Prevalence of breast cancer in patients undergoing microdochectomy for a pathological nipple discharge

Dr Chiapo Lesetedi (584356)

LIST OF CORRECTIONS AS PER EXAMINERS’ REPORT

Examiner 1

Abstract

1. Correction required as per Examiner’s report 1- page 5, 1st paragraph:
   In the second sentence the current recommendation for treatment of pathological nipple discharge is referenced: is this a recommendation or gold standard (as stated later)?

   Response: Added on page 5, line 4 to read;
   The current gold standard for diagnosis is microdochectomy and this means that many women will undergo this invasive procedure for benign causes.

2. Correction required as per Examiner’s report 1- page 5, 2nd paragraph:
   In paragraph 2 a concept of an African population is introduced. I am not sure what is meant by this term:
   - Black patients- however it does not appear this is what is meant as all patients were included – in the protocol
   - Patient living in South Africa. What period prior to be classified as African must you live in Africa?
   - Doing this in private may indicate a different type of population- More White Eurocentric population
   - A patient that has moved here from England a week ago- maybe classified as African as far as I can see

   Response: To address this, on page 5, line 12 African population was changed to read “population in South Africa”.

3. Correction required as per Examiner’s report 1- Abstract:
   Breast cancer has a large genetic basis- this is more relevant than environment- maybe race could therefore be used as a surrogate marker of genetics.

   Response: Race cannot be used as a surrogate marker because of philosophical and practical reasons- such as the heterogeneity of genetics within one race, and multiple classification issues in South Africa
Objectives(s) of the study

4. **Correction required as per Examiner’s report 1**: page 26, study objectives:
The objectives in this study is clearly defined and well thought out. The objectives are clearly and concisely worked on and achieve the aim as stated. However when it comes to the conclusion the objectives are forgotten about and a treatment algorithm is put forward, a treatment algorithm was not part of your objectives.

**Response**: Recommendations on treatment has been added as an objective on page 9, lines 21-24. Also, the study outcomes were added to address the objectives on page 17, lines 22-24 and page 18 lines 1-2;

*The prevalence of malignancy in patients who had microdochectomy for a pathological nipple discharge was 7.8% and benign papilloma was the most common histopathological finding. Preoperative radiological investigations were inaccurate in diagnosing significant pathology in patients with pathological nipple discharge.*

5. **Correction required as per Examiner’s report 1**: Radiological investigations were less considered and as a reader you are left with questions

**Response**: Information on radiological investigated added on page 8, lines 23-25 and page 9, lines 1-3.

*Mammogram, ultrasound, magnetic resonance imaging, and ductography had a sensitivity of 37.5%, 25.5%, 100%, 50.0% respectively in diagnosing malignancy (14). In another study, magnetic resonance imaging had a sensitivity of 86% to 100% in detecting invasive cancer and a sensitivity of 40% to 100% in detecting ductal carcinoma insitu.*

Study population and selection

6. **Correction required as per Examiner’s report 1**: I felt that you have two different types of populations, this was never commented on... The fact that you had these two populations could in fact have added to your study.

**Response**: The objectives of this study did not necessitate dividing the study population into Private vs State. Also, when grouping the study patients according to histology and then according to nipple discharge or radiology, the numbers become too small to then get any statistical information from a divided population.

7. **Correction required as per Examiner’s report 1**: I think a clearer statement of local treatment guidelines at the time of the study could be made.
Response: local treatment guidelines at the time of the study added to page 10, lines 21-23 and page 11, lines 1-5 under ‘Data Acquisition’:

At the time of the study, patients with palpable breast masses with or without nipple discharge were investigated by biopsy and treated according to the biopsy findings. Patients with suspicious breast findings on mammogram (i.e calcifications) had either stereotactic or hook wire guided biopsy and were managed according to the biopsy results. Patients with pathological nipple discharge without any palpable breast masses had microdochectomy done, while those with physiological nipple discharge were followed up and the cause of the discharge treated if identified.

8. Correction required as per Examiner’s report 1:
Data included continuous and categorical variables. However age while continuous was allocated categorical values, I would have liked an explanation of why 50 years was used.

Response: Explanation of why 50 years added in page 11, lines 13-15 under statistical analysis;
Breast cancer is more prevalent in the older age group, especially in postmenopausal women. Fifty years was used as it is the mean age around which menopause starts.

9. Correction required as per Examiner’s report 1:
While radiological information was included (secondary objective) the role of MRI must be brought in e.g. did any patients not receive their surgery due to MRI findings. In modern breast management MRI is playing a more and more significant role.

Response: At the time of this study, MRI was not routinely funded for benign disease in private, and no MRI scanner was available in public under ‘Data acquisition’.

Results

10. Correction required as per Examiner’s report 1:
Total number of patients (physiological and pathological) presenting with nipple discharge may also help to put this into perspective. This however gave a clear group (cohort) that was well discussed.

Response: We do not have these numbers available to us to do this retrospectively.
11. Correction required as per Examiner’s report 1:
   Regarding age a differentiation was made at the age of 50 years; this was not supported by your table which showed no significant p value between Ca and No Ca in the >50. A ROC curve should probably be applied to determine the most appropriate age for determining those that must undergo surgery vs those that must not.

   Response: As we have used the age cut-off at the mean menopausal age, we have analysed our data accordingly. We have not included a ROC curve as we are not using age alone as an indicator (test) for requiring surgery. However, as the examiner clearly points out, this mean menopausal age cut-off does not show a significant difference for mean age between those with and without cancer (59.3 vs 50.7 years, respectively; P=0.04). Based on this, we have now also included an age category cut-off of <=55 years (P=0.03) in Table 1 (page 21) and on page 12 lines 18-20, and have adjusted our conclusion accordingly on page 17 lines 5-6.

12. Correction required as per Examiner’s report 1:
P-values were calculated for multiple data points one must be concerned about looking for p values. While I found most of them relevant and added to the study a few added little in the way of extra information e.g. report of a bloody nipple discharge vs serous in cancer and in the next line a very similar p value.

   Response: Point noted and similar p value of 0.02 was removed from page 13 line 6 as it did not add value.

Discussion

13. Correction required as per Examiner’s report 1- page 14, 1st paragraph, 1st line:
The term African Women is again misleading (refer above), I most likely would just leave this out of my discussion and refer to them as women been treated at a South African Hospital.

   Response: page 15, line 4: The term African Women changed to ‘women treated in two South African hospitals’

14. Correction required as per Examiner’s report 1- page 15, 2nd paragraph:
Discussing high income- I have a problem with this discussion as a number of your data set were obtained from high income group- medical aid patients. So is this then your argument for a correlation? You have not mentioned the number obtained from the private cohort.

   Response: The word high income removed in page 16, line 13.
15. **Correction required as per Examiner’s report 1-page 15 and 16:**
   
   Stepwise approach to your treatment while elegant in its simplicity I feel this is not collaborated by your evidence/data. This is then transferred to later conclusions.

   **Response:** Stepwise approach removed from the discussion and transferred to the conclusion, page 18, lines 3-12.

### Conclusion

16. **Correction required as per Examiner’s report 1-page 17:**
   
   I would hesitate that a patient of 45 years of age with a bloody nipple discharge does not get a microdochectomy, even if history and imaging do not suggest malignancy. The numbers in your study might be too small to prove significance.

   **Response:** Step three, page 18 lines 8-12 rephrased:
   
   Step three is microdochectomy of patients with bloody nipple discharge and age above 55 years and selective microdochectomy for those with bloody discharge and aged 55 years and below, with good education and close follow-up of all other women with a nipple discharge.

### References

17. **Corrections required as per Examiner’s report 1- references:**
   
   Well laid out. Consistency lacking in the reference section (I am not concerned regarding which to use e.g Harvard, Vancouver etc): but would like them to be the same throughout. E.g if you want to refer to a journal in short hand then do that for all.

   **Response:** All references done with long hand pages 19-21.
Examiner 2

1. **Corrections required as per Examiner’s report 2- Abstract page 5 and 6:**
   This should be rewritten in the usual format of introduction, aim, patients and methods, results and conclusion
   
   **Response:** Abstract rewritten on pages 5-6 in the format of introduction, aim, patients and methods, results and conclusion

2. **Corrections required as per Examiner’s report 2- Abstract page 5:**
   In results, the specificity, sensitivity, positive predictive value and negative predictive value of the observation relating to bloody nipple discharge must be documented
   
   **Response:** This has now been documented on page 5 line 21 to page 6 line 1.

3. **Corrections required as per Examiner’s report 2-page 7, line 3, reference 2:**
   The statement that “this incidence is up to 37.0%” should be qualified to specify that of patients with a pathological nipple discharge, the diagnosis of cancer required duct excision in 20% cases.
   
   **Response:** Page 7, Lines 7-9, qualifying statement added: In this group of patients with pathological nipple discharge, the diagnosis of cancer required duct excision in 20% of cases.

4. **Corrections required as per Examiner’s report 2-page 7, line 8:**
   The other causes of physiological nipple discharge should be listed here
   
   **Response:** The following has been added on page 7, lines 13-16 (paragraph 1):
   “Other causes of physiological nipple discharge are idiopathic, pituitary adenoma, hypothyroidism, ectopic prolactin production, hypothalmic disorders, and medications (including some antidepressants, antipsychotics and H2 antagonists).”

5. **Corrections required as per Examiner’s report 2-page 8, 2nd paragraph:**
   Spelling error in line 4. ‘under cytological investigations of nipple discharge fluid, no reference is made to testing for occult blood, the author should re-read his references, in particular reference 15.
   
   **Response:** page 8, lines 19-23 (2nd paragraph):
   Corrected to also make reference to testing for occult blood.
6. Corrections required as per Examiner’s report 2-page 8, 2nd paragraph, last line:
‘Good’ sensitivity is not a scientific statement, the sensitivities and specificities of the listed investigations require a more detailed comparison.

Response: page 8, lines 22-23 (2nd paragraph):
‘Good’ sensitivity replaced with ‘high’ sensitivity

CHAPTER 2

7. Corrections required as per Examiner’s report 2-page 10, last line:
The types of physiological nipple discharge should be listed to clearly identify those patients who were excluded from the study.

Response: The following has been added on page 7, lines 13-16 (paragraph 1):
“Other causes of physiological nipple discharge are idiopathic, pituitary adenoma, hypothyroidism, ectopic prolactin production, hypothalmic disorders, and medications (i.e antidepressants, antipsychotics, H2 antagonists).”

8. Corrections required as per Examiner’s report 2-page 11, line 8:
What were the common findings of retroareolar abnormalities?

Response: “most common findings of retroareolar abnormality (such as filling defects in the retroareolar area and lesion/papilloma in the retroareolar region)”, and this has been added on page 11, lines 17-18.

CHAPTER 3

9. Corrections required as per Examiner’s report 2-page 12, line 5:
“radiology findings are shown in table 1”. No details are given of the se’radiological findings’. Should be “Radiological findings”

Response: Corrected and “mammography and ultrasound” added on page 13 line 8.

10. Corrections required as per Examiner’s report 2-page 13, paragraph 1, line 3:
“majority” should be replaced by the exact number (%).

Response: page 14 lines 1-4 exact numbers and % have been added.
11. Corrections required as per Examiner’s report 2-page 13, paragraph 2, line 3:
“specifically in the cancer group” – give the actual number with % in brackets. The “retroareolar abnormalities” should be described.

Response: Actual numbers have been added on page 14 lines 9-11. Retroareolar abnormalities were described and refer to under Examiner 2 report point 8 above.

12. Corrections required as per Examiner’s report 2-page 13, line10:
“picking up” is a Layman’s term, replace with “identifying”

Response: Done on page 14, line 16

13. Corrections required as per Examiner’s report 2- chapter 3:
A table of Sensitivity, Specificity, PPV, NPV must be given here. The researcher is reference 15, table 2. “results of sensitivity and specificity analysis”

Response: Table not given as we were not entirely focusing on specificity, PPV, and NPV analysis

CHAPTER 4

14. Corrections required as per Examiner’s report 2-discussion, line 1:
Line 1 should read: In this study of South African women

Response: Corrected as in Examiner 1’s comment 13 above - page 15, line 4: The term African Women changed to ‘women treated in two South African hospitals’

15. Corrections required as per Examiner’s report 2-discussion, line 3:
The figure of 37.0% should be explained as a % of the total group where cancer was identified by biopsy or surgery. The relevant fact in this study is the 20% of patients identified by duct excision alone.

Response: Discussion, page 15 lines 8-9:
Done as in point 3 of Examiner 2’s report above.

16. Corrections required as per Examiner’s report 2;
In reference 8, blood was identified in 35 nipple discharges and occult malignancy found in 2 of these, i.e 5.7% which is not so different from the 7.5% of the current study. The researcher should note and discuss this finding to compare it to his own.
Response: It was noted and looking at reference 8 again, the 2 patients with occult malignancy did not have bloody nipple discharge.

17. Corrections required as per Examiner’s report 2:
Following line 4, the NPV’s where there is no bloody nipple discharge, must be discussed: In reference 1(meta-analysis) the findings of cancer in the “clear/serous” groups are clearly listed. The researcher is advised to reproduce these in his research and to compare sensitivity/specificity of a bloody nipple discharge in diagnosing cancer in his report to other workers’ findings

Response: We have removed reference to these as in our study we were not entirely focusing on the sensitivity/specificity

18. Corrections required as per Examiner’s report 2; page 15, line 3
“The general statement that a mammogram is poor in identifying pathology in patients with nipple discharge” should be illustrated by reproducing the results of documented studies in his list of references to substantiate statement.

Response: Documented on page 8, line 23-25

19. Corrections required as per Examiner’s report 2; page 15-paragraph 2
Again ‘retroareolar abnormalities’ are mentioned without describing what these are. A review of the S/S results in his patients may provide this information

Response: Done on page 11, line 17-18

20. Corrections required as per Examiner’s report 2; page 15, line 11
“Discharging breast” is not a scientific or specific term. It should be replaced by referring to the “presence of a nipple discharge”

Response: Done on page 16, line 19

21. Corrections required as per Examiner’s report 2; page 16, line 2
Re ‘cytology etc: these methods should include haemoccult testing (ref 15) and discussed in greater detail, not mentioned only in passing: similarly, magnetic resonance imaging, discussing the pros’ and cons’ of this methodology in presence of an isolated nipple discharge
Response: Documented on page 9, line 4-13

22. Corrections required as per Examiner’s report 2-discussion, page 16, line 7:
Details should be given for ‘immune clinical studies’ what are these?. Do they have a role in further examination of the nipple discharge fluid?

Response: Documented on page 17, lines 3-6, to read;
Immune clinical studies involves the detection of nipple discharge autoantibodies against tumour antigens. Examples of these are CA15-3, CA125 and CEA. Their role in further examination of the nipple discharge fluid is promising and need to be studied further.

CONCLUSION

23. Corrections required as per Examiner’s report 2-page 17, line 5:
A definition of ‘adequate experienced breast imaging’ should be given

Response: On page 18, line 6-7, ‘adequate experienced breast imaging’ defined to mean breast imaging done by a radiologist with experience in performing and interpreting breast images using different imaging modalities.

24. Corrections required as per Examiner’s report 2-page 17, line 5:
Re ‘age above 50’: this sentence should include the importance of careful surveillance of women with a serous discharge and their risk of ductal neoplasia.

Response: Summarised in the final sentence of the conclusion, page 18, line 8