Histopathological distinctions of Ovarian Solid tumours at three academic hospitals in Johannesburg

UNIVERSITY OF THE
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A thesis submitted in partial fulfilment for the degree Master of Medicine in Obstetrics and Gynaecology in the School of Clinical Medicine, Faculty of Health Sciences, University of The Witwatersrand.

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DECLARATION

I Dr Motlhokomedi Morapedi declare that this Thesis/Dissertation/Research Report is my own, unaided work. It is being submitted in partial fulfilment of the Degree of Masters of Medicine (Obstetrics and Gynaecology) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_____

(Signature of candidate)

4th day of October 2024 in Johannesburg

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ABSTRACT

Background: Ovarian tumours are a major cause of morbidity and mortality, exhibiting a wide range of histopathological variations. Despite their high incidence and association with cancer-related deaths, there is a lack of data regarding the histopathological profile of these tumours in resource-limited settings. Therefore, this study aims to provide insights into the histological patterns of solid ovarian tumours in Adolescents and Young Adults (AYA), 16 – 40 years within our population.

Methods: A descriptive, retrospective, quantitative study of histologically proven solid ovarian tumors over 7 years, (1st of January 2011 to 31st December 2017) was conducted in Johannesburg tertiary hospitals. Histopathological reports were analysed and classified according to the World Health Organization's ovarian tumour classification system. The details evaluated were, demographics, date of surgery, histological classification and subtype, tumour behaviour, tumour laterality, secondary site, and type of surgery.

Results: 68 patients with solid ovarian tumours on histopathological examination were included over the study period. Out of all the tumours, malignant tumours were 64.8% while benign and borderline tumours constituted 23.5% and 11.8% respectively. In addition, surface epithelial tumours were the most common tumours accounting for 55.9%, with mucinous adenocarcinoma being the most frequent subtype (16.2%). The age category with the most disease burden was 36-40 (38.2%). The right ovary was the most affected site with 36.8% of the total tumours. Fertility sparing surgery was perfomed in (34/68, 50%) while the remaining half underwent radical surgery.

Conclusion: Most solid ovarian tumours were malignant and of epithelial origin managed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. It is unknown why most unilateral tumours were found on the right ovary.

Keywords: Solid ovarian tumour, histopathology, incidence, adolescents, young adults

Contribution

All authors contributed to the manuscript. LM and MM contributed to the conception of the project and the protocol draft. VDM and TL reviewed and edited the protocol. MM drafted the initial manuscript and all authors reviewed, edited, and approved the final manuscript that was submitted.

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LIST OF ABBREVIATIONS

AYA	Adolescents and Young Adults
BOT	Borderline Ovarian Tumours
CEO	Chief Executive Officer
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
EOT	Epithelial Ovarian Tumours
HJH	Helen Joseph Hospital
LSO	Left Salpingo-oopherectomy
NHLS	National Health Laboratory Service
RMMCH	Rahima Moosa Mother and Child Hospital
RSO	Right Salpingo-oopherectomy
SOT	Solid Ovarian Tumours
TAH	Total Abdominal Hysterectomy
WHO	World Health Organization

CHAPTER 1: SUBMISSSIBLE ARTICLE

Histopathological distinctions of Ovarian Solid tumors at three academic hospitals in Johannesburg

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Abstract

Background: Ovarian tumours are a major cause of morbidity and mortality, exhibiting a wide range of histopathological variations. Despite their high incidence and association with cancer-related deaths, there is a lack of data regarding the histopathological profile of these tumours in resource-limited settings. Therefore, this study aims to provide insights into the histological patterns of solid ovarian tumours in Adolescents and Young Adults (AYA) within our population.

Methods: A descriptive, retrospective, quantitative study of histologically proven solid ovarian tumors over 7 years, (1st of January 2011 to 31st December 2017) was conducted in Johannesburg tertiary hospitals. Histopathological data was sourced from a pre-existing cancer prevalence database. This database was collated for a project titled: "Malignant solid tumours in young adult South Africans (16-40 years) - A 7-year audit on histopathological records of patients seen in three academic hospitals of the University of the Witwatersrand circuit." Histopathological reports were analysed and classified according to the World Health Organization's ovarian tumour classification system. The details evaluated were, demographics, date of surgery, histological classification and subtype, tumour behaviour, tumour laterality, secondary site, and type of surgery.

Results: 68 patients with solid ovarian tumours on histopathological examination were included over the study period. Out of all the tumours, malignant tumours were 64.8% while benign and borderline tumours constituted 23.5% and 11.8% respectively. In addition, surface epithelial tumours were the most common tumours accounting for 55.9%, with mucinous adenocarcinoma being the most frequent subtype (16.2%). The age category with the most disease burden was 36-40 (38.2%). The right ovary was the most affected site with 36.8% of the total tumours. Fertility sparing surgery was perfomed in (34/68, 50%) while the remaining half underwent radical surgery.

Conclusion: Most solid ovarian tumours were malignant and of epithelial origin managed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. It is unknown why most unilateral tumours were found on the right ovary.

Keywords: Solid ovarian tumour, histopathology, incidence.

Contribution

All authors contributed to the manuscript. LM and MM contributed to the conception of the project and the protocol draft. VDM and TL reviewed and edited the protocol. MM drafted the initial manuscript and all authors reviewed, edited, and approved the final manuscript that was submitted.

Introduction and background

Ovarian tumours are a major cause of morbidity and mortality, exhibiting a wide range of histopathological variations. Despite their high incidence and association with cancer-related deaths, there is a lack of data regarding the histopathological profile of these tumours in resource-limited settings. These tumours are ranked among the top seven in terms of both incidence and cancer-related deaths in limited-resource settings. (1) In 2020, it was estimated that approximately 19.3 million individuals were diagnosed with cancer, resulting in roughly 10 million deaths. A review of cancer survival in six Sub-Saharan Africa (Kenya, Mauritius, Uganda, Cote d'Ivoire, Ethiopia and South Africa) by Gizaw *et al* found a 1, 3- and 5-year survival rate of 67.4%, 47.8%, and 37.9% respectively. (1)In SSA, Ethiopia has the highest age-standardized incidence rate of ovarian cancer at 8.5 per 100 000 person-years which is double that of other countries in the region. (2,3) According to the Global Cancer Observatory, there were 1 421 cases reported in South Africa in 2020 with over 900 deaths. (4) Furthermore, ovarian cancer represents about 1% of all cancer cases in South Africa, trailing only behind breast and cervical cancers.(5)

Effective screening methods for ovarian tumours are currently lacking, leading to advanced disease at the time of diagnosis and poor survival rates (2,7). The primary diagnostic approach remains histopathological examination of specimens obtained during surgery. According to the 2014 classification by the World Health Organization (WHO), the most common histopathological types of ovarian tumours are epithelial, sex cord-stromal, germ cell, and mesenchymal tumours (8). However, the distribution of these tumour types varies significantly worldwide. For instance, surface epithelial tumours account for 90% of all ovarian cancers globally, whereas germ cell and sex cord-stromal tumours are more common in Asia and Africa, with germ cell tumours representing 10–15% of all ovarian cancer cases (1).

Borderline ovarian tumours, classified as epithelial tumours, primarily consist of serous and mucinous histology. Clear cell, endometrioid, and Brenner's histology are less commonly

observed, accounting for less than 5% of all borderline cases (9). Within the wider spectrum of ovarian neoplasms, borderline tumours are found in 8.3% to 23.6% of cases of ovarian, with serous and mucinous subtypes making up 65% and 32% respectively (9).

Research indicates that different subtypes of ovarian tumours exhibit unique pathogeneses, molecular characteristics, natural histories, and prognostic outcomes. Therefore, the proper pathological classification is essential for determining prognosis and guiding therapeutic approaches. However, there is a notable dearth of research on the histopathological patterns and distributions of these tumours among adolescents and young adults women in Africa, particularly in South Africa. This is a matter of concern as the incidence and mortality rates of ovarian cancer are on the rise. Hence the aim of this study was to, to provide insights into the histological patterns of solid ovarian tumours in Adolescents and Young Adults (AYA) within our population.

Research Methods

This study retrospectively analysed solid ovarian tumours over a seven-year period (January 1, 2011, to December 31, 2017) at three academic hospitals in Johannesburg: Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Rahima Moosa Mother and Child Hospital (RMMCH), and Chris Hani Baragwanath Academic Hospital (CHBAH). National Health Laboratory Service (NHLS) histopathological data was obtained from a pre-existing cancer prevalence database owned by the Department of Surgery. The study included data from adolescents and young adult patients (16 – 40 years) who were diagnosed with solid ovarian tumours. Patients outside of this age range or without a confirmed diagnosis were excluded. The data was extracted and stored in a Microsoft Excel document (2019) and then analysed using STATA 15® (College Station, Texas, USA). The collected parameters included patient demographics, tumour histology and subtype, tumour behaviour, tumour laterality, secondary site, and type of surgery performed. Descriptive statistics were used to summarize and describe the demographic data of the patients. Additionally, a Chi-square test or Fisher's exact test was conducted to determine the level of association between demographic factors (age group), tumour type, histology, clinical characteristics, and their management. A significance level of $p < 0.05$ was applied.

Results

A total of 9,581 solid tumours were identified in the National Health Laboratory Service database, of which 189 (2%) were ovarian tumours. However, only 68 tumours met the inclusion criteria and were included in the analysis. The mean age of the patients was 31.9 years (± 6.57), with the youngest patient being 18 years old. The age group with the highest disease burden was 36-40 years (38.2%), followed by the 31-35-year age group (23.5%). The least affected age group was 16-20 years (5.9%). The majority of patients (36/68; 53%) underwent surgery at CMJAH, while CHBAH and HJH accounted for 30/68 (44%) and 2/68 (2.9%) of the cases, respectively. Approximately two-thirds of the patients (44/68; 64.7%) had malignant tumours, with borderline tumours having the lowest proportion (8/68; 11.8%). Benign tumours accounted for 16/68 (23.5%) cases. In terms of histological subtype, the majority of the tumours (41, 60.3%) were ovarian adenocarcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, endometrial, and endometrioid. The above information is summarized in Table 1.

Table 1: Summary of demographics, tumour characteristics and facility of surgical procedure

Variable		**Number**	**Percentage**
Age	16 - 20	4	5.9%
	21 - 25	10	14.7%
	26 - 30	12	17.6%
	31 - 35	16	23.5%
	36 - 40	26	38.2%
Facility	CMJAH	36	52.9%
	CHBAH	30	44.1%
	HJH	2	2.9%
Tumours behaviour	Benign	16	23.5%

	Borderline	8	11.8%
	Malignant	44	64.7%
Laterality	Right Ovary	25	36.8%
	Left Ovary	17	25.0%
	Both	16	23.5%
	Unknown	10	14.7%
Classification	Epithelial Tumour	38	55.9%
	Germ Cell Tumour	17	25.0%
	Sex Cord/Stromal tumour	5	7.4%
	Others*	8	11.8%
Histological Subtype	Mucinous Adenocarcinoma	11	16.2%
	Mature Teratoma	5	7.4%
	Serous Carcinoma	4	5.9%
	Choriocarcinoma	4	5.9%
	Fibroma	3	4.4%
	Others**	41	60.3%

Other*= these include adenocarcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, endometrial and endometrioid.

Other** = these include Adenocarcinoma, borderline cystadenoma, borderline mucinous cystadenoma, borderline mucinous cystic tumour borderline mucinous tumour, brenner tumour, endometrioid endometrial adenocarcinoma, endometroid adenocarcinoma, endometroid carcinoma, invasive adenocarcinoma, invasive mucinous adenocarcinoma, invasive papillary serous adenocarcinoma, invasive serous adenocarcinoma, mature cystic teratoma (squamous cell carcinoma), mature teratoma, mixed germ cell tumour, mixed sex cord – stromal, moderately differentiated adenocarcinoma, monodermal teratoma (struma ovarii), mucinous borderline tumour, mucinous cystadenoma, serous adenocarcinoma, serous borderline tumour, serous cystadenocarcinoma, serous cystadenoma, serous papillary cystadenocarcinoma, sertoli-leydig, signet ring, adenocarcinoma, small cell carcinoma, yolk sac tumour.

Figures 1a and 1b represents a comparative analysis of uterine, vulvar, vaginal, and ovarian tumours within the study group. The incidence of ovarian tumours demonstrated a gradual increase starting at the age of 21, reaching its highest peak in the 36-40 age group. Notably, ovarian tumours ranked second in frequency, following vulvar cancer tumours.

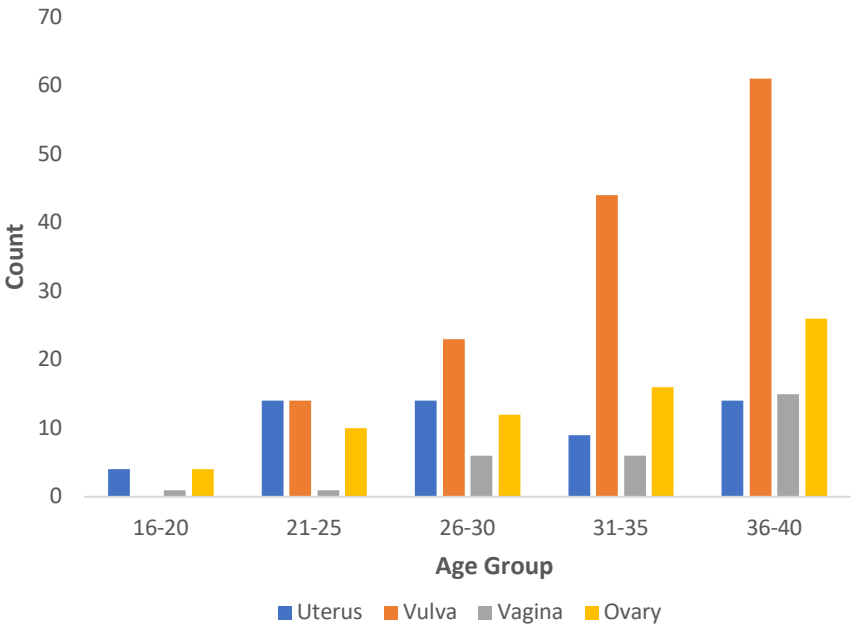


Figure 1a: Age distribution and comparison of the Uterine, Vulval and Vaginal cancers.

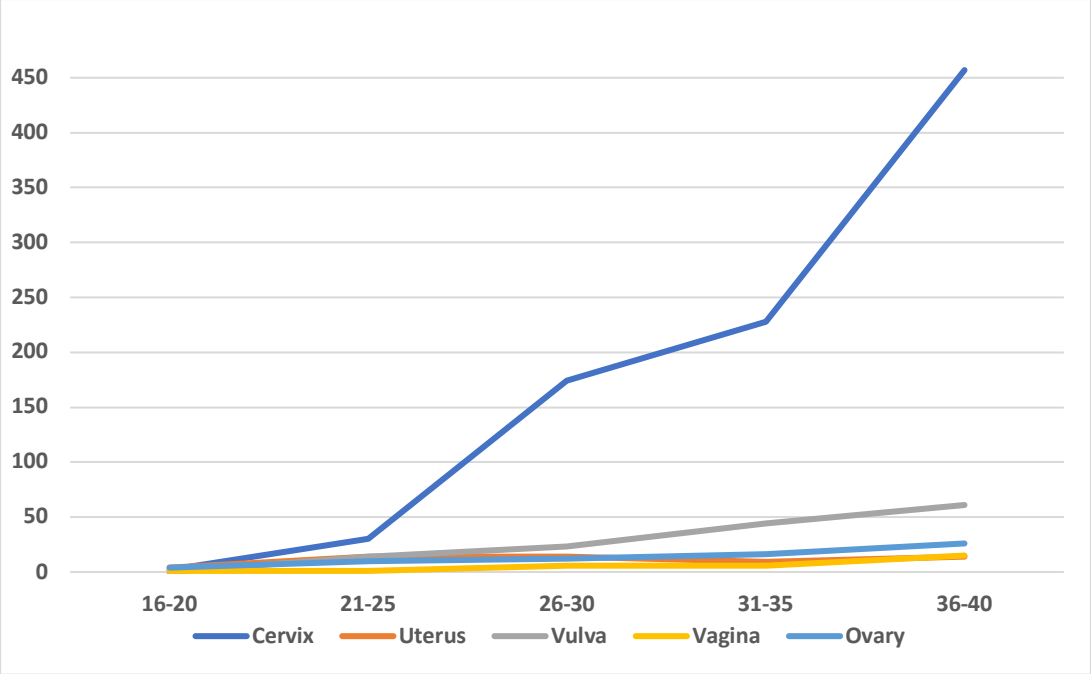
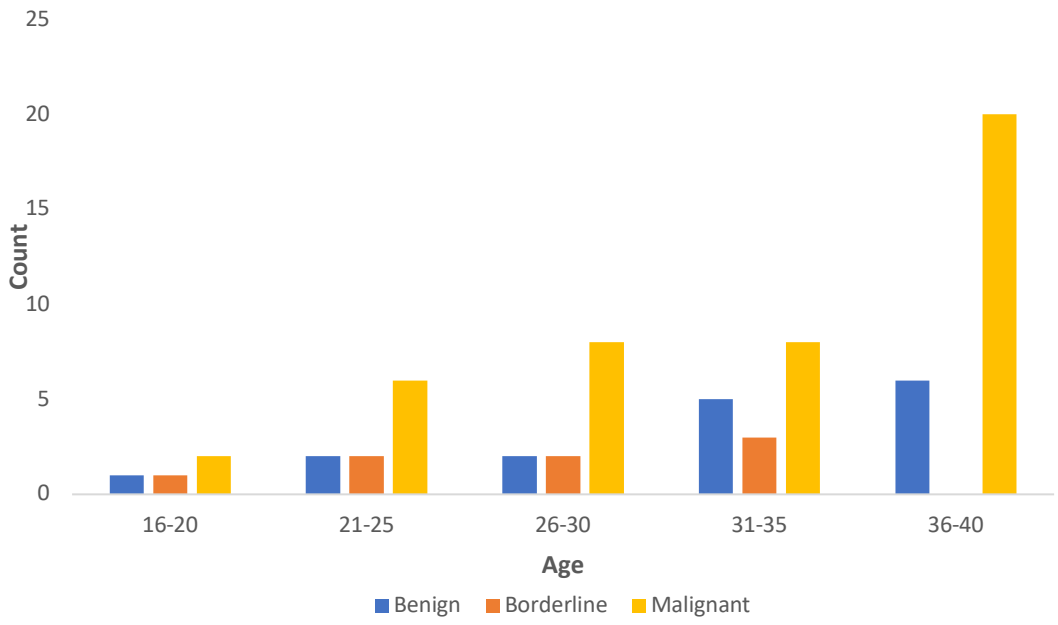


Figure 1b: Age distribution and comparison of solid ovarian tumours with other solid gynaecological tumours including cervical cancer.

Epithelial tumours accounted for 55.9% (38/68) of ovarian tumour cases, followed by Germ cell tumours at 25.0% (17/68) and sex cord/Stromal tumours at 7.4% (5/68). Colorectal adenocarcinoma comprised 4.4% (3/68) of all the cases. Adenocarcinoma of the cervix, endometrium, endometrioid tumours, and mixed epithelial and mesenchymal tumours each contributed 1.5% (1/68). These were metastasis to the ovary.The most common histological subtypes of epithelial ovarian tumours were mucinous adenocarcinoma (16.2%), followed by mature teratoma (5/68, 7.4%), with serous carcinoma and choriocarcinoma both contributing 5.9% (4/68).

Concerning the biological behavior of tumours, about two-thirds of tumours (44/68, 67.4%) were malignant, affecting mainly the age group 36-40 years (20/68, 29.4 %). Benign tumours were almost a quarter of cases, (16/68, 23.5%) while borderline tumours were the least (8/68, 11.8%) (Figure 2).



fFigure 2: Age distribution of solid ovarian tumours according to biological behaviour.

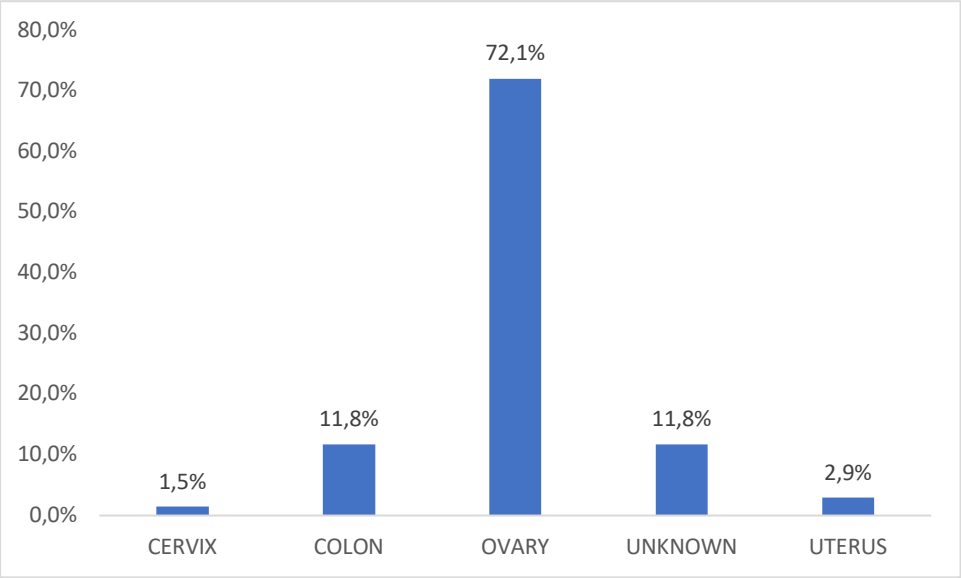


Figure 3: Shows primary tumour site of solid ovarian tumours

There was no significant association found between the age of patients and tumour behaviour (benign, malignant, or borderline) (p-value = 0.520, p > 0.05). The laterality of the tumour was specified in only 58 out of 68 histology reports (85.3%). The right ovary was the most affected anatomical site in 25 out of 68 cases (36.8%), followed by the left ovary in 17 out of

68 cases (25%). Both ovaries were affected in less than a quarter of patients (16 out of 68; 23.5%) (Table 2). Our study did not find any statistically significant relationship between tumour laterality and age groups (p-value = 0.215). Out of the 68 patients, 49 (72.1%) were reported to have primary ovarian tumours through anatomical reports, while 8 (11.8%) were metastases from the colon, 2 (2.9%) were from the uterus, and 1 (1.5%) was from the cervix (Figure 3)

Laterality	Classification								Total	
	Epithelial Tumor		Germ Cell Tumor		Sex Cord/Stromal		Others			
	n	%	n	%	n	%	n	%	n	%
Right Ovary	14	20.6	8	11.8	2	2.9	1	1.5	25	36.8
Left Ovary	7	10.3	7	10.3	1	1.5	2	2.9	17	25
Both	11	16.2	1	1.5	1	1.5	3	4.4	16	23.5
Unknown	6	8.8	1	1.5	1	1.5	2	2.9	10	14.7
Total	38	55.9	17	25	5	7.4	8	11.8	68	100

Table 2: Tumour laterality and classification as reported by anatomical pathology report post-surgery.

Half of the patients underwent fertility-sparing surgery (34/68, 50%), while the other half underwent non-fertility-sparing procedures (Fig. 4). The fertility-sparing surgery involved preserving either the uterus or one or both ovaries. This type of surgery was performed in a quarter of the cases (4/16, 25%) for benign tumours and in over a third of the cases (3/8, 37.5%) for borderline tumours. Among those who underwent a radical procedure, the majority (12/44, 27.3%) underwent total abdominal hysterecromy/bilateral salpingo-oopherectomy/omentectomy for malignant tumours. The study did not find any significant

association between age categories and the type of surgery performed (p-value = 0.871). However, there was a strong association between the type of surgery and the histological classification of tumours (p-value = 0.016).

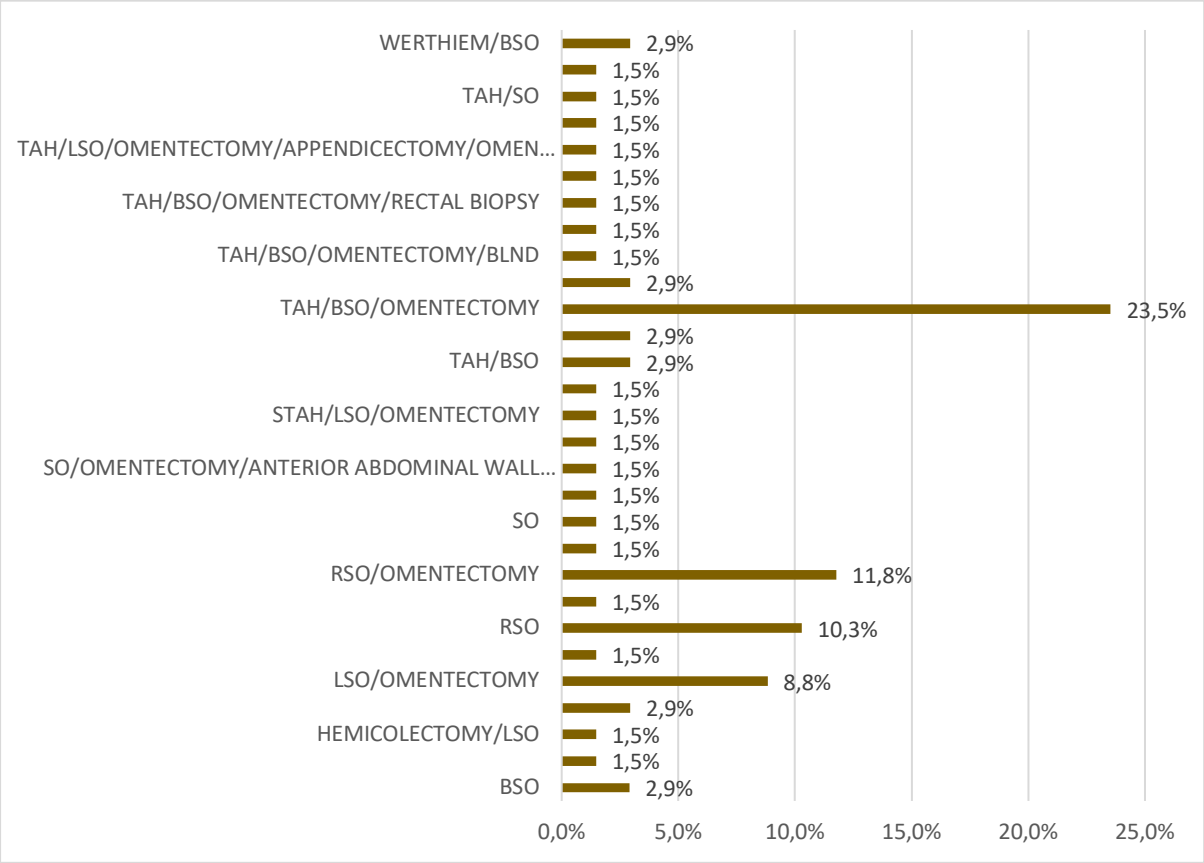


Figure 4: Types of surgery performed in patients with solid ovarian tumors

Discussion

There is a lack of data regarding the prevalence and histopathological characteristics of solid ovarian tumours in Africa, including South Africa. The available research either focuses on all ages or includes other non-solid ovarian tumours. In our study, we observed an increasing trend in the frequency of solid ovarian tumours with advancing age, with a mean age of diagnosis at 31.88 years (± 6.573). Unlike other studies conducted within the South African population without age limits, our study specifically focused on Adolescents and Young Adults (AYA). A study conducted by Gizaw *et al*. in 2024 reported a mean age at diagnosis of ovarian tumours of 51.2 years (± 17.4) in an Eastern Cape- Province in South Africa. Consistent with the International Ovarian Tumours Analysis (IOTA) classification, it is not

surprising that the highest percentage (67.4%) of cases in our study cohort, involving AYA, were malignant, indicating that monographically solid tumours are likely to be histopathologically malignant.

Borderline tumours constituted 23.5% of cases, approximately a third of the malignant counterparts. This is concerning considering the relatively young age group in which the study was conducted. Interestingly, the benign tumour group constituted only 11.8%. Our findings differ significantly from a study conducted by Itha *et al*. in 2019, which reported a benign tumour frequency of 76%, with malignant and borderline tumours accounting for 14% and 10%, respectively. This difference can be explained by the fact that the majority (63%) of their participants had cystic tumours, which according to the IOTA classification, are likely to be benign. Sushma and colleagues, however, found that among solid tumours, 60.5% were malignant, while 36.8% were benign. Their findings align more closely with ours.

As for tumour laterality, the right ovary was involved in 36.8% of patients, followed by the left (25%). Both ovaries were affected in less than a quarter (23.5%) and undocumented in the rest of the patients. Although some studies have noted a higher incidence of involvement of the right ovary, we believe that there is no scientific explanation for this observation, and it could simply be an incidental finding. Furthermore, we did not find any statistical significance between laterality and age groups (p-value 0.215) however data on tumour laterality was not reported in 14.7% of patients. In this study, surface epithelial tumours accounted for 55.9% of ovarian tumours, followed by germ cell tumours (17, 25%). Our findings are in line with studies conducted by Abena and colleagues in Ethiopia. Mucinous adenocarcinoma was the most common malignant tumour (11/68; 16.2%). This differs from a retrospective study by Pillay et al. conducted at CMJAH, which showed that serous adenocarcinoma was the most common malignant tumour. However, this study analysed all age categories, which may explain the observed difference.

Fertility-sparing surgery (FSS) is a reasonable option for women of reproductive age who present with ovarian tumours. The primary goal of FSS is to preserve organ function (uterus and ovary) and maintain sexual and psychological well-being. Assessing the effectiveness and safety of FSS in ovarian tumours of adolescents and young adults inherently involves exploring the various surgical approaches available. These approaches range from cystectomy and unilateral salpingo-oophorectomy to bilateral salpingo-oophorectomy, with the surgical decision often guided by tumour type, size, and malignancy extent. These

procedures, which increasingly characterize modern management of ovarian tumours in adolescents and young adults, replace traditional tumour resections. In our study, we found that TAH/BSO/Omentectomy was the most commonly performed operative procedure, accounting for 23.5% of cases. This finding is not surprising considering the high rates of malignant tumours observed.

Study limitations.

This was a retrospective study and by default has many limitations including incomplete information and loss of records.

Conclusion

This study uncovered an increasing trend in solid ovarian tumours among adolescents and young adults (AYA), with the highest incidence (38.2%) observed in the age group of 36-40 years. Epithelial cell tumours were found to be the most common, followed by germ cell tumours and sex cord/stromal tumours. The majority of these tumours were malignant. The most frequently performed surgical procedure was AH/BSO/Omentectomy, although half of the patients underwent fertility-sparing surgery. It is crucial to rule out malignancy in adolescent and young women who present with solid ovarian tumours.

Disclaimers

Histopathological data was sourced from a pre-existing cancer prevalence database. This database was collated for a project titled: “Malignant solid tumours in young adult South Africans (16-40 years) - A 7-year audit on histopathological records of patients seen in three academic hospitals of the University of the Witwatersrand circuit.”

Acknowledgements

The National Health Laboratory Service is highly appreciated for granting permission to use their data to conduct this study.

Funding

No external funding was obtained for this project. All expenses were the responsibility of the principal researcher.

Conflict of Interest

The authors affirm no conflict of interest.

Ethical considerations:

Ethical approval was granted by the University of Witwatersrand Human Research Ethics Committee (M220726). Further approval was granted by the NHLS. The study was also registered with the National Health Research Database online. The data was stored in a password-controlled computer. No patients were interviewed or contacted to augment any missing information.

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Submitted manuscripts that are not in the correct format and without the required supporting documentation specified in these guidelines will be returned to the author(s) for correction and will delay publication.

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Named authors must consent to publication by signing a covering letter which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**); and

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All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated as follows: No funding source to be declared.

RESEARCH ETHICS COMMITTEE APPROVAL

The submitting author must provide written confirmation of Research Ethics Committee approval for all studies including case reports. The ethics committee as well as the approval number should be included. Please provide the Ethics Committee approval letter.

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The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

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Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles

Original articles on research relevant to surgery should not exceed 3 000 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 250 words. Five keywords should be included.

Scientific letters/short reports

Short reports should not exceed 1 500 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings, Background, Methods, Results, and Conclusions, is a requirement and should not exceed 250 words. Five keywords should be included.

Case reports

Case reports should not exceed 1 500 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version. Five keywords should be included.

Video case reports (SAJS-VIDEO)

Video case reports should not exceed 1 500 words with 10 references and 6 figures. Heading should include Summary (not exceeding 100 words) and Case description (with three subheadings: Introduction, Case presentation and Discussion). The video file format must be only MP4 or MOV and should not exceed 300 MB and 8 minutes. Video case reports will be published online only. The summary and the URL will appear in the printed version. Five keywords should be included.

How to do it

How to do it submissions should address a practical aspect of surgical or interventional (endoscopic or radiological) patient management in which a best practice technique or method to advance optimal patient management is presented in a standardised format. The submission should be structured with a short contextual introduction focussing on the indications for the procedure, followed by numbered sequential points that explain and illustrate the procedure and its complications. The total word count should not exceed 1500 words with a maximum of 10 references and 6 figures. Five keywords should be included.

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Letters to the editor should be 400 words or less with only one image or table.

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- ORCID number of ALL authors must be provided – if authors do not have ORCID, please register at https://orcid.org/.
- Disclaimers: Acknowledgements, Declaration of conflict of interest, Funding declaration, Ethics declaration and ORCID.
- *A signed copy of the title page including the declarations must be provided in PDF format. An unsigned copy of the title page MUST be submitted in MSWord format.*

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All 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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Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age) should also be preceded by a space e.g. > 20 years. No spaces should precede ± and °, i.e. '35±6' and '19°C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

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Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

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ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

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Figures must be numbered in Arabic numerals (1,2,3, …) and referred to in the text e.g. '(Figure 1)'. Figure legends: Figure 1: 'Title...'. All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft PowerPoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists may be generated with the use of reference manager software, but the final document must be delinked from the reference database or otherwise generated manually. Citations should be inserted in the text in numerical order as superscript numbers, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] The superscript reference number should come after the punctuation mark.

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link.** Authors are encouraged to use the DOI lookup service offered by **CrossRef**. Crossref DOIs should always be displayed as a full URL link in the form https://doi.org/10.xxxx/xxxxx

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A covering letter to the editor is mandatory and must include statements that the manuscript has not been published previously and is not under review elsewhere. It should state details of any prior publication of the research in abstract form or in Congress proceedings. The letter must declare if any of the authors have a conflict of interest and that the requirements for submission, including ethics approval and patient permission for case reports have been fulfilled. All authors must sign the covering letter.

Please provide the names and email addresses of three possible reviewers for this manuscript.

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CHAPTER 3 – PROTOCOL

Literature Review and Background

By definition, solid tumours are abnormal mass of tissue that usually does not contain cysts or liquid areas. These may be benign (not cancerous), or malignant (cancerous). Examples of solid tumours include sarcomas, carcinomas, and lymphomas. The term solid tumour is used to distinguish between a localized mass of tissue and fluid properties of the organ affected such as the case in leukaemia. (1)(2)

The ovary is reported as a frequent site of both primary and metastatic solid tumours of the female genital tract. It may present with diverse histological types. It is reported that malignant ovarian tumours are one of the leading causes of death from female solid cancers. (3)(4) The risk of malignancy in solid ovarian tumours (SOT) is more common than other tumours such as the fibroma as opposed to Brenner's and other non-epithelial tumours. (5)

Incidence of Ovarian tumours

A 30 years retrospective study from 1971 to 1990 reported that the overall incidence of SOTs in this study's cohort was 23.4% of all the ovarian tumours. Benign lesions were surprisingly few with only 16.2% reported and the rest (83.8%) were malignant. Epithelial ovarian tumours (EOT) were even in that period the commonest (28.2%) followed by germ cell tumours (22.2%), sex cord stromal tumours (21.4%), metastatic tumours (19.7%) and non-specific tumours (8.5%). (6)

Varied morphological picture has been seen in other solid ovarian tumours such as endometrioid carcinoma. Dysgerminoma constituted 6.8% of solid ovarian tumours. There was a negligible percentage of cases of Gliomatosis peritonei in cases of immature teratoma. Granulosa cell tumours were reported as 11.1% of all the solid ovarian tumours. (6)

Incident and age

The average age for SOTs ranged from below 15 years to 45 years depending on the histological subtype. (6) With regard to solid tumours in the general population inclusive of males, the general incidence of solid tumours is known to differ in age groups and by gender. In females, central nervous system tumours are common in those under 15years of age and carcinomas are common in the older age groups. For age groups 0-14, gender- specific solid tumours such as gonadal germ cell tumours have been reported to be commonest followed by non-gonadal germ cell tumours, and central nervous system tumours (8.6%, 5.4%, and 2.2% respectively) whereas the group 15-24-year-olds have a female-specific increases for melanoma, osteosarcoma and thyroid cancer (4.6%, 3.5% and 2.8% respectively). (7)

Presentation

Women with solid ovarian masses or cancers often present with abdominal symptoms. More than 60% of cases are likely to present with abdominal pain/discomfort. About 54% report abdominal distension. Pain and lump or growth in the abdomen are also common presenting symptoms. Ascites is often seen in those tumours that are malignant unless a benign cyst has ruptured. Few cases (about 8%) present with associated menstrual disturbances which may include amenorrhea, polymenorrhea, dysmenorrhea and metrorrhagia as defined. (3) (4)

Histological Classifications

SOTs are histologically classified into epithelial, sex cord-stromal tumours, germ cell tumours or metastatic. The sex cord-stromal tumours include granulosa cell tumours of adult type and malignant Sertoli cell tumour as the commonest. (8)(9) In the benign subgroup of solid ovarian tumours, the most common histopathological type are the benign serous cystadenomas (18.8%) whereas the commonest malignant types are serous carcinomas. (10)

The prevalence of diagnosed mucinous carcinoma is significantly higher in perimenopausal women (77%) compared to postmenopausal women (23%) ($p < 0.0001$) and borderline ovarian cancer are common in premenopausal women compared to postmenopausal women ($p < 0.0001$). The malignant variant of Borderline ovarian tumour (BOT) is also diagnosed commonly in women before their ages of 40 years. (11)

Lymphomas are cancers of the lymphatic tissues that make up the body's lymphatic system. These are broadly divided into Hodgkin's disease and non-Hodgkin's lymphomas. They may affect peripheral nodes, the neck, armpit, or groin. They are common in younger children. The Non-Hodgkin's subtype may also occur in organs systems such as the liver, spleen, bone marrow, lymph nodes, central nervous system, and bones. (12)

Solid Ovarian tumours histological classification and age

Unilateral tumours are commonly seen in benign lesions and the majority of both benign and malignant tumours are likely to be right sided. (1) The majority of benign lesions are seen in young women in the age ranges between 20-39 years and patients are generally under the age of 40 years. (3)

The epithelial ovarian tumours are commonest in women less than 40 years of age, involving approximately 10% in ages 10-20 years range, 13% in ages 21-30 years rang, 35% in the ages 31-40 years range, 30% in the ages 41-50 years range and 12% in the women 51 years and older. These tumours are about 40% of all ovarian tumours, with sex-cord stromal tumours comprising about 9%, germ-cell tumours about 4%, and others, 1% (including primary leiomyomas of the ovaries). (13) (14)

In a 2015 study, over 58% of benign ovarian neoplasms were seen in patients younger than 40 years of age. Non-neoplastic ovarian lesions occurred in all age groups but were commonest in the age group 20-40 years. These lesions accounted for more than 68% of all ovarian tumours. (3)

Imaging in solid ovarian tumours

Ovarian solid tumors of variable histological types including benign and malignant provide characteristic findings on imaging including MR imaging. Several ovarian solid tumors show characteristic findings. However, some findings may be similar or not vary with different histological characteristics and the correct diagnosis may sometimes be difficult. Some findings to differentiate between benign and malignant tumors include low signal intensity (SI) within solid tissue on T2-weighted imaging (T2WI) that suggests that the tumor is benign. (15)

Justification of the study

The commonest known histological subtypes of solid ovarian tumours in women of all ages are documented in literature as benign. The incidence of malignant lesions is low in women less than forty years. Our institution presents a unique environment due to high population of women from different races as well as a significant population of women from other African regions who may present differently from South African women in both the histological types of tumours and clinical presentation and other parameters. However, such is not documented and this study offers the opportunity for us to explore the hypothesis that seeks to suggest that characteristics of solid ovarian tumours in this population cohort will be different from what is documented in the available literature.

Study aim

The aim of the study is to review the solid ovarian tumours from women who were managed at Johannesburg tertiary hospitals over the past 7 years with regards to histology, clinical characteristics and how they were managed.

Objectives of the study

Primary study objective

- To describe the histological characteristics of solid ovarian tumours in patients investigated and managed in our setting.

Secondary study objectives

- To describe the demographics of the subjects in our study.

- To compare malignant and benign rate in age groups younger than forty.

Research Methods

Research Design

This will be a retrospective descriptive study of solid ovarian tumour data collected over the period of seven years from three academic hospitals in Johannesburg (Charlotte Maxeke Johannesburg Academic, Rahima Moosa Mother and Child and Chris Hani Baragwanath Academic Hospitals.)

Study Site

Data from the following three academic hospitals in Johannesburg will be analysed: Chris Hani Baragwanath Academic Hospital (CHBAH), Rahima Moosa Mother and Child Hospital (RMMCH), and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Study Population

The study population will include patients who are by definition considered adults (more than 16 years old) older than 16 diagnosed with ovarian tumours at CHBAH, RMMCH, and CMJAH. This study will include women of all races and countries all countries of origin. Patients who fall below the inclusion age of 16 will be excluded from the study and those with no confirmed diagnosis.

Study Period

Data will be collected retrospectively from 1st January 2011 to 31st August 2017 limited to the confirmed available data.

Sampling

This will be a convenience sample of the data sourced from an already existing cancer-prevalence database whose gatekeeper is Prof T Luvhengo from the Department of Surgery. This database was collated for a project titled: "Malignant solid tumours in young adult South Africans (16-40 years) - A 7-year audit on histopathological records of patients seen in three academic hospitals of the University of the Witwatersrand circuit". Therefore, it is expected that our study will meet the inclusion criteria as it was designed in line with the primary study. It is expected, based on the size of the database, that there will be in excess of 1000 cases that meet the criteria.

Data Collection Process

Data from the database will be extracted and stored onto a Microsoft Excel document (2019). Data will then be sorted, cleaned and coded. The data will be analysed using STATA 15® (College Station, Texas, USA)

Data analysis plan

The following data are expected to be obtained: 1. Patient age, sex, and race 2. The date of diagnosis 3. Histopathology report of cancer type and subtype (where applicable), and tumour location on the patient's body site/location (left or right) 4. Recorded risk factors

Data will be managed and analysed in STATA 15® Software (College Station, Texas, USA). The demographic characteristics and clinical factors will be analysed. All the categorical variables will be summarised using frequencies and percentages, whilst continuous variables will be described using means (with standard deviations) for normally distributed data and medians (with inter-quartile range [IQR]) for non-normally distributed data.

The trends in cases of solid ovarian tumours will be described by plotting the number of cases of each type against the month and year, using a scatter plot. Appropriate regression analysis techniques will be used to test the statistical significance of the trend in cases.

We will describe the histological type by calculating the percentage of the malignant versus benign tumours and compare them through the association (with Chi2 calculation) of each histological type with the anatomical site, age, race, other risk factors and management. A p-value of 0.05 will be used as a significance level.

Histograms will be used to compare the calculated percentage of malignant versus benign lesions in the age groups less than 40.

Study Limitations

Only the data captured from the previous study can be collected and analysed, hence limiting the amount of data that can be collected.

Ethics

The study will only commence after approval by the Charlotte Maxeke Johannesburg Academic hospital's office of the CEO and received clearance from the University of Witwatersrand Human Research Ethics Committee. The data requested for this research project was collated as part of a study on malignant solid tumours in young South Africans, aged 16-

40 (HREC clearance certificate number: M170923). Application to access data will be made to the gatekeeper. The gatekeeper will also be the research supervisor and co-author of the paper to be published. The study will also be registered with the National Health Research Database online. The data will be stored in a password-controlled computer. No patients will be interviewed or contacted to augment any missing information.

Timelines/Gantt Chart

	Mar '22	April	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan '23	Feb
Protocol preparation												
Submission to Committee												
Corrections												
Ethics and Hospital application												
Data collection												
Data analysis												
Write-up and submission												

Project Funding

No external funding for the project is applied for, obtained, or needed. All expenses related to printing, data collection, data analysis, publication, and travel, will be the responsibility of the principal researcher. The estimated budget for the study is approximately as follows. The principal investigator will apply for funding for publication from the University of Witwatersrand School of Health Sciences. The budget will include:

	Quantity	Cost per unit	Subtotal
Travel			R3000
Printing and photocopy	900	0.50	R450
Professional editing and proof reading	1	R3000	R3000
Publication	1	R6000	R6000
Total Cost			R 19450

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APPENDIX A: DATA COLLECTION SHEET

Study number: ☐

Age (in years)											
Race	African		Caucasian		Indian		Coloured				
Anatomical site of tumor	R Ovary		L Ovary		Both						
If Secondary, Primary site	Endometrium	Appendix	Liver	Bowel	Others						
Type of diagnosis	Biopsy		Excision								
Histology report at diagnosis	Benign		Borderline		Malignant						
	Histological type										
Surgery done											

Final histological report	Benign		Borderline		Malignant	

Outcome	

APPENDIX B: HOSPITAL APPROVAL

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: *Ms N. Mzila*
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 13 August 2022

Dear Dr Motlhokomedi Morapedi

RE: PROVISIONAL APPROVAL OF STUDY

TITLE: HISTOPATHOLOGICAL DISTINCTIONS OF OVARIAN SOLID TUMORS AT THREE ACADEMIC HOSPITALS IN JOHANNESBURG

Permission to conduct the above-mentioned study is provisionally granted subject to:

1. Submitting an Ethics Clearance Certificate from the University of Witwatersrand Human Research and Ethics Committee (HREC).
2. Submitting documentation proof of NHRD registration with a GP reference number
3. Submitting the research protocol

Please submit the above documents at your earliest convenient within 3 months from the date of this letter. This will prompt the Chief Executive Officer (CEO) of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) to grant you a final approval. It is important to note that your research can only commence once a final approval is granted. Failure to comply with the above-stated requirements may result in the withdrawal of your application.

Supported / ~~Not Supported~~

Signed by:Jayshina Punwasi
Signed at:2022-08-15 07:33:55 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Senior Clinical Manager

Approved / ~~Not Approved~~

Signed by:Gladys Magugudi Bogoshi
Signed at:2022-08-16 13:28:13 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms. G Bogoshi
Chief Executive Officer: CMJAH

APPENDIX C: ETHICS APPROVAL

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Drs M Morapedi and V Maringa School of Clinical Medicine Department of Obstetrics and Gynaecology Medical School University E-mail: thokot2010@gmail.com
CC:	Supervisor: Professor T Luvhengo and Dr L Mbodi <Thifhelimbilu.Luvhengo@wits.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2022/09/05
REF:	R14/49
PROTOCOL NO:	**M220726** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Histopathological distinctions of ovarian solid tumors at three academic hospitals in Johannesburg*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

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UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Drs M Morapedi and V Maringa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220726

NAME: (Principal Investigator)	Drs M Morapedi and V Maringa
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Medical School University
PROJECT TITLE:	*Histopathological distinctions of ovarian solid tumors at three academic hospitals in Johannesburg*
DATE CONSIDERED:	2022/07/29
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor T Luvhengo and Dr L Mbodi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/09/05

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **July** and therefore reports and re-certification will be due in the month of **July** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

APPENDIX D: PERMISSION TO ACCESS DATA

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

University of the Witwatersrand

Department of Surgery: Charlotte Maxeke Johannesburg Academic Hospital

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6th July 2022

To: The Chairperson
Human Research Ethics Committee
University of the Witwatersrand
Jubilee Road
Parktown
Johannesburg

Dear Professor Penny

Re: Access to data for secondary analysis (Dr. Morapedi and Ovarian Solid Tumours)

Good day. **This is to confirm that we have data that was used for the study titled*: "Malignant solid tumours in young South Africans (16-40 years) – A 5 years audit based on histopathological records of patients seen in three academic hospitals of the University of the Witwatersrand circuit".*** The study received prior ethics approval **(M170923)** on the 29/09/2017 and was done for an MMed (Surg) by Dr. Gabriel. Dr. Ugare has completed the MMed and has left Wits. Dr. Thifhelimbilu Luvhengo was the main supervisor of the study. The study was recently published in a peer-reviewed journal. Dr. Ugare looked at all malignant tumours broadly. Dr. Morapedi would like to look specifically at ovarian tumours. The data we received and have from the National Health Laboratory services cover the period January 2011 to June 2017.

We therefore would be prepared to share the data specifically for ovarian tumours once Dr. Morapedi has obtained HREC approval. Thank you very much for your understanding.

Yours faithfully

Dr. T E Luvhengo
Clinical Head of Department of Surgery
Charlotte Maxeke Johannesburg Academic Hospital

APPENDIX E – TURNITIN REPORT

SAJS Article_Morapedi Draft 4 final.docx

ORIGINALITY REPORT

10%	9%	9%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	3%
2	Shisana Baloyi, Afra Basera, Sheynaz Bassa, Meshack Bida et al. "Contributors", Elsevier BV, 2024 Publication	1%
3	Prasanthi, Chidipudi. "Histomorphological Patterns of Ovarian Tumors- a Case Series", Rajiv Gandhi University of Health Sciences (India), 2023 Publication	1%
4	Zamalunga Lunga, Maritz Laubscher, Simon Matthew Graham, Michael Held, Nando Ferreira, Ramanare Magampa, Sithombo Maqungo. "Optimising the Orthopaedic Trauma Society Open Fracture Classification system: a proposal for modification in the context of high civilian gunshot fractures", European Journal of Orthopaedic Surgery & Traumatology, 2024 Publication	1%