Manuscript ID: 72848

Revised Title:

Is there a Utility of 18F-FDG PET Scan before Surgery in Breast Cancer? A 15-Year Overall Survival Analysis.

Response to Reviewers.

Dear Editor,

We are most grateful for the opportunity to revise the manuscript. We are indebted to Reviewers for the time dedicated to improving its quality. Point-by-point response are provided below. We hope that all issues are addressed adequately.

Yours sincerely,

Vincent Vinh-Hung, on behalf co-authors.

Reviewer #1:

Scientific Quality: Grade D (Fair) **Language Quality:** Grade B (Minor language polishing) **Conclusion:** Minor revision **Specific Comments to Authors:**
1. This study is a retrospective study, so there is a data bias.
Response: we agree. **Revision:** Discussion inserts the following: Limitations of the study include bias inherent to its retrospective design.
2. SUV value and region selection, how to ensure consistency？
Response: consistency would need CT to delineate anatomic regions of interest (AROI) according to guidelines, repeated delineation and measurement, and inter-observer evaluation. Circumstances require these to be deferred. **Revision**: Discussion inserts the following: But unexpectedly when returning to the PET server workstation, the 3-dimensional irregular free-hand volumetric measurement tool (Figure 1) had been wiped out by an upgrade to the system. We could not verify the consistency of our earlier AROI delineations and SUVmax measurements. Repeated delineation measurements and extending the present study to a larger cohort have to be deferred to another time.
3. Why choose 2cm for tumor size and what is the basis？
Response: based on TNM staging. **Revision**:

Results and Table 1 insert the following:

>...20 mm (TNM T1 classification[16]).

Response: many authors have investigated molecular subtypes in much larger studies. Adjusting for subtypes would require a multivariate approach, contingent on enough patients. Nevertheless, our data do provide links to relevant information.

Revision:

Discussion inserts the following:

> Molecular subtypes are known to affect PET positivity as already mentioned[20-22]. However, the small study size with only 28 events for OS (Table 1) precluded extensive analyses. By the one-in-ten rule of thumb of one variable for ten events[29], the choice in the multivariate analysis was made to retain only the three-variables parsimonious model of Table 4 as built onto the precursor study[6]. Interestingly, despite the small study size these three variables illustrate distinct facets relevant to breast cancer management: PET as an indicator of disease aggressivity, age as a potential surrogate of increased risk of co-morbidity, and adjuvant hormone therapy as a surrogate of tumor subtype reflecting that hormone therapy is normally given only when the breast tumor expresses hormone receptors.

Reviewer #2:

Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors:

1. "surgery was done without delay in 85 (81.7%) and was preceded by neoadjuvant therapy in 19 (18.3%). What surgery were taken? Without delay was mean how long?

Response: we thank Reviewer for the remark very useful to interpret the study.
Revision:

Results insert the following:

> surgery was done at a median of 6 days after PET imaging in 85 (81.7%) patients who did not receive neoadjuvant therapy, and at a median of 83 days (range 5–201, one date unknown) after PET in the 19 (18.3%) patients who received neoadjuvant therapy. The type of breast surgery was lumpectomy in 26 (25.0%) patients, mastectomy in 77 (74.0%), exclusive radiotherapy assimilated to mastectomy in 1 (1.0%).

2. "SUVs were measured on regions of interest, regardless of visual enhancement; hence, these were available in all breast, axillary, and sternal sites." Why done as this way?

Response: the regions of interest, renamed anatomic regions of interest (AROI) to avoid confusion with the ROI commonly used in PET studies, were drawn from a radiation oncologist perspective.

Revision:

Methods inserts the following:

> The AROI selected for the study conformed to anatomical regions considered in the radiotherapy of the breast[10].

Discussion inserts the following:

> preoperative PET would have been an important tool to tailor radiation treatment fields in breast cancer, as demonstrated by Bral et al who showed how ignorance of PET imaging caused radiation target miss of hypermetabolic lymph nodes

3. " Survival differences were not evident when comparing positive PET breast or distant status separately"." Survival differences were also not evident on subgroup analyses on PET axillary status for tumors ≤ 20 mm." Maybe authors had any conjecture?

Reponse: these are tip of icebergs to huge topic. Nevertheless, we tentatively try to discuss. Regarding the breast, many patients had mastectomy, which could have negated the effect of PET (size) in breast. Regarding distant sites, due to selection that excluded metastatic disease, small number of 8 additional distant cases, too few.

Revision:

Discussion inserts the following:

> • PET status in the breast was not prognostic. The primary breast tumor size, which affects PET detection, is a long standing debate (Bernard Fisher 1969[26]; Claire Verschraegen, Modeling the Effect of Tumor Size in Early Breast Cancer, Ann Surg 2005;241:309–318). The issue is beyond the scope of this report. We can only remark that most patients (74%) received mastectomy.
> • Our study was not designed to correlate between distant metastasis and survival. Metastatic patients were excluded from the selection, hence, there were few remaining cases afterwards detected with additional distant localizations (8 in this series).

4. " Measures of variation and separation show the importance of PET for OS, which represent a strong prognostic factor at 15 years." Does this sentence was got from table 3?

Response: yes, the measures were derived from Table 3 (renamed Table 4). Measures renamed as "indices" to avoid confusion with "D measure" (also from Royston and Sauerbrei).

Revision:

Results inserts the following:

> In contrast, regarding OS, the R2N and R2D indices of variation of 0.077 and separation of 0.159 for PET at 15 years in Table 4

5. table 3, "The hazard ratios for age", the age was about how old? Full model means what?

Response: we thank Reviewer for the question that will be helpful.

Revision:

Table 1 inserts a row:

> Median age at diagnosis 58.9 years.

Results insert the description:

> That is, despite patients becoming older, from 58.9 years old at diagnosis (Table 1) to near 75 years old in the present study

Full model:

Results insert the clarification:

...from a full model that was computed by taking into account all three covariates together.

Table 3 inserts in legend:

the full model (computed with all three PET, age, adjuvant hormone therapy variables together)

6." the sensitivity and the specificity of the PET were 61% (range: 54%–67%) and 80% (79%–81%) respectively", in this article, maybe authors have had considered the sensitivity and the specificity of the PET?

Revision:

Discussion inserts the following:

The focus of the study was on prognosis rather than diagnostic accuracy. Nevertheless, a note on the latter is warranted. Out of the 63 patients who had negative axillary PET (Table 2, Axillary ipsilateral), 29 (imputed) had histopathological involved lymph nodes, and out of the 41 positive axillary PET, 5 had no pathological node involvement. That is a sensitivity of 55% (95% CI: 43%–68%) and a specificity of 87% (73%–96%) which indicate that PET, like other imaging modalities, cannot replace pathology to determine microscopic involvement.

7." A diagnostic check of proportional hazards found departure of proportionality with DFS." The sentence means what?

Revision:

Discussion inserts the following:

A diagnostic check of the DFS model found a violation of the proportional hazards assumption of the Cox model. The assumption requires that the ratio of hazards between two treatment groups is independent of time[27]. The assumption fails if the survival curves cross over, or overlap for a long time, or when the treatment has an early effect but the initial separation gets smaller over time[27]. This latter pattern of violation is evidenced in Figure 3 where the differences between the pairs of DFS curves tend to narrow with longer follow-up, in contrast to Figure 2 where the OS curves remain proportionally distinct.

Reviewer #3:

The subject of your study is very interesting. I would like you to describe the scene, places, and corresponding dates, including possible exposure, monitoring and data collection?

Response: we thank Reviewer for the question on the background which address the reality of studies done in adverse conditions without funding.

Revision:

Methods inserts the following:

- follow-up data was collected with the last update on January 31, 2020.
- All clinical data have been described previously[6]. The steps to the data acquisition are detailed on https://dx.doi.org/10.17504/protocols.io.bf7jjrkn . The data is available on https://doi.org/10.17632/sfvtmrd8z9.2 .

Discussion inserts the dates and data collection:

- (2002) To place the present study in context, it started twenty years ago with the first patient diagnosed and receiving preoperative PET in 2002,
- (2004) The first case series was presented at the San Antonio Breast Cancer Symposium in 2004...
- (2008) preoperative PET would have been an important tool to tailor radiation treatment fields in breast cancer, as demonstrated by Bral et al
- (places) It was however impossible to implement pre-operative PET Scan in daily practice because of Belgium healthcare restriction on PET Scan at the time. Only 13 facilities in the whole country were tolerated to implement PET; these were considered to exceed population requirements, and breast cancer was not a recognized indication[17].
- (2010) The study was reconducted without funding by investigators devoting volunteer time in 2010, accruing the present cohort of 104 patients. That confirmed the nodal correlation and indeed showed as expected an impact on early DFS.
- (2012) The analysis was published two years later in 2012[6].
- (2015) Perplexingly, the literature did not change, guidelines still considered PET inappropriate for the early assessment of breast cancer. To address that issue, in 2015 we established a quasi-prospective protocol with the intent to increase the number of observations with a second cohort of patients.
- (2020) As planned and reported herein, we updated the follow-up of the present cohort on January 31, 2020.
- (future) But unexpectedly when returning to the PET server workstation, the 3-dimensional irregular free-hand volumetric measurement tool (Figure 1) had been wiped out by an upgrade to the system. We could not verify the consistency of our earlier AROI delineations and SUVmax measurements. Repeated delineation measurement and extending the present study to a larger cohort have to be deferred to another time.

The clinics/hospital location, area is not mentioned clearly.

Revision:

Methods inserts the web address of the hospital:
    https://www.uzbrussel.be/
Discussion inserts the following:
    the UZ Brussel, a university hospital in Belgium.

Table titles are incomplete.

Revision:

Titles updated as follows (Table 2 split into 2 and 3 and simplified):

- Table 2 PET negative or positive status according to anatomical region of interest and according to tumor size.
- Table 3 Maximum standardized uptake value (SUVmax) according to anatomical region of interest and according to tumor size.
- Table 4 Multivariate models, original model with 5 years follow-up, vs current models with 15 years follow-up.
- Table 5 Mortality hazard ratio of the maximum standard uptake value (SUVmax) according to the anatomical region of interest, single or combined, where the SUVmax was measured.

It would be interesting to put the location and date of the analyzed data.

Revision:

Discussion inserts location and the dates in the second paragraph.

What are the limitations of your study?

Revision:

Discussion inserts the following paragraph:

Limitations of the study include bias inherent to its retrospective design. Investigators were not blinded to patients' outcomes, which could have affected the scoring of the PET images. Scoring depended on the visual appreciation of screen printouts. Pre-defined rules to abstract images were not established. There was no assessment of inter-observer agreement on the scores. Patients were treated 15 years ago which represent both a strength and a weakness: since then, the medical management and treatments have changed. Most patients presented with advanced tumors, for which a high prevalence of lymph node involvement could be expected. Few patients presented with T1 tumors (Table 2); most presented with advanced disease which increased the likelihood of PET positivity, but no conclusion could be drawn for the smaller tumors.

Reviewer #4:

Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors:

The use of abbreviations in titles is not recommended.

Revision:

The title replaces the non-standard "[18F]FDG-PET" with "18F-FDG PET Scan", in concordance with the National Library of Medicine (NLM) Medical Subject Headings (MeSH).

Discussion:

- In NLM, "18F-FDG" is a recognized entry term to "fluorodeoxyglucose", https://www.ncbi.nlm.nih.gov/mesh/68019788
- "PET Scan" is a recognized entry term to "Positron-Emission Tomography", https://www.ncbi.nlm.nih.gov/mesh/68049268

We remark that the full spelling "Fluorine 18 fluorodeoxyglucose Positron-Emission Tomography" – which is incorrect and should be fluorine-18-labeled 2-fluoro-2-deoxy-d-glucose Positron emission tomography (as we used in our San Antonio poster in 2004) has serious drawbacks.

1. Clinicians and patients use neither "fluorodeoxyglucose" nor "Positron-Emission Tomography".
2. Insurance companies and medical imaging departments do not use "Positron-Emission Tomography". This is evidenced in medical imaging official request forms from medical providers.
3. The full term "Positron-Emission Tomography" would classify the paper among archaic papers and would incur the risk of being overlooked by readers interested in PET and breast cancer.

A PubMed search of
<"fluorodeoxyglucose Positron-Emission Tomography" [ti] breast cancer>
([ti] specifies search in the title) yields 151 references, of which:
7 in 2020
9 in 2021
1 in 2022 (as of Feb 13th, 2022).
A search of < "18F-FDG PET" [ti] breast cancer > yields 297 references, of which:
14 in 2020
25 in 2021
9 in 2022 (as of Feb 13th, 2022).

Over the past years, the full spelling has undergone various changes from "fluorine-18-labeled 2-fluoro-2-deoxy-d-glucose" through "Fluorine 18 fluorodeoxyglucose Positron-Emission Tomography" to the simpler MeSH terms, full spelling is increasingly abandoned in favor of the shorter terms that are now 2–3 times more frequent.

Informed consent is not in english.

Revision:
Methods replaces the sentence with the following:
> All patients received appropriate information and provided informed consent to undergo the procedures.

Reviewer #5:

Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)

Specific Comments to Authors:

The article is interesting. At the present, PET scan is only indicated in breast cancer advanced cases in which further suspicion symptoms of tumoral spread are present; this is due to the relative non-specificity of the imaging technique with a considerable number of false-negative items, since the Authors report 26 positive lymphnode metastases in 63 negative PETs.

Response: we thank Reviewer for identifying our shortcoming.
Revision:
Discussion inserts the following:

> The focus of the study was on prognosis rather than diagnostic accuracy. Nevertheless, a note on the latter is warranted. Out of the 63 patients who had negative axillary PET (Table 2, Axillary ipsilateral), 29 (imputed) had histopathological involved lymph nodes, and out of the 41 positive axillary PET, 5 had no pathological node involvement. That is a sensitivity of 55% (95% CI: 43%–68%) and a specificity of 87% (73%–96%) which indicate that PET, like other imaging modalities, cannot replace pathology to determine microscopic involvement.

Furthermore, they use PET scan in stage IIIB tumors in which nodal involvement is strongly suspected, regardless a PET scan execution.

Revision:
Discussion inserts the following:

> Most patients presented with advanced tumors, for which a high prevalence of lymph node involvement could be expected. Few patients presented with T1 tumors (Table 2); most presented with advanced disease which increased the likelihood of PET positivity, but no conclusion could be drawn for the smaller tumors.

However, the long time study and the strong significativity of the SUV ratio between involved and non involved breast/axilla make the hypotesis of introducing PET scan in pre-treatment evaluation of advanced breast cancer patients interesting, in the way to plane a more aggressive therapy.

Response: we agree.
Revision:
Discussion inserts the following:

> We hypothesized that the larger number of nodes retrieved in PET-positive cases suggested lymphangiogenesis factors associated with an increased tumor metabolic activity. Obviously, preoperative PET would have been an important tool to tailor radiation treatment fields in breast cancer, as demonstrated by Bral et al who showed how ignorance of PET imaging caused radiation target miss of hypermetabolic lymph nodes

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

Response:

   The manuscript underwent certified professional English language editing.

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6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The authors' study showed that preoperative pet was valuable in predicting long-term survival. This is a well written paper and covers an interesting topic. Nevertheless, there are a number points that may deserve some revisions. For a large figure with many small figures, figure legend should be written separately. For example, Fig1 ABCD... Abbreviations should be avoided in the title. Self Citation Count: 3 The self-referencing rate should be less than 3%. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade B (Very good)

For a large figure with many small figures, figure legend should be written separately. For example, Fig1 ABCD...
Revision: Figure 1 (revised as Figure 2) and 2 (revised as Figure 3) have been labeled with A–F.
The self-referencing rate should be less than 3%.
Revision: Self-citations [5] and [11] are deleted.
It is unacceptable to have more than 3 references from the same journal.
Revision: Citations [26] and [29] are deleted, retaining only 3 references from *World J Gastroenterol*;   Citation [6] is deleted, retaining only 3 references from *Eur J Nucl Med Mol Imaging*.   These 3 citations are replaced with 3 references from *World J Radiol*.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".
Revision: Figure 1 (revised as Figure 2) and 2 (revised as Figure 3) have been labeled with A–F.
Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Revision: Figures are submitted in PowerPoint.
In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper).
Revision: All figures are original.
If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.
Revision: PowerPoint figures add the Copyright.
Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.
Revision: Tables formatted accordingly.