Difficulties and challenges in implementing screening for lung cancer in high-risk group patients in the respiratory clinic at Groote Schuur Hospital

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In partial fulfilment of the requirements of the degree

Master of Philosophy (MPhil) in Pulmonology

Faculty of Health Sciences

University of Cape Town

Date of Submission: 15/05/2024

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Declaration

I, Mohamed Emhemed, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Acknowledgements
I want to thank my supervisor, Professor Richard van Zyl-Smit, who always gave me his time so willingly and worked very hard and supportively with me during this project, I thank him greatly. I shall never forget his outstanding guidance and support. He embodies the standards I aspire to in thoughtfulness, leadership, and compassion. I am privileged to have him as a role model.
Above all, thanks be to God Almighty for giving me the strength and courage to undertake and complete this thesis.

Format
This is a publication ready format manuscript. We are in the process of submitting it to the South Africa Medical Journal, SAMJ.

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List of abbreviations

6 MWT	6-minute walk test
AIDS	Acquired immunodeficiency syndrome
COPD	Chronic obstructive pulmonary disease
CT	Computed Tomography
CXR	Chest X-Ray
DLCO	Diffusing capacity of the lung for carbon monoxide
DM	Diabetes
eCRF	Electronic Case Report Form
FEV	Forced Expiratory Volume
GSH	Groote Schuur hospital
HIV	Human immunodeficiency virus
HPT	Hypertension
HRCT	High-resolution computed tomography
ICS	Inhaled corticosteroid
LABA	Long-acting B2-agonist
LAMA	Long-acting muscarinic antagonist
LDCT	Low dose computed tomography
mMRC	Modified Medical Research Council
NELSON	The Nederlands-Leuvens Longkanker Screening Onderzoek
NLST	National Lung Screening Trial
OCS	Oral corticosteroids
SA	South Africa
SABA	Short-acting beta 2-agonists
SATS	South African Thoracic Society
TB	Tuberculosis

PUBLICATION READY MANUSCRIPT

Difficulties and challenges in implementing screening for lung cancer in high-risk group patients in the respiratory clinic at Groote Schuur Hospital

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Introduction: Lung cancer is the leading cause of cancer related deaths in South Africa. The high prevalence of cigarette smoking in our population continues to contribute to the high burden of lung cancer. Screening high risk groups with annual low dose computed tomography (LDCT) has demonstrated the potential benefit of being able to identify individuals with early-stage disease and offer potential curative therapy from this deadly disease.

Objective: To determine the barriers and challenges of implementing lung cancer screening in a group of high-risk patients with underling Chronic Obstructive Pulmonary Disease (COPD).

Methods: We retrospectively analysed patient records of COPD patients attending the respiratory clinic at Groote Schuur Hospital, Cape Town in the year 2022. Eligibility for lung cancer screening included formal diagnosis of COPD, age 55-74 years, at least 30 pack year history of smoking or stopped smoking within the past 15 years, no history of lung cancer, good general health, fitness for surgery and patients' willingness to undergo further invasive investigations and treatment. Fitness for surgery was objectively determined by a modified Medical Research Council (mMRC) score less than 3 and FEV_1 greater than one litre.

Results: 116 patients with COPD were screened for eligibility for lung cancer screening. The mean (SD) age was 62.84(10.4) years and 56.1% were male. 44 (37.9%) patients were current smokers, 68 (58.6) were ex-smokers and 4 (3.5%) never smoked. Hypertension (46.6%) was the most common medical comorbidity, followed by previous tuberculosis (19.0%) and diabetes (7.8%). 16 (13.8%) patients were potentially eligible for lung cancer screening. 47 patients had a $FEV_1 < 1L$, 54 participants had a mMRC of 3 and above and 38 patients were excluded because of age.

Conclusion: Common clinical factors which made patients ineligible for lung cancer screening in our study are age and poor surgical candidates based on mMRC class and low FEV_1. Tertiary service severe/multimorbid COPD clinics provide few patients for lung cancer screening, community-based service may provide a better yield of patients for active lung cancer screening.

Introduction

Lung cancer is the leading cause of cancer related deaths worldwide. In South Africa, lung cancer is the top cause of cancer-related deaths for both men and women (1). The prognosis of lung cancer is directly proportional to the stage of disease at time of diagnosis. In developed countries only a quarter of patients are amenable to surgery at the time of diagnosis (2). In South Africa, poor access to specialised health care, delayed referral pathways, high burden of infectious diseases and trauma contribute to patients presenting with advanced disease with poor outcomes.

Smoking is a major risk factor contributing to the high incidence of lung cancer in South Africa. According to the South African Medical Research Council, around 37% of adults in the country are smokers, significantly higher than the global average of 22% (3). In addition to smoking, other risk factors for lung cancer in South Africa include exposure to air pollution, mining, and a high prevalence of HIV/AIDS, which can weaken the immune system and increase the risk of cancer (4).

Based on the strong association between smoking and lung cancer, the high morbidity and mortality of lung cancer particularly with advanced disease, high prevalence of lung cancer and potential of curative therapy with very early-stage disease, the benefit of lung cancer screening in high-risk patients is overwhelming (5,6). However, screening has the potential of exposing patients to radiation (7), patient distress (8) and overdiagnosis (9) and potential complications from invasive testing (10).

The National Lung Screening Trial (NLST), randomised patients between the age of 55-74 with a history of at least 30 pack years of smoking to receive an annual LDCT or chest radiograph for at least three years (11). LDCT was superior to chest radiograph in reducing mortality from lung cancer in this high-risk population. A second landmark study, The Nederlands-Leuvens Longkanker Screening Onderzoek (NELSON) trial, demonstrated that screening using LDCT led to a 24% reduction in lung cancer related mortality at ten years (12).

The South African Thoracic Society (SATS) recommends that annual LDCT should be offered to patients between age 55–74 years who are current or former smokers (having quit within the preceding 15 years) with at least a 30-pack year history, no history of lung cancer, patients should be in general good health, fit for surgery and willing to undergo further investigations if deemed necessary. High risk individuals should be screened annually until 15 years have elapsed from smoking cessation, they turn 80, become unfit for surgery, or significant changes are observed (1).

Healthy patients at risk of lung cancer (age 55-79 years, ex-smoker in past 15 years with at least 30 pack years) benefit the most from lung cancer screening (11,12). Given the high rate of lung cancer and burden of tuberculosis (TB) in South Africa in South Africa, we set out to explore the feasibility and challenges in implementing a lung cancer screening programme in a high-risk population of patients with COPD attending a tertiary respiratory clinic in Cape Town.

Methods

Study Design

We retrospectively analysed patient records of 116 participants with COPD attending the respiratory clinic at Groote Schuur Hospital, Cape Town in the year 2022. Patients captured in the respiratory clinic COPD registry, approved by Human Research Ethics Committee (HREC R007/2021), University of Cape Town, South Africa were identified. Ethical approval was obtained from the Human Research Ethics Committee, University of Cape Town, South Africa: HREC 354/2023 and the study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki.

Eligibility for lung cancer screening included formal diagnosis of COPD, age 55-74 years, at least 30 pack year history of smoking or stopped smoking within the past 15 years, no history of lung cancer, good general health, fitness for surgery and patients' willingness to undergo further invasive investigations and treatment. Exclusion criteria included: age <55 years or >74 years and poor surgical candidates (determined by a modified medical Research Council (mMRC) class≥3 and FEV_1<1 litre). Potential challenges to radiological screening were determined by a specialist thoracic radiologist and pulmonologist consensus review of all plain film chest X-rays and the presence of substantial background changes (scarring / bronchiectasis etc.)

Data Collection

Data was collected using electronic Case Report Forms (eCRFs). Data collected included demographics, clinical characteristics, comorbidities, spirometry findings, medication history, radiological findings (chest radiograph/CT scan) and vaccine history.

Patient data was anonymized and stored in an excel workbook. Data was available to the study investigators through strict password control access. Due to the retrospective study design, UCT HREC waived the need for consent.

Statistical analysis

Continuous data were expressed as means and standard deviations for normal distribution or as median and interquartile ranges for skewed distribution. Categorical data was expressed as percentages. No formal comparative statistics were conducted due to the observational nature of the study, and the entire population of patients in the registry were included, thus no sample size calculations were performed.

Results

A total of 116 COPD patients identified in the E16 respiratory clinic registry were reviewed for eligibility for lung cancer screening. The mean age of the participants was 62.84 (SD ± 10.4) years and 56.1% were male. 44 (37.9%) patients were current smokers, 68 (58.6) were ex-smokers and 4 (3.5%) never smoked. The mean pack years of smoking was 35 (SD ± 21.3). Hypertension (46.6%) was the most common medical comorbidity, followed by previous tuberculosis (19.0%) and diabetes (7.8%). 36.2% of the participants had an mMRC grade of 2, 35.3% had mMRC grade 3, 19.8% had mMRC 4 and 6.9% had mMRC grade 1 dyspnoea. **(Table 1)**

16 (13.8%) patients were finally deemed eligible for lung cancer screening based on fulfilling the SATS criteria. The mean age of this group was 64.4 (SD ± 6.1) with a male predominance of 56.2%. 11 patients were active smokers (>30pack years), and 5 patients were former smoker who quit within the past 15 years. 9 (56.2%) patients had hypertension, 4(25%) had previous tuberculosis and 2(12.5%) patients had diabetes. 12 patients had mMRC grade 2 and 4 patients had mMRC grade 4. **(Table 2)**.

Plain film chest x-rays were available for all patients deemed eligible for screening. Nearly half (7/16) of the plain films had evidence of upper lobe scarring/post-TB changes, making radiological evaluation for lung cancer potentially challenging.

100 participants were ineligible for lung cancer screening. 21 patients were <55 years and 17 were >74 years. The majority of patients were male (56.0%). 31 patients had an mMRC grade of 3 and 23 patients had an mMRC grade 4 respectively. 47 participants had a FEV_1<1L **(Table 3)**.

Table 1. Demographic, comorbidities, clinical characteristics, and medication history of all participants (n=116)	
Age, Mean (SD)	**62.8 (10.4)**
Distribution	
<55 (%)	**21 (18.1)**
55-74 (%)	**78 (67.2)**
>74	**17 (14.7)**
Male (%)	**65 (56.1)**
Female (%)	**51 (43.9)**
Comorbidities	
Smoking history	
Current smoker (%)	**44 (37.9)**
Former smoker (%)	**68 (58.6)**
Never smoked (%)	**4 (3.5)**
Pack years of smoking, Mean (SD)	**35 (21.3)**
Previous tuberculosis infection (%)	**22 (19.0)**
Diabetes (%)	**9 (7.8)**
Hypertension (%)	**54 (46.6)**
GOLD Classification	
A (%)	**7 (6.0)**
B (%)	**51 (44.0)**
C (%)	**1 (0.9)**
D (%)	**42 (36.2)**
Unclassified (%)	**15 (12.9)**
mMRC Grade	
1 (%)	**8 (6.9)**
2 (%)	**42 (36.2)**
3 (%)	**41 (35.3)**
4 (%)	**23 (19.8)**
Unclassified (%)	**2 (1.7)**

Table 2. Characteristics of patients eligible for lung cancer screening (n=16)	
Age, Mean (SD)	**64.4 (6.1)**
Male (%)	**9 (56.2)**
Female (%)	**7 (43.8)**
Weight, Kg, Mean (SD)	**74.7 (12.2)**
Comorbidities	
≥ 30 pack year smoker (%)	**11 (68.7)**
Former smoker in past 15 years (%)	**5 (31.3)**
Previous tuberculosis infection (%)	**4 (25.0)**
Diabetes (%)	**2 (12.5)**
Hypertension (%)	**9 (56.2)**
GOLD Classification	
A (%)	**4 (25.0)**
B (%)	**10 (62.5)**
C (%)	**0**
D (%)	**2 (12.5)**
mMRC Grade	
1 (%)	**4 (25.0)**
2 (%)	**12 (75.0)**

Table 3. Characteristics of participants ineligible for lung cancer screening (n=100)	
Age < 55	**21 (21.0)**
Age 55-74	**62 (62%)**
Age > 74	**17 (17.0)**
Male (%)	**56 (56.0)**
Female (%)	**44 (44.0)**
Comorbidities	
≥ 30 pack year smoker (%)	**22 (22.0)**
Former smoker in past 15 years (%)	**39 (39.0)**
Previous tuberculosis infection (%)	**18 (18.0)**
Diabetes (%)	**7 (7.0)**
Hypertension (%)	**45 (45.0)**
GOLD Classification	
A (%)	**4 (4.0)**
B (%)	**41 (41.0)**
C (%)	**1 (1.0)**
D (%)	**40 (40.0)**
Unclassified (%)	**14 (14.0)**
mMRC Grade	
1 (%)	**4 (4.0)**
2 (%)	**30 (30.0)**
3 (%)	**31(31.0)**
4 (%)	**23 (23.0)**
Unclassified (%)	**12 (12.0)**
FEV_1 < 1L (%)	**47 (47.0)**

Discussion

Our study assessed the feasibility and challenges in implementing a lung cancer screening program at a tertiary centre in a resource limited environment. Out of a total of 116 high risk participants with COPD, only 16 patients (13.8%) were eligible for lung cancer screening as per the SATS guidelines, the major reasons for ineligibility were low FEV_1 and severe dyspnoea (mMRC>2). These data suggest that screening patients at a tertiary hospital may not have a major impact in reducing mortality from lung cancer, given the small numbers eligible. A primary care level approach targeting healthy smokers who fit criteria for screening within the community may have a more favourable yield.

The National Lung Screening Trial (NLST) recruited 53454 patients who were eligible for lung cancer screening across 33 centres within the United States of America (USA) (11). We acknowledge the small number of patients in our study however the male distribution of our patients was similar to the NLST (56% vs 59%) respectively, current smokers were similar to the NLST (44% vs 48%) however only 67% of patients were between the age of 55-74 compared to the NLST where 99% were in the range of 55-74 years.

The main reasons for ineligibility for lung cancer screening included age and fitness for major surgery. The two main determinants in assessing fitness for major surgery included a mMRC grade of 3 or higher and a FEV_1 less than 1L. In the NELSON trial, patients who could not climb at least two flights of stairs were excluded. Other exclusion criteria included weight more than 140kg, history of renal, breast and melanoma cancers respectively, a CT scan in the past year and previous diagnosis of lung cancer (12). Our study was not formally able to evaluate exercise capacity and the exclusion was extrapolated from the mMRC.

A functional lung cancer screening program requires a multidisciplinary team which includes a dedicated radiology service, pulmonology team, nursing staff and appropriate referral pathways. These services are only available at specialist/tertiary services in South Africa. Such programs have been integrated into primary care in developed countries and have shown to have a public health impact (13).

The majority of the South African public relies on the state hospital for care. Most patients are managed at primary and secondary health facilities within SA with minimal access to specialised care (14). A good example is patients with COPD who are mostly managed at primary and secondary levels. Unfortunately, most of the health facilities do not have access to a CT scan, lung function, lack equipment and expertise to do invasive tests such as CT guided biopsies and bronchoscopies and lastly minimal access to thoracic surgery. To provide such a service in the South African context would require either more services at primary care such as

radiology including CT and biopsy or require referral to tertiary level services for the diagnostic work up once basic screening is completed at primary level.

Annual CXR would potentially be a cheaper and more feasible approach in our environment, however the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial did not show a mortality benefit when used for screening high risk patients (15). Based on our sample of chest x-rays, in this severe cohort of patients nearly half had pre-existing underlying changes making interpretation of small nodules etc. difficult over time, and thus likely to be very challenging to implement appropriate CT referrals. Approximately 20% of participants in our cohort had a history of previous tuberculosis (TB). Standard CT reporting of lung nodules follow's the Lung-RADS™ classification system, created by the American College of Radiology (ACR) (16). Previous or current TB infection may impact the interpretation of lung nodules in TB endemic settings like ours. The validation of the Lung-RADS classification in our context where we see a high burden of TB, is a potential area of future research.

In conclusion, screening individuals at high risk of developing lung cancer has the potential to identify early-stage disease and achieve positive outcomes. Implementing active screening programs within the community and establishing timely and efficient referral pathways to tertiary institutions would be a feasible approach to lung screening in our resource limited setting.

Study Limitations

This was a retrospective study with a small number of participants. However, it provides insights into the size of a lung cancer screening programme in our center if embarked upon. It furthermore provides some context to where a lung cancer screening service should be set up to maximise the numbers screened. The formal evaluation of surgical fitness was not possible, and we may have overestimated the mMRC exclusion, with more patients being eligible if formally tested. Very few participants had "routine" CT scans – making the evaluation of significant upper lobe scarring and its impact on screening interpretation need for biopsy, limited to expert opinion.

Conclusions

Implementing lung cancer screening programs in a tertiary service at Groote Schuur would only benefit a small number of patients, many being excluded because of disease severity. Community based programmes may generate a larger number of eligible patients to screen but would likely be limited by access to specialist support/radiology during the process given the nature of our services.

Acknowledgements
None

Competing Interests
The authors declare no competing interest that may have influenced the study and writing of this manuscript.

Author Contributions
ME overlooked data collection, processed the data, wrote the manuscript drafts. EK and SK assisted with data collection. QSH reviewed all the radiology scans for the patients and reports. RVZS conceptualised the idea, performed final review and revision.

Funding Information
Not applicable.

Data Availability
Raw data was generated at Groote Schuur Hospital. Data derived from the study is available from the corresponding author on request.

Disclaimer
The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agenda of the authors.

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08 June 2023

HREC REF: 354/2023

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Dear Prof van Zyl-Smit

PROJECT TITLE: DIFFICULTIES AND CHALLENGES IN IMPLEMENTING SCREENING FOR LUNG CANCER IN HIGH-RISK GROUP PATIENTS IN THE RESPIRATORY CLINIC AT GROOTE SCHUUR HOSPITAL- LINKED TO R007/2021-
(MPHIL CANDIDATE-DR MOHAMED EMHEMED)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 June 2024.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Mohamed Emhemed will also be involved in this study.

Please quote HREC REF 354/2023 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

South African Medical Journal-SAMJ: Author Guidelines

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- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
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SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:
- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
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- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results, and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion, and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

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- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social, or cultural factors (e.g. smoking status, socioeconomic group, educational attainment,

- -existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers.
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain). –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ | | then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':
Rather:
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Combine into one column, n (%):
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Use <> symbols or numbers that don't overlap:

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must not be used.

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others. [3,4-6]
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- First and last page, in full, should be given e.g.: 1215-1217 not 1215-17.
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Some examples:

- Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

Publication

Online v. print

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