery-MRI interval ≤ 36 months had a slightly longer mean US-MRI interval (6.3 months vs. 5.9 months, p < 0.001). However, with a 0.4 month difference, this would not be clinically significant. As this is a retrospective study, we were unable to control for the actual intervals between imaging examinations, which would vary according to patient compliance and the referring physician. We agree that a more detailed description and discussion on the fact that supplemental screening US was routinely performed should be included, and have revised the manuscript.
Regarding the question on whether previous studies also had supplemental US, one retrospective study on surveillance breast MR imaging also included patients who had previously undergone supplemental US surveillance [1]. In two other recent prospective studies which performed breast MRI either within 1 year or between approximately 1-3 years after surgery, US was performed simultaneously with breast MRI [2-3]. Several other retrospective studies do not state whether supplemental US was performed, although these are from a Western population and its routine application is unlikely [4-6]. In our revised manuscript, we have discussed more on this aspect in the discussion section and have provided information on the intervals between previous surveillance mammography with US and MR examinations.

(Amended text:

“All patients had previously received supplemental surveillance with ultrasound”, Abstract, Page 1 Line 9-10/

“Previous studies have reported that breast MR imaging depicted additional cancers even after prior or concurrent negative findings of mammography and ultrasound (US)”, Introduction section Page 3 Line 18-20/

“..These patients had previously undergone routine supplemental surveillance with US”, Introduction section Page 3 Line 25-Page 4 Line 1/

“The median interval between prior surveillance US and MR examinations was 6.1 months (range, 0–13.9 months). In 19 cases (1.8%), surveillance US and MR imaging were performed on the same day at the request of the referring physician. The median interval between prior mammography and MR examinations was 11.5 months (range, 0–65.1 months)”, Methods Post-treatment Surveillance section, Page 5 Line 9-12/

“All of the four MR-detected intramammary cancers were not detected on prior surveillance US which was performed at a median interval of 5.5 months (range, 4.6–12.4 months)”, Results Section Page 9 Line 11-13/
“The mean interval between prior US and MR examinations was slightly greater in MR examinations performed \( \leq 36 \) months than those performed \( > 36 \) months following initial surgery (6.3±1.0 months vs. 5.9 months±1.6 months, \( p < 0.001 \)), but with a mean difference of 0.4 months”, Results section Page 11 Line 14-17)

“In addition, our study population had received routine supplemental surveillance US, with a median interval of 6.1 months between prior surveillance US and MR imaging. All of the four MR-detected intramammary cancers in our study were not detected by previous surveillance US performed prior to MR imaging. Therefore, the MR-detected cancers in our study are more likely to represent truly newly developed cancers after treatment of initial breast cancer, which may be difficult to detect with surveillance US”, Discussion section Page 11 Line 6-12)

“In another study on women with a history of breast conservation therapy, of whom 91.8% underwent preoperative MR imaging and all had undergone supplemental surveillance US…”, Discussion section Page 11 Line 19-21)

“Further research on the appropriate timing for surveillance breast MR imaging initiation is required, especially in patients who have undergone preoperative breast MR imaging and supplemental surveillance US”, Discussion Conclusions section Page 13 Line 6-8)

Reference)


2. I find figure 1 confusing, and not adequately explained in the text. Please explicitly describe selection process in Methods, which may make figure 1 superfluous.

: Response – Thank you for your comment. In the revised manuscript, we have included a short description for the reasons why patients were excluded, according to the suggestions of Reviewer #1.

(Amended text:

“Among them, 222 women were excluded either because they underwent MR imaging for reasons other than postoperative surveillance (n=70); they had BRCA genetic mutations (n=20); they had undergone screening breast MR imaging prior to the study period (n=4); or their 12-month imaging follow-up information was unavailable (n=128) (Figure 1)”, Methods section Page 4 Line 12-15)

3. Why was the time point of 36 months used as a cutoff to define your "time intervals?" Perhaps an explanation in the text regarding this decision is appropriate. Also, are there any statistics performed to support that the difference in numbers (difference in cancer detection rate...) for the
two groups are statistically significant, and appropriately powered? (The absolute numbers seem relatively small....)

: Response – Thank you for your comment. As mentioned in the Discussion section, a previous study has reported that more than a 24-month interval between initial surgery and MR imaging was an independent factor associated with MR-detected cancers [1], and another study has mentioned that second breast cancer events were observed within two years in only 14.0% of women with events [2]. A more recent study on average-risk women has also reported that the first screening-diagnosis of breast cancer was not made until almost 3 years later after a negative MR imaging screening study [3]. Based on these studies, we thought that a difference in cancer detection rate may be observed by stratifying patients using 2-3 years as a cut-off. Another more practical reason for this cut-off is that at our institution, breast MR imaging is performed at approximately two and five years after surgery as part of the routine post-treatment surveillance protocol. Therefore, patients will likely receive MR imaging between 2-3 years following surgery. The decision for our surveillance protocol was also influenced by the national health insurance policy in our country, which provides capacious coverage for cancer patients during the first five years following diagnosis. Because our post-treatment surveillance protocol is described in the Methods section and the results of other studies are mentioned in the discussion section, we did not add an additional explanation in the revised manuscript. If considered necessary, we are willing to do so in the next revision.

As you have suggested, we have performed additional statistical analysis to compare outcome measures between patients with an initial surgery-MR interval ≤ 36 months vs. > 36 months.

(Amended text:

“Performance statistics were compared between the two groups using the Fisher exact test. We also compared the intervals between prior surveillance US and MR examinations by using the Student t test. Statistical analyses were performed by using statistical software (SPSS version 23.0; IBM Corp, Armonk, NY.)”, Methods Statistical Analysis section Page 8 Line 6-9)

“The overall cancer detection rate for MRI was significantly greater in MR examinations performed with more than a 36-month interval following initial surgery than those performed at or less than a 36-month interval (17.4 per 1000 examinations vs. 1.4 per 1000 examinations, p = 0.006). None of the other performance statistics showed a significant difference between the two groups (Table 2)”, Results section Page 10 Line 9-13)