The Rate and Risk Factors for Local Recurrence of Phyllodes Tumours in a South African Population

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MMed Masters in Medicine in Surgery

Declaration

I, Janice Spinks, do hereby declare that this research report is my own work. It is being submitted for fulfilment of the requirements for the degree of Masters in Medicine in Surgery in the Faculty of Health Sciences at the University of the Witwatersrand, Johannesburg, South Africa. Any assistance that I received is stated in the acknowledgements. This work has not previously been submitted for any degree or examination at this, or any other, University. I certify that the protocol has been approved by the Human Research Ethics Committee (Medical) at the University of the Witwatersrand, Johannesburg (Appendix; Ethics Clearance Certificate number M160122).

Signed by: ..... Janice Spinks

On this the 9th.....day of...October.....2019

Acknowledgements

I would like to thank Professor J Oettle, Dr Sarah Rayne and Dr Kirstin Fearnhead for editing assistance, the Department of Biostatistics at the University of the Witwatersrand for help with the statistical analysis, and Professor Hale and his Department of Anatomical Pathology, National Health Laboratory Service, University of Witwatersrand, Johannesburg for the use of their data.

Abstract

Background: Phyllodes tumours are rare fibroepithelial neoplasms of the breast. The dilemma with phyllodes tumours is their tendency to local recurrence. This retrospective review of phyllodes tumours in a South African population aims to describe the most common histological and clinical features, and describe the clinical and histological risk factors for local recurrence.

Methods: All histological reports of patients diagnosed with a phyllodes tumour after surgery at the University of the Witwatersrand Anatomical Pathology Laboratories in Johannesburg were assessed from 1 January 2005 to 30 June 2016. Clinical and histological parameters were analysed.

Results: Over the study period, 185 patients were identified. The median age of the patients was 42 years. There were 89 (48.1%) patients with a benign tumour, 34 (18.4%) with a borderline tumour and 62 (33.5%) with a malignant tumour. The size of the tumours ranged from 11 to 460mm, with a median of 85.0mm ± 79.6 SD. Breast conserving surgery (BCS) was performed on 64.3% of patients and 35.7% of patients had a mastectomy. There was an overall local recurrence rate of 3.78% (2.2% for benign and 8.1% for malignant tumours). No clinical or histological factors, including margin status, were found to significantly predict local recurrence. Most recurrences (71.4%, n=5) occurred within the first two years.

Conclusion: Our study did not find any predictors of local recurrence, but we provide further support to the recent suggestion of revising the common practice of wide local excision with a 1cm margin, to an excision with negative margins combined with close follow-up for two years.

Word Count: 255

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Abbreviations

FNA Fine Needle Aspirate

HPF High Power Field

MRI Magnetic Resonance Imaging

NHLS National Health Laboratory Service

NOS Not Otherwise Specified

WHO World Health Organisation

WLE Wide Local Excision

Section 1: Draft article to *World Journal of Surgery*

The Rate and Risk Factors for Local Recurrence of Phyllodes Tumours in a South African Population.

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Cover Letter to the Editor

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John G Hunter
Editor-in-Chief
World Journal of Surgery
9th October 2019

Dear John G Hunter

I am pleased to submit an original research article entitled "The Rate and Risk Factors for Local Recurrence of Phyllodes Tumours in a South African Population" by Janice Spinks, Kirstin Fearnhead and Sarah Rayne for consideration for publication in *World Journal of Surgery*. Phyllodes tumours are rare fibroepithelial neoplasms of the breast. One of the problems with this group of neoplasms is their tendency to locally recur, therefore 1cm resection margins have been advocated to prevent this. However, more recent studies have challenged this and recommended obtaining a negative resection margin but not necessarily a specific length. This manuscript describes the Johannesburg, South African experience with phyllodes tumours.

In this manuscript, we identified 185 patients with a phyllodes tumour between 2005 and 2016. And we had an overall local recurrence rate of 3.78% (2.2% for the benign tumours and 8.1% for the malignant tumours). No clinical or histological factors were found to significantly predict local recurrence.

We believe that this manuscript is appropriate for publication by *World Journal of Surgery* because it is an original scientific paper, it is one of the largest series recorded, and it is only the second paper written about phyllodes tumours in the South African population. It adds to the work done by Jang *et al.* and Moutte *et al.* that shows that 1cm resection margins are probably unnecessary, and recommends that a negative resection margin, irrespective of the length, should be obtained when excising a phyllodes tumour, followed by close follow up for 2 years to look for local recurrence.

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Thank you for your consideration.

Sincerely,

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Abstract

Background: Phyllodes tumours are rare fibroepithelial neoplasms of the breast. The dilemma with phyllodes tumours is their tendency to local recurrence. This retrospective review of phyllodes tumours in a South African population aims to describe the most common histological and clinical features, and describe the clinical and histological risk factors for local recurrence.

Methods: All histological reports of patients diagnosed with a phyllodes tumour after surgery at the University of the Witwatersrand Anatomical Pathology Laboratories in Johannesburg were assessed from 1 January 2005 to 30 June 2016. Clinical and histological parameters were analysed.

Results: Over the study period, 185 patients were identified. The median age of the patients was 42 years. There were 89 (48.1%) patients with a benign tumour, 34 (18.4%) with a borderline tumour and 62 (33.5%) with a malignant tumour. The size of the tumours ranged from 11 to 460mm, with a median of 85.0mm ± 79.6 SD. Breast conserving surgery (BCS) was performed on 64.3% (n=119) of patients and 35.7% (n=66) of patients had a mastectomy. There was an overall local recurrence rate of 3.78% (n=7/185) (2.2% (n=2/89) for benign and 8.1% (n=5/62) for malignant tumours). No clinical or histological factors, including margin status, were found to significantly predict local recurrence. Most recurrences (71.4%, n=5) occurred within the first two years.

Conclusion: Our study did not find any predictors of local recurrence, but we provide further support to the recent suggestion of revising the common practice of wide local excision with a 1cm margin, to an excision with negative margins combined with close follow-up for two years.

Word Count: 255

Background

Phyllodes tumours are rare fibroepithelial neoplasms of the breast. According to the World Health Organization (WHO), phyllodes tumours account for 0.3-1% of primary tumours of the breast in western countries [1]. They affect middle-aged (40-50 years old) women and are classified according to the WHO Classification system [1-2]. The histological features used are: tumour border, stromal cellularity, stromal atypia, mitotic activity, and stromal overgrowth, which classifies the tumour into one of three categories: benign, borderline and malignant [1]. (Table 1) Although the parameters of the classification are clear, there remains inter-pathologist variation in its application. [3]

Table 1 Histological features of Phyllodes Tumours [1]

Histological Feature	Benign	Borderline	Malignant
Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Tumour border	Well defined	Well defined, may be focally permeative	Permeative
Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic activity	<5 per 10 HPF	5-9 per 10 HPF	≥10 per 10 HPF
Stromal overgrowth	Absent	Absent or very focal	Often present

HPF high-power field

Due to the relative rarity of phyllodes tumours, there are currently no published treatment protocols for phyllodes tumours, and treatment principles are based primarily on retrospective studies and case reports. Surgery is the mainstay; however, the extent of surgery has been questioned. Currently, the recommendation is to excise the tumour with 1cm margins or perform

a mastectomy if the size of the tumour makes breast-conserving surgery with an acceptable cosmetic result impossible [4-9].

The dilemma with phyllodes tumours is their tendency to local recurrence. According to the WHO, the overall rate of local recurrence is 21%, more specifically, 10-17% for benign lesions, 14-25% for borderline lesions and 23-30% for malignant lesions [1]. Because the risk of local recurrence is high even for the benign variant, much research has been done to elicit the risk factors for local recurrence. Surgical margins, nuclear atypia, stromal overgrowth, numbers of tumours, histology, tissue border and pleomorphism have been shown to be associated with local recurrence [1,5, 10-11]. The only data from South Africa was published in 1999, by de Roos *et al* and describes a retrospective analysis of 37 patients with phyllodes tumours from 1975 to 1996 [7]. We aim to supplement this relatively small sample with a greater sample to describe the presentation of phyllodes tumours in South Africa and review the pertinence of factors associated with recurrence in surgical decision-making.

Method

A retrospective review was performed on the histological reports of patients diagnosed with a phyllodes tumour after surgery at the University of the Witwatersrand National Health Laboratory Service (NHLS) Anatomical Pathology Laboratories in Johannesburg, from 1 January 2005 to 30 June 2016. A Systematized Nomenclature of Medicine - Clinical Terms (SNOMED-CT) search was performed on the NHLS database of all pathology specimens processed for “phyllodes NOS (not otherwise specified)”, “phyllodes benign” and “phyllodes malignant”. 301 histological reports were identified from this search. Core biopsies were excluded (n=104) as non-contributory, due to lack of important parameters such as definitive grading, border, and margins. Double entries (n=5) and reports of local recurrence (n=7) were

also excluded, therefore 185 histological reports were used for the data analysis as illustrated in Figure 1. From the histological reports the outcomes listed in Figure 1 were collected, as risk factors for local recurrence described in previous studies [1,5,10-11]. Cases of local recurrence were identified during the SNOMED search, as a second entry for a patient, matched for name and date of birth, as well as a description in the clinical scenario describing that this was a recurrence.

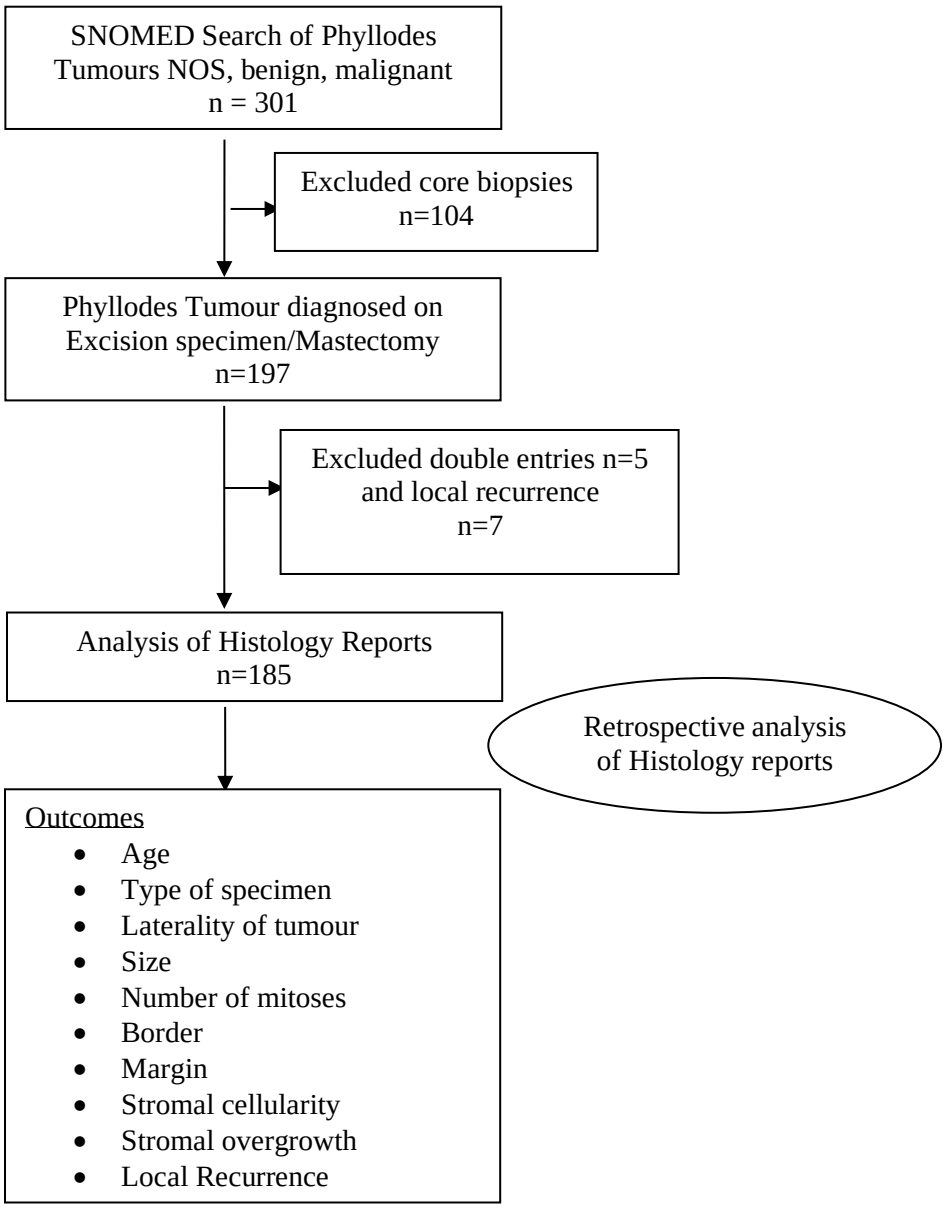

Figure 1 Consort Diagram

Age and histological features of both benign and malignant tumours that recurred versus those that did not was performed using a t-test and Fisher's Exact test as appropriate. A p-value <0.05 was considered statistically significant. All statistical analysis was performed using the statistical package STATA Version 14.2 (College Station, TX).

Results

From 1 January 2005 to 30 June 2016, 185 patients had a histological diagnosis of a phyllodes tumour confirmed at excision. Of these,184 were female and 1 was male with a median age of 42 years (range of 12 to 84 years). Histological categorisation were predominantly benign (48.1%; n=89) with 18.4% borderline tumours (n=34) and 33.5% malignant tumours (n=62). The size of the tumours ranged from 11 to 460mm, with a median of 85.0 mm ± 79.6 SD. Further clinical and histological features are shown in Table 2.

Only 11.3% of reports had a full set of histological characteristics described. The border and stromal overgrowth were the most poorly commented on with border mentioned in only 30.2% of reports (n=56) and stromal overgrowth in 46.5% (n=86). Margin measurement was only reported on in 82.2% of the reports, and of these 29.2% (n=54) were positive. These positive margins were fairly evenly distributed amongst the three groups (benign 35.9%, borderline 23.4%, malignant 22.6%). Very few patients had the commonly recommended 10mm margin: 11.2% of the benign cases (n=10), 8.8% of the borderline cases (n=3) and 21.0% of the malignant phyllodes cases (n=13).

Table 2 Clinicopathologic Characteristics

	Benign (n = 89) No. (%)	**Borderline (n = 34)** No. (%)	**Malignant (n = 62)** No (%)	**Total (n=185)** No (%)
Total	89	34	62	185
Gender				
Male	1	0	0	1 (0.5)
Female	88	34	62	184 (99.5)
Site				
Left	42 (47.2)	17 (50)	40 (64.5)	99 (53.5)
Right	40 (44.9)	15 (44.1)	19 (30.6)	74 (40.0)
Not stated	7 (7.9)	2 (5.9)	3 (4.8)	12 (6.5)
Surgery				
Excision	80 (89.9)	20 (58.8)	19 (30.6)	119 (64.3)
Mastectomy	9 (10.1)	14 (41.2)	43 (69.4)	66 (35.7)
Border				
Pushing	15 (16.9)	14 (41.2)	7 (11.3)	36 (19.5)
Infiltrative	1 (1.1)	2 (5.9)	17 (27.4)	20 (10.8)
Not stated	73 (82.0)	18 (52.9)	38 (61.3)	129 (69.7)
Margin				
At least 0.1mm	9 (10.1)	7 (20.6)	10 (16.1)	26 (14.1)
At least 1.0mm	13 (14.6)	11 (32.4)	20 (32.3)	44 (23.8)
At least 10.0mm	10 (11.2)	3 (8.8)	13 (21.0)	26 (14.1)
Positive	32 (35.9)	8 (23.4)	14 (22.6)	54 (29.2)
Not stated	25 (28.9)	5 (14.7)	5 (8.0)	35 (18.8)
Stromal cellularity				
Mild	51 (57.3)	4 (11.8)	0 (0)	55 (29.7)
Moderate	19 (21.3)	18 (52.9)	1 (1.6)	38 (20.5)
Marked	3 (3.4)	3 (8.8)	44 (71.0)	50 (27.1)
Not stated	16 (18.0)	9 (26.5)	17 (27.4)	42 (22.7)
Stromal Overgrowth				
Negative	16 (18.0)	7 (20.6)	3 (4.8)	26 (14.1)
Positive	18 (20.2)	13 (38.2)	29 (46.8)	60 (32.4)
Not stated	55 (61.8)	14 (41.2)	30 (48.4)	99 (53.5)

There were seven detected cases of local recurrence with an overall local recurrence rate of 3.78% (n=7/185); five were malignant (8.1%, n=5/62), two were benign (2.2%, n=2/89) and no borderline phyllodes recurred. The median time for local recurrence in malignant phyllodes was eight months, versus 21 months for the benign phyllodes.

Table 3 compares the features of cases of local recurrence with those without recurrence. No histological feature was found to be a significant risk factor for local recurrence. Patients with recurrence of benign phyllodes, when compared to those that did not recur, were significantly younger (mean of 14 years versus 37 years respectively p=0.016), with a marginally larger initial tumour (82.5mm versus 68.1 mm respectively, p=0.317. These features were not present in malignant recurrences (mean age 46 years versus 48 years, p=0.630; mean initial tumour size 156.5 mm versus 155 mm respectively, p=0.357). Three of the malignant cases recurred with histologically more aggressive features than the original tumour, one showing liposarcomatous differentiation, one rhabdomyosarcomatous differentiation, and the third showing osteosarcomatous differentiation.

Table 3 Risk Factors for local recurrence

	Benign Phyllodes (n=89)			Malignant Phyllodes (n=62)		
	No recurrence (n = 87)	Local recurrence (n = 2)	p-value	No recurrence (n = 57)	Local recurrence (n = 5)	p-value
Mean age (years)	37	14	0.016	46	48	0.630
Mean tumour size (mm)	68.1	82.5	0.317	156.5	155	0.519
Surgery						
BCS	78	2		19	2	
Mastectomy	9	0		43	3	
Border			**			0.708
Pushing	15	0		7	0	
Infiltrative	1	0		17	1	
Not stated	71	2		34	4	
Margin			0.545			1.00
Positive	31	1		13	1	
0.1mm or less	9	0		9	1	
0.2- 1.0mm	13	0		19	1	
1.1-10.0mm	9	1		12	1	
Not stated	25	0		5	1	
Stromal cellularity			0.515			0.933
Mild	50	1		0	0	
Moderate	18	1		1	0	
Marked	3	0		41	3	
Not stated	16	0		15	2	
Stromal Overgrowth			0.515			0.751
Negative	16	0		3	0	
Positive	18	1		29	3	
Not stated	55	1		30	2	

**could not be calculated as the border was not commented on in both cases of local recurrence

Discussion

Phyllodes tumours are rare fibroepithelial neoplasms of the breast, known to recur in both their benign and malignant manifestations. Although they account for 0.3-1% of primary tumours of the breast in high-income countries [1], less is known about these tumours' clinical and histological behaviour globally. In this study, describing the largest cohort of patients from a

limited-resource setting, we found that less than 4% of tumours recurred in total, despite large sizes at presentation and often sub-optimal excision margins.

Despite a similar age range as described by the WHO [1], the average size of phyllodes tumours at the time of diagnosis is normally 40-50mm, although lesions as small as 20mm may be picked up in high-income areas where there is mammographic screening[1]. In our study the average size of tumours was significantly larger than this, with a mean of 106mm, and this may be due to lack of screening, lack of awareness of breast symptoms and difficulty accessing healthcare, which have all been noted in studies of breast disease in this community [12-13].

As mentioned previously, the dilemma with phyllodes tumours is their tendency to recur locally. In our study, the overall recurrence rate was 3.78%. For our benign lesions it was 2.2% and for malignant lesions it was 8.1%. These figures are far lower than those quoted by the WHO, 10-17% for benign and 23-30% for malignant [1]. The reasons for the low recurrence rate in our study could not be ascertained.

The first two years after the initial surgery has been shown to be the most critical period for follow up, as this is when most tumours typically recur [5]. We found that the malignant phyllodes recurred more quickly than their benign or borderline counterparts, with 60% of the recurring within two years with a median time of 8 months. This is in comparison to the benign tumours, where the two recurrences occurred at 15 and 27 months. These findings would reaffirm the importance of expectant management of all phyllodes tumours for at least two years.

Although surgical margins, nuclear atypia, stromal overgrowth, numbers of tumours, histology, tissue border and pleomorphism have previously been shown to be associated with local recurrence [1,5, 10-11]. In our study, we did not find any relationship between these clinical and histological factors and local recurrence. In particular, many studies have

demonstrated that the risk of local recurrence is directly related to resection margin length. The current guideline is to perform a wide local excision with 1 cm margins, irrespective of the tumour grade or variant [4-9]. However, in recent years many studies have challenged this recommendation. Jang *et al.* in their retrospective review of 164 patients with benign, borderline and malignant phyllodes tumours, compared 0.1mm, 1.0mm and 10.0mm margin lengths and found that only positive resection margins were associated with local recurrence, rather than the size of margin when negative [14] and this has been ratified endorsed in series of patients [15,16]. In addition, Moutte *et al.*, in a retrospective review of 76 patients with benign and borderline phyllodes tumours [17] found a local recurrence rate of 3.94%, also far lower than the 21% reported by the WHO, but more consistent with the findings for this current larger study. In their study, 90% of the patients had negative margins, but the vast majority (71%) had resection margins of <1mm. Therefore, it is recommended that at least for benign and borderline phyllodes tumours, if the resection margin is positive or close, revision surgery should not be done but rather the patients should be closely followed up for 2 years[17], and this current study would provide further support for that.

From this study, resection margin was not found to be a risk factor for local recurrence. (p = 0.545 for benign and p = 1.00 for malignant) Even though there was a high rate of positive margins in our study (29.2%), the local recurrence rate was low. In the benign and borderline cases with a negative resection margin, only 10.6% had a resection margin more than the recommended 10mm margin, however the recurrence rate remained acceptably low.

Preoperative diagnosis of a phyllodes tumour is often very difficult as it may be misdiagnosed clinically or radiologically as a fibroadenoma[18]. Even on needle biopsy, both stromal and epithelial elements need to be present in the core biopsy for diagnosis to be clear

[18]. The high rates of positive or inadequate negative margins seen in our study may indicate that a preoperative diagnosis of phyllodes tumour was not made, and therefore tumours may have been enucleated or excised as a biopsy with no margin. In a retrospective review of 165 patients with benign, borderline or malignant phyllodes tumours in 2011, Guillot *et al.* found that 28% of patients in their study had inadequate margins (<10mm) [18]. Although 52% of these patients had revision surgery, only 16% of those patients were found to have residual disease, indicating that inadequate surgical margins is not a significant risk factor for local recurrence [18]. This is similar to the findings of this current study where although 75.4% of patients had inadequate margins (29.2% positive margins and 46.2% <10mm), our rate of local recurrence was very low (3.78%). Therefore, this further emphasizes that when excising a known phyllodes tumour or a lesion that is suspicious for a phyllodes tumour, negative margins should be obtained but a 10mm margin is unnecessary. Revision surgery to obtain 10mm resection margins should be reserved for patients with positive margins or patients with close margins that may be non-compliant with follow-up.

This study is one of the largest series of phyllodes tumours described in the literature, and a significant contribution to understanding this rare tumour, particularly in a limited-resource setting where presentation is often delayed and tumours large. In addition, pre-operative assessment may mean that primary surgery as an excisional biopsy is carried out for diagnosis and management. From 185 cases only seven cases of local recurrence were found, much lower than that reported by the WHO but similar to that in other studies [17]. It may be that some cases of local recurrence may have presented to other areas of South Africa, and this is a limitation that should be acknowledged, however would be a consistent bias also present in many of the other

studies in the literature. Future research to further characterise this tumour should include a multi-centre review encompassing all major laboratories.

Our study does have some limitations that should be acknowledged before we recommend a change in clinical practice. Firstly, this was a retrospective review of histological reports, and not patient files. Therefore, important information such as preoperative diagnosis, duration of symptoms, and duration of follow up after surgery could not be ascertained. Secondly, as was mentioned before, we only analysed the reports from one academic laboratory in South Africa. To completely characterise phyllodes tumours in the South African setting, we should do a multi-centre review encompassing all major laboratories. Lastly, there were many pathologists involved in analysing the histological specimens. To obtain a more complete data set, without missing parameters, one pathologist should have reviewed all 185 cases. However we did not ethics for this. Therefore, this could be planned as a follow-up study to this current one.

Conclusion

The dilemma with phyllodes tumours is their tendency to locally recur. This is the reason why a 10mm margin has been recommended as the standard of care; to prevent local recurrence. However, in our study we found a much lower rate of local recurrence, as well as showing that margin length is not a risk factor for local recurrence. We provide further support to the recommendation of excising a confirmed phyllodes tumour or a lesion that is suspicious for a phyllodes tumour with a negative margin and closely following the patient up with serial examinations and imaging for two years, rather than performing revision surgery to obtain 10mm margins.

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The authors would like to thank Professor J Oettle for editing assistance, the Department of Biostatistics at the University of the Witwatersrand for help with the statistical analysis, and

Professor Hale and his Department of Anatomical Pathology, National Health Laboratory Service, University of Witwatersrand, Johannesburg for the use of their data.

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Section 2: Appendices

2.1 Approved Research Protocol

Title

The Rate and Risk Factors for Local Recurrence of Phyllodes Tumours in a South African Population.

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2.1.1 Introduction

Phyllodes tumours are rare fibroepithelial neoplasms of the breast. According to the World Health Organization (WHO), phyllodes tumours account for 0.3-1% of primary tumours of the breast in western countries.[1] They affect middle-aged (40-50 years old) women compared to fibroademonas that affect women who are 15-20 years younger.[2] In Asian countries there is a higher prevalence of phyllodes tumours and they occur at a younger age.[1] The only data from South Africa was published in 1999, by de Roos *et al*. It was a retrospective analysis of 37 patients with phyllodes tumours from 1975 to 1996. Due to the small number of patients in the study, additional research is needed in order to gather information on how and when phyllodes tumours present in the South African context, as well as what the rate of local recurrence is as well as what the risk factors are.

Clinical Presentation

The presentation of Phyllodes tumours are similar to other benign breast lesions except that they often present as rapidly growing masses.[3,4] They usually occur in the upper outer quadrant of the breast and have no preference to the right or left breast.[5,6] Due to the rapid growth of these tumours, dilated veins and a bluish discolouration of the skin is common.[1]

Ulceration of the overlying skin is uncommon, but has been documented.[1] Nipple retraction is rare, but a bloody nipple discharge has been documented and is thought to be due to tumour infarction as the tumour grows so rapidly that it outgrows its own blood supply.[1] Palpable lymph nodes are seen in approximately 20% of patients but metastases to lymph nodes are very rare.[7]

Radiological Features

Radiologically, fibroadenomas are difficult to distinguish from Phyllodes tumours on both sonar and mammogram. Both tumours appear as well circumscribed, solid and hyperechoic masses on sonar. On mammography, they both appear as smooth polylobulated masses. The only feature that may favour a Phyllodes tumour is cystic areas seen on sonar.[8] Due to the two entities being difficult to differentiate on sonar and mammography, the role of MRI in identifying Phyllodes tumours in the breast has been increasingly researched. Yaabuchi H *et al* found that malignant Phyllodes tumours are seen as well-circumscribed lesions with irregular walls, and high signal intensity on T1-weighted images and low signal intensity on T2-weighted images.[9] The enhancement pattern of Phyllodes tumours seen on MRI is opposite to that seen in adenocarcinomas, i.e. a rapid enhancement pattern is seen in benign Phyllodes tumours.[9] Although MRI may be useful in differentiating a Phyllodes tumour from a fibroadenoma, in the South African resource-poor setting, access to MRI might be difficult and it may be easier and quicker to obtain a tissue diagnosis.

Tumour Characteristics

Macroscopically, Phyllodes tumours are round to oval multinodular masses that may be impossible to differentiate from a fibroadenoma by the naked eye.[1] However, the tumours have a characteristic leaf-like structure caused by tongues of stroma that protrude through the pseudocapsule of the tumour into normal breast tissue. Microscopically, epithelial lined

cystic spaces with a characteristic intracanalicular growth pattern are seen,[14] and the accompanying stroma shows hypercellularity, relative overgrowth, cytological atypia and increased mitotic count, to varying degrees, relative to a fibroadenoma. Over the years, various classification systems have been devised. Treves and Sunderland were the first to classify these tumours in 1951, into benign and malignant variants.[15] In 1978, Pietruszka and Barnes reclassified Phyllodes tumours into benign, borderline and malignant subgroups.[16] Then, Azzopardi altered this classification system by using the same subgroups, but used different diagnostic criteria for each category.[17] The WHO then developed the classification system that is currently being used by anatomical pathologists in 2003 and a revised version in 2012.[1] It is based on specific histological features of the stromal component, and not the epithelial component of the tumour.[1] The histological features it looks at are: tumour border, stromal cellularity, stromal atypia, mitotic activity, and stromal overgrowth, which classifies the tumour into one of three categories: benign, borderline and malignant.[1] (Table 1)

Table 1 Histological features of Phyllodes Tumours

Histological Feature	**Benign**	**Borderline**	**Malignant**
Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Tumour border	Well defined	Well defined, may be focally permeative	Permeative
Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic activity	<5 per 10 HPF	5-9 per 10 HPF	≥10 per 10 HPF
Stromal overgrowth	Absent	Absent or very focal	Often present

HPF high-power field

Cytological and Histological Diagnosis

In order to obtain a tissue diagnosis of a palpable breast mass, a fine needle aspirate (FNA) or a core biopsy can be performed. A FNA is a cytological examination and easily obtainable even in small breast masses. However, accurate diagnosis of a phyllodes tumour from a FNA is difficult,[10,11] as both the stromal and epithelial components must be supplied in order for an accurate diagnosis to be made.[12] Subtle cytological changes in the stromal component may lead to a suspicion or suggestion of the diagnosis of a benign or borderline Phyllodes tumour, but FNA is seldom definitive in this differential diagnosis. If there is diagnostic uncertainty in a particular patient where the clinical suspicion is high, it is advised that a core biopsy be performed.[11,13] A core biopsy is a histological examination of the mass and tumour will be classified according to the WHO classification system. But, due to the small amount of tissue supplied with a core biopsy, the pathologist may still be unable to give a definitive diagnosis of a Phyllodes tumour.

Treatment

Due to the relative rarity of Phyllodes tumours, treatment principles are based primarily on retrospective studies and case reports. There are currently no published treatment protocols for Phyllodes tumours. Surgery is the mainstay of treatment; however the extent of surgery is very controversial. Currently, the recommendation is to excise the tumour with 1cm margins, or perform a mastectomy if the size of the tumour makes breast-conserving surgery with an acceptable cosmetic result impossible.[7,8,14,18-20] Despite the recommendation for 1cm resection margins, there has been a recently published study that challenges the need for 1cm margins.[29] Axillary dissection is not recommended as lymph nodes are rarely involved even in the malignant variant of Phyllodes tumours.[18]

Recurrence Rates and Factors affecting Recurrence

The dilemma with Phyllodes tumours is their tendency to locally recur. According to the WHO, the overall rate of local recurrence is 21%, more specifically, 10-17% for benign lesions, 14-25% for borderline lesions and 23-30% for malignant lesions.[1] The first two years after the initial surgery has been shown to be the most critical period for follow up, as this is when most tumours typically recur.[7] According to some authors, the recurrent tumours usually resemble the original tumour histologically.[6,16,21,22] However, it has been documented that the recurrent tumour can be more histologically aggressive and show increased cellularity compared to the original tumour.[21, 23-25] The malignant variant has been shown to recur quicker compared to the benign and borderline variants.[7] Because the risk of local recurrence is high even for the benign variant, much research has been done to illicit the risk factors for local recurrence. Surgical margins, nuclear atypia, stromal overgrowth, numbers of tumours, histology, tissue border and pleomorphism have shown to be associated with local recurrence.[1,7, 21,26]

Positive histological margins have been demonstrated to be an obvious risk factor for local recurrence.[18] The ability to accurately diagnose Phyllodes tumours preoperatively is a problem, which has been mentioned previously. Often, a Phyllodes tumour is misdiagnosed as a fibroadenoma. The surgeon merely does an enucleation or a shelling-out of the tumour, and the post-operative histology reveals a Phyllodes tumour. These cases have been shown to have very high recurrence rates.[18,27] de Roos *et al.* in his retrospective review of 38 patients found a local recurrence rate of 23.7% and all patients had positive resection margins.[18] They emphasized the difficulty they had with preoperative diagnosis in their setting, therefore, an excisional biopsy/enucleation was done to make the diagnosis of a Phyllodes tumour in many cases.[18] When the diagnosis was confirmed, the patients were

reluctant to have additional surgery to ensure a 1cm resection margin in all directions.[18] This emphasizes that it is imperative in such cases that re-excision with wider margins be done as soon as the formal histological diagnosis is made.[7,8,18, 27, 28]

Many studies have demonstrated that the risk of local recurrence is directly related to resection margin length. This is why the current guideline is to perform a wide local excision with 1 cm margins irrespective of the tumour grade or variant. [7,8,14,18-20] Rowell MD *et al.*, Reinfuss M *et al.*, de Roos WK *et al.*, and Chaney AW *et al.* recommend a 1cm margin based on the findings of their retrospective reviews of patients where they looked at rates and risk factors of local recurrence of Phyllodes tumours. Table 2 shows a summary of their results.

Table 2 Summary of Studies looking at Risk factors for local recurrence of Phyllodes Tumours

Study	**No. Patients in study**	**No. Of Local Recurrences**	**Percent of local recurrences with positive margins**	**Risks factors for local recurrence**
Rowell MD *et al.*	18	3 (16.6%)	33.3%	Unable to identify histologic parameters that predict outcome and prognosis
Reinfuss M *et al.*	170	14 (8.2%)	28.6%	Size of tumour, histotype and extent of surgery do not significantly influence local recurrence.
De Roos *et al.*	38	9 (23.7%)	100%	Positive resection margins is risk factor for local recurrence but not age, delay, side, size, histological grade or type of primary operation.
Chaney *et al.*	101	4 (3.9%)	0%	No significant risk factors that predicted local recurrence.
Jang JH *et al.*	164	31 (18.9%)	Doesn't comment specifically	Positive resection margins ($p = 0.029$) Tumour size ($p = 0.001$)

From these studies it is clear that it is difficult to predict Phyllodes tumour behaviour since no two trials show the same results. On one hand, Chaney *et al.* had the lowest rate of local recurrence (3.9%), and all 4 patients had negative margins.[19] On the other hand, de Roos *et al.* had the highest rate of local recurrence (23.7%), and all 9 patients had positive resection margins.[18] Comparing the results of Chaney *et al.* to de Roos *et al.*, it is clear that positive margins will lead to local recurrence, but it is not guaranteed that if negative resection margins are obtained, that local recurrence will not occur. Therefore, it is imperative for a negative resection margin, but what length should it be?

Interestingly, J.H. Jang *et al.* in their retrospective review of 164 patients published in 2012, tried to determine the exact length the negative margin needs to be in order to decrease risk of local recurrence.[29] They compared a 0.1mm, 1.0mm and 10.0mm margin lengths and found that positive resection margins were associated with local recurrence but the resection margin length was not.[29] There was no significant difference between the 0.1mm, 1.0mm and 10.0mm margin lengths.[29] Therefore, they are advocating a wide local excision with margins that are negative for tumour cells, but not a specific length of negative tissue.[29] From a surgical perspective, it may be very difficult to palpate the border of the tumour especially since the nature of a Phyllodes tumour is not encapsulated, but that tongues of tumour infiltrate a pseudocapsule into normal breast tissue, making it very difficult to ensure a 0.1mm or 1.0mm margin.

The role of tumour size in predicting local recurrence is also unclear. Some studies have reported a low risk of recurrence in tumours less than 2cm.[22, 30,31] However, no correlation between tumour size and the risk of local recurrence has been shown in the majority of

published series. Tumour size does appear to be an important determinant to predict the behaviour of a Phyllodes tumour including its metastatic potential.[16,18]

Many histological features have been evaluated as being possible prognostic markers for local recurrence: stromal overgrowth, tumour necrosis, infiltrating margins, mixed mesenchymal components, high mitotic rate and stromal atypia. However, each marker individually has been shown to have a low predictive value.[14]

To conclude, Phyllodes tumours are rare fibroepithelial tumours that occur more readily in middle-aged woman and tend to grow more rapidly than fibroadenomas. The mainstay of treatment is surgical resection with 1cm margins. Phyllodes tumours have a high rate of local recurrence, and often when the tumour recurs it is histologically more aggressive than the original tumour. This results in the need for additional surgery, and possible adjuvant therapy thereafter. In light of the above information and the paucity of data published from South Africa, it is imperative that we describe the histological and clinical features of the phyllodes tumours that are commonly seen, including grade, size, and margins, as well as to extrapolate this to determine the risk factors for local recurrence. By doing this we can compile evidence-based locally-specific protocols, that are currently not available, to offer our patients the best chance of cure and the lowest risk of local recurrence. Therefore, the aim of my study is to describe the most prevalent histological and clinical features of Phyllodes tumours in South Africa as well as to determine the rate of local recurrence including a description of the specific histological and clinical features that influence this rate.

2.1.2 Study Objectives

- To describe the histological and clinical features most prevalent in Phyllodes tumours
- To determine the rate of local recurrence of Phyllodes tumours

- To describe the clinical and histological risk factors for local recurrence of Phyllodes tumours

2.1.3 Methods

Design - A retrospective study

Site of Study – All NHLS (National Health Laboratory Service) Anatomical Pathology laboratories in South Africa

Study Population – Patients diagnosed with Phyllodes tumours after surgery from 1 January 2005 to 31 December 2012

Sampling - The patients will be identified by obtaining a list from a SNOMED search on the National Health Laboratory Service (NHLS) database of all breast specimens that were diagnosed as Phyllodes NOS (not otherwise specified), phyllodes benign and phyllodes malignant codes according to the WHO classification regardless of histological grade. Once all specimens with histology and a Phyllodes diagnosis are determined, only the wide local excision (WLE) and mastectomy specimens will be used and the core biopsies will be excluded. The reason for this is that many parameters, such as definitive grading, border, and margins that are to be collected, are not reported on for the core biopsies.

Sample Size – Approximately 56 patients will be identified. This number is based on search for the year 2010, where 8 patients were identified. If this number is extrapolated for the 7 years I will be covering, approximately 56 patients will be identified.

Data Collection - The following information will be collected from the histology report and tabulated for each patient (Appendix A): age at the time of diagnosis, preoperative cytology or histology, type of surgery, site of surgery, right or left, number of tumours, histology: benign, borderline, or malignant, border: pushing or infiltrative, resection margin: positive or negative and length, and stromal cellularity: low, moderate or high.

Sources of bias – Not all specimens will have been analysed by the same Anatomical Pathologist, therefore there may be variance between reports and information reported on.

2.1.4 Data Analysis

Continuous variables (i.e. age and tumour size) will be reported as a mean ± standard deviation. A comparison of tumours of a specific type with specific histological features that recurred versus tumours that did not recur with the same type and

histological features will be performed using a t-test or Chi-squared test. Multivariate analysis will be performed according to the Cox regression model. *P* values <0.05 will be considered statistically significant.

2.1.5 Ethics

Ethics clearance will be obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical). I intend to submit my Ethics application in December 2015.

2.1.6 Timing

	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Literature review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collecting data												
Data analysis												
Writing up – thesis												
Writing up – paper												

2.1.7 Funding

Summary of Costs

Item	**Cost**	**Responsible Party**

Printing of Protocol, Ethics application, Thesis etc	R200	Dept of Surgery, University of the Witwatersrand
Data Capture	Time	Principal Investigator

2.1.8 Problems

The only possible problem may be obtaining the required information from each pathology report as each specimen was analyzed by different anatomical pathologists, and therefore the information reported on may be slightly different.

2.1.9 References

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2.2 Ethics Approval

RI 4/49 Dr Janice Spinks

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M160122

NAME: Dr Janice Spinks
(Principal Investigator)

DEPARTMENT: Surgery

National Health Laboratory Service, South Africa

PROJECT TITLE: The Rate and Risk Factors for Local Recurrence of Phyllodes Tumours in a South African Population

DATE CONSIDERED: 29/01/2016

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Sarah Rayne and Kirstin Fearnhead

APPROVED BY: Professor P. Cleaton-Jones,Chairperson, HREC (Medical)

DATE OF APPROVAL: 22/04/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. l/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and l/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, l/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in January and will therefore be due in the month of January each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

2.3 Postgraduate Approval

University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
FACULTY OF HEALTH SCIENCES
ASSESSORS MEETING

CANDIDATE: Dr. J. Spinks Student no: 0603152X

Date of Assessor Group Meeting: 5th November 2014 School / Department / Division: General Surgery

Yes [ ] No [X] Is the research question clearly identified and described?

Comments: Needs to be rephrased

Yes [X] No [ ] Not entirely [ ]

Is the design of the study and methods used appropriate for the research question being asked?

Comments: Describe histological features
Change 36 patients to 56
Remove the term "Prevalence" Report and describe feature of recurrence
Extend to national database

Title change "Remove prevalence"

Is the study feasible within:

i. the applicant's resources? Yes [X] No [ ]

ii. the departments resources? Yes [X] No [ ]

iii. the time frame? Yes [X] No [ ]

Do you recommend:

i. shortening / lengthening of the protocol? Please specify and explain.

Yes | No (checked)

ii. the appointment of a co-supervisor?

Nominee/s :

Overall recommendation regarding the protocol :

i. revision of the protocol to the Supervisor (if HOD approval is also required, please specify):
(**Candidates**: one copy, list of corrections, supervisor approval letter – submit to PG Office) — Yes (checked) | No

ii. revision of the protocol to the satisfaction of the Assessor Group:
(**Candidates**: six copies, list of corrections, supervisor approval letter – submit to PG Office) — Yes | No

iii. revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting:
(**Candidates**: six copies, list of corrections, supervisor approval letter – submit one copy to PG Office / 5 to school assessor group administrator/ for PhD all six copies to be submitted to the PG Office) — Yes | No

iv. candidate goes ahead: — Yes | No

Assessor Names and Signatures :

Prof.M. Smith

Dr. M. Sparacos

Dr. C. Penny

~~Dr. S. Rayne~~

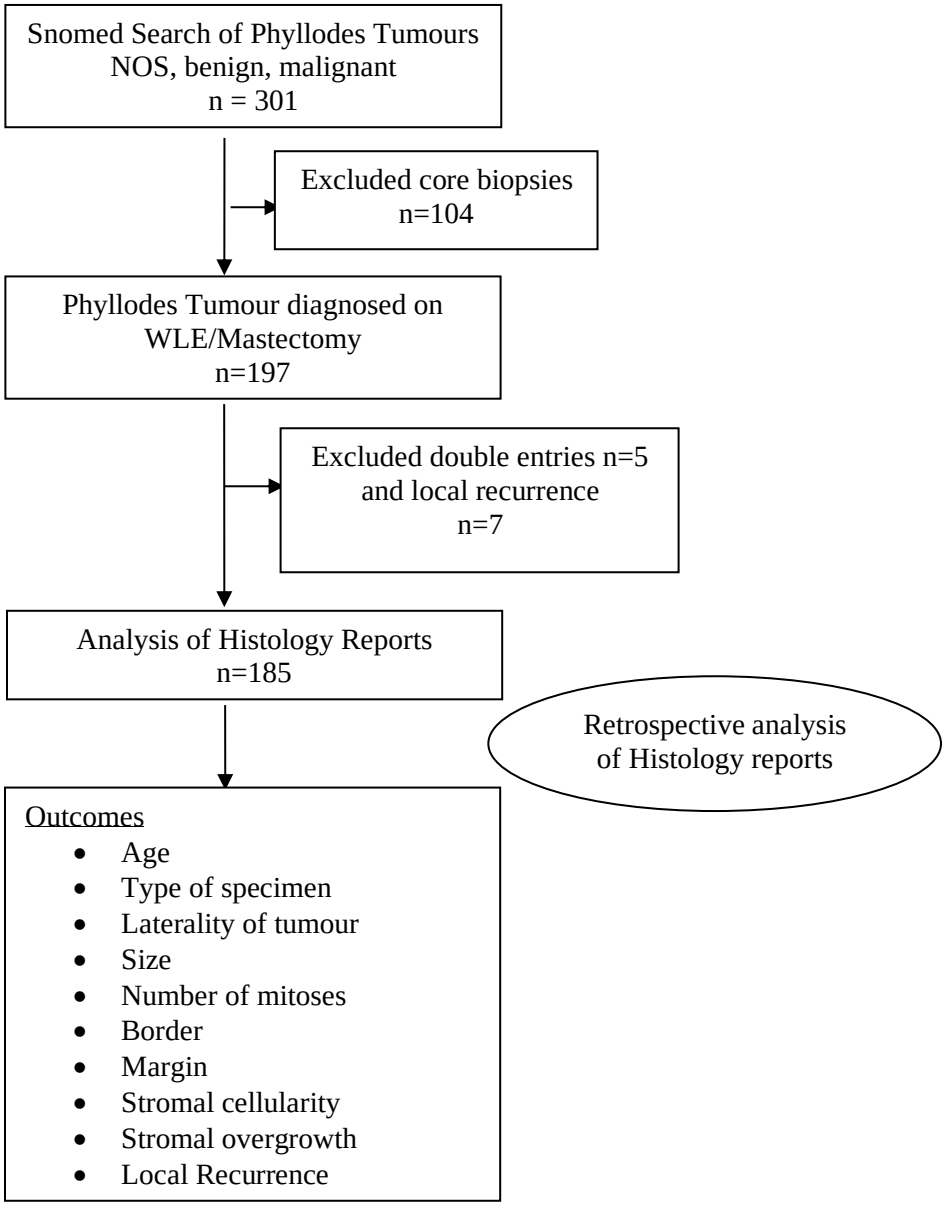
Assessor Group Chair

Date 05/11/2014

2.4 List of figures

1. **Draft article to *World Journal of Surgery***

Figure 1 Consort Diagram



2.5 List of tables

Draft article to the World Journal of Surgery

Table 1: Histological features of Phyllodes Tumours

Histological Feature	Benign	Borderline	Malignant
Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Tumour border	Well defined	Well defined, may be focally permeative	Permeative
Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic activity	<5 per 10 HPF	5-9 per 10 HPF	≥10 per 10 HPF
Stromal overgrowth	Absent	Absent or very focal	Often present

HPF high-power field

Table 2: Clinicopathologic Characteristics

	Benign (n = 89) No. (%)	**Borderline (n = 34)** No. (%)	**Malignant (n = 62)** No (%)	**Total (n=185)** No (%)
Total	89	34	62	185
Gender				
Male	1	0	0	1 (0.5)
Female	88	34	62	184 (99.5)
Site				
Left	42 (47.2)	17 (50)	40 (64.5)	99 (53.5)
Right	40 (44.9)	15 (44.1)	19 (30.6)	74 (40.0)
Not stated	7 (7.9)	2 (5.9)	3 (4.8)	12 (6.5)
Surgery				
Excision	80 (89.9)	20 (58.8)	19 (30.6)	119 (64.3)
Mastectomy	9 (10.1)	14 (41.2)	43 (69.4)	66 (35.7)
Border				
Pushing	15 (16.9)	14 (41.2)	7 (11.3)	36 (19.5)
Infiltrative	1 (1.1)	2 (5.9)	17 (27.4)	20 (10.8)
Not stated	73 (82.0)	18 (52.9)	38 (61.3)	129 (69.7)
Margin				
At least 0.1mm	9 (10.1)	7 (20.6)	10 (16.1)	26 (14.1)
At least 1.0mm	13 (14.6)	11 (32.4)	20 (32.3)	44 (23.8)

At least 10.0mm	10 (11.2)	3 (8.8)	13 (21.0)	26 (14.1)
Positive	32 (35.9)	8 (23.4)	14 (22.6)	54 (29.2)
Not stated	25 (28.9)	5 (14.7)	5 (8.0)	35 (18.8)
Stromal cellularity				
Mild	51 (57.3)	4 (11.8)	0 (0)	55 (29.7)
Moderate	19 (21.3)	18 (52.9)	1 (1.6)	38 (20.5)
Marked	3 (3.4)	3 (8.8)	44 (71.0)	50 (27.1)
Not stated	16 (18.0)	9 (26.5)	17 (27.4)	42 (22.7)
Stromal Overgrowth				
Negative	16 (18.0)	7 (20.6)	3 (4.8)	26 (14.1)
Positive	18 (20.2)	13 (38.2)	29 (46.8)	60 (32.4)
Not stated	55 (61.8)	14 (41.2)	30 (48.4)	99 (53.5)

Table 3: Risk Factors for local recurrence

	Benign Phyllodes (n=89)			Malignant Phyllodes (n=62)		
	No recurrence (n = 87)	Local recurrence (n = 2)	p-value	No recurrence (n = 57)	Local recurrence (n = 5)	p-value
Mean age (years)	37	14	0.016	46	48	0.630
Mean tumour size (mm)	68.1	82.5	0.317	156.5	155	0.519
Surgery						
BCS	78	2		19	2	
Mastectomy	9	0		43	3	
Border			**			0.708
Pushing	15	0		7	0	
Infiltrative	1	0		17	1	
Not stated	71	2		34	4	
Margin			0.545			1.00
Positive	31	1		13	1	
0.1mm or less	9	0		9	1	
0.2-1.0mm	13	0		19	1	
1.1-10.0mm	9	1		12	1	
Not stated	25	0		5	1	
Stromal cellularity			0.515			0.933

Mild	50	1		0	0	
Moderate	18	1		1	0	
Marked	3	0		41	3	
Not stated	16	0		15	2	
Stromal Overgrowth			0.515			0.751
Negative	16	0		3	0	
Positive	18	1		29	3	
Not stated	55	1		30	2	

Research Proposal

Table 1: Histological features of Phyllodes Tumours

Histological Feature	Benign	Borderline	Malignant
Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
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Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic activity	<5 per 10 HPF	5-9 per 10 HPF	≥10 per 10 HPF
Stromal overgrowth	Absent	Absent or very focal	Often present

HPF high-power field

Table 2: Summary of Studies looking at Risk factors for local recurrence of Phyllodes Tumours

Study	No. Patients in study	No. Of Local Recurrences	Percent of local recurrences with positive margins	Risks factors for local recurrence
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De Roos *et al.*	38	9 (23.7%)	100%	Positive resection margins is risk factor for local

				recurrence but not age, delay, side, size, histological grade or type of primary operation.
Chaney *et al.*	101	4 (3.9%)	0%	No significant risk factors that predicted local recurrence.
Jang JH *et al.*	164	31 (18.9%)	Doesn't comment specifically	Positive resection margins ($p = 0.029$) Tumour size ($p = 0.001$)

2.6 Authors Guidelines

WORLD JOURNAL OF SURGERY INSTRUCTIONS FOR AUTHORS

GENERAL

World Journal of Surgery (*WJS*) publishes original articles that offer significant contributions to knowledge in the broad fields of clinical surgery, innovative developments in surgery, global surgical practice and economics, surgical education, rural surgery and surgical history. *WJS* welcomes predominantly human research, including clinical research, outcomes, and health service research. Laboratory research will be published only if it is highly significant and with clear and immediate translational potential to surgical care. *WJS* has an international circulation and is designed to serve as a medium for rapid dissemination of new and important information about the science and art of surgery throughout the world. In the interests of a wide international readership, use of the English language is required. Articles that are accepted for publication are done so with the understanding that they, or their substantive contents, have not been and will not be submitted to any other publication.

TYPES OF MANUSCRIPTS

PLEASE NOTE: *World Journal of Surgery* does not accept Case Reports and Book Reviews for review or publication. *WJS* will consider publication without prior invitation the following types of manuscripts:

Original Scientific Reports: Original Scientific Reports are full-length reports of original basic or clinical investigations. Original Scientific Reports must adhere to a 2,500 word limit (not including the title page, abstract, references, tables, and figures). The final word count should be included in the title page of the manuscript. All clinical trials must be registered through a public trials registry that is acceptable to the International Committee of Medical Journals Editors (ICMJE). For information on ICMJE's statement to register clinical trials, please go to **http://www.icmje.org/publishing_10register.html**. The trial registration number and agency should be listed on the title page and at the end of the abstract. Randomized clinical trials should be reported following the CONSORT criteria and provide a completed checklist and flow diagram upon manuscript submission. For information on CONSORT and to download the CONSORT checklist and flow diagram, please go to **http://www.consortstatement.org/**.

Brief Original Scientific Reports: Brief communications describing an original observation or new technique. All efforts will be made to expedite review and publication of noteworthy brief reports. Brief Original Scientific Reports must adhere to a 1,500 word limit (not including the title page, abstract, references, tables and figures). The final word count should be included in the title page of the manuscript.

Innovative Techniques in Surgery around the World: The WJS in interested in publishing high quality descriptions of innovative surgical techniques that have the potential to improve the quality or efficiency of care. While techniques with universal appeal are most sought after, novel techniques that allow broader access to care in resource challenged environments are also desirable. The successful manuscript

will contain a detailed description of the technique and be richly illustrated with figures, and/or video. Line drawings are much superior to intraoperative photos, generally. A brief description of the authors experience with the technique should also be included, if possible. Qualifying manuscripts should be less than 1250 words, have no more than 3 authors, have no more than 5 references, and no more than 8 figures/video segments. A brief unstructured abstract is also required. Please see our instructions for submitting streaming video, below.

Papers Presented at ISW Congress: Includes manuscripts presented at an International Surgical Week (ISW) World Congress or at an Integrated Society meeting.

Multimedia Scientific Reports: *WJS* seeks manuscripts that contain brief video clips of surgical techniques or operative findings. Please see the "**MULTIMEDIA MANUSCRIPT SUBMISSION**" below for submitting video augmented manuscripts.

Surgery in Rural Settings and Low and Middle Income Countries: *WJS* seeks high quality manuscripts describing the unique problems and unique solutions facing surgeons in rural and impoverished settings, globally. *WJS* requires that manuscripts that use primary data from a low- or middle-income country should include one or more local co-authors. A local co-author is defined as a national of that country who is living and working in their home country. All other author requirements need to be met for the author(s) from the low and middle income country. The editors understand that there may be extenuating circumstances in which this requirement cannot be met. In such cases, a cover letter should explain why a local co-author is not included. Further details on this editorial policy can be found at: World J Surg (2011) 35:2367–2368.

Letter to the Editor: Letters should pertain to material previously published in *WJS*. Letters should not exceed 500 words with no more than five references, the first of which should be the article on which you wish to comment.

WJS will also consider for publication the following types of manuscripts by invitation only:

- Editorial Perspective
- Invited Scientific Review
- Invited Symposium Papers
- Reply to Letter to the Editor
- Invited Commentary
- Surgical History

MANUSCRIPT SUBMISSION GUIDELINES AND REQUIREMENTS

All manuscripts must be submitted online to *WJS* via the ScholarOne Manuscripts website (formerly Manuscript Central). Please login directly onto the site at **http://mc.manuscriptcentral.com/*WJS*** and upload your manuscripts following the instructions given on the screen. Authors should keep copies of all manuscript files. WJS accepts no responsibility for files that are lost or destroyed due to electronic

problems. Upon manuscript submission, the Editorial Office will review all manuscript files to verify that guidelines and policies stated in this document are adhered to. Your manuscript will be unsubmitted if it does not meet the proper submission requirements.

Authors entering the ScholarOne Manuscripts website can either create a new account or use an existing one. If you have an existing account, please use it for all your submissions and you can track their status on the same page. If you are unsure about whether or not you have an account, or have forgotten your password, enter your email address into the "Password Help" section. You will then receive an automatic e-mail with a new password which you will be prompted to change after logging in. Otherwise please create a new account and then follow the instructions given on the screen. Once you have logged into your account, ScholarOne Manuscripts will lead you through the submission process in a step-by-step orderly process. If you cannot finish your submission in one visit, you can save a draft and re-enter the process at the same point for that manuscript. At any point during this process, there are Help buttons available to see common questions and a support link to ask a specific question via email. After submission, you may return periodically and monitor the progress of your submission through the review process. Authors should go to **https://mc.manuscriptcentral.com/wjs** and click on "System Requirements" for the most updated list of system and browser requirements that should be used with ScholarOne Manuscripts.

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- Selection of the appropriate manuscript type
- Full title of the manuscript
- Structured abstract (up to 250 words)
- Selection of the appropriate keywords associated with the manuscript
- Names and details of all contributing authors [i.e., e-mail, first name, middle initial(s), surname, degree(s); the departmental and institutional affiliation(s); complete street or mailing address for each affiliation, including the city, state or province, and country where the work was performed].
  NOTE: Fellowships are not included in the Journal and NO MORE THAN 6 AUTHORS will be accepted for all manuscripts without a letter detailing explicit contribution to all 3 phases of authorship as stated in the "Consensus Guideline on Surgery Journal Authorship" published in World J Surg. 2006; 30:1135-1136. Individual contributors who have not reached this level of contribution should be acknowledged at the end of the manuscript text.
- Copyright Transfer Statement signed and dated by the corresponding author on behalf of all authors must be uploaded with each manuscript submission. To download the form, please go to **www.springer.com/00268** and click on "Copyright Transfer Statement".

If you are unable to submit your manuscript via the ScholarOne Manuscripts website or have any questions about *WJS*, please contact the editorial office:

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Fax: (503) 274-9433

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MANUSCRIPT PREPARATION AND ORGANIZATION

General instructions:

- Use a normal, plain font (e.g., 10-12 point Times Roman or Arial) for text
- Double-space the text
- Use italics for emphasis
- Use the automatic page numbering function to number the pages
- Do not use field functions
- Use tab stops or other commands for indents, not the space bar
- Use the table function, not spreadsheets, to make tables

Manuscript style and text formatting: Styling and text formatting refers to the use of special effects to enhance the appearance of the published article. Please make note of the following "Dos and Don'ts" regarding styling:

- **DO** enter all lists as single column lists.
- **DO** use your word processing features to indicate bold, italic, superscript, and subscript text within a • paragraph or heading.
- **DO NOT** center text for headings. All text should be justified left, with ragged (unjustified) right margins.
- **DO NOT** use italic, underline, or other type effects for the entire text of a heading.
- **DO NOT** use all capital letters for a heading; use initial caps instead.
- **DO NOT** use multiple spaces to set up columns or tables; use tabs instead.
- **DO NOT** use carriage returns at the end of each line of text (use the word wrap feature).

Manuscript organization: Manuscripts should be organized and follow the sequence as indicated below:

TITLE PAGE: The title page should include:

- A concise and informative title
- The name(s) of the author(s) including the affiliation(s) and address(es) of each author. The complete name and address of the author to whom correspondence should be sent, as well as his/her phone number, fax number, and email address.
- A short title for use as a running head.
- Keywords: 2-3 keywords relevant to the manuscript
- Trial registration number for randomized clinical trials (see "Types of Manuscripts: Original Scientific Reports" above)
- Grant support for the research reported
- Potential and real conflicts of interest
- Manuscript word count

ABSTRACT (if applicable): The abstract must appear between the title page and the Introduction section of the manuscript, even if it has been uploaded separately. Manuscripts should contain a structured abstract of not more than 250 words. It should be a factual description of the study performed organized with the headings of ***Background*** (includes aims, hypotheses, or objectives), ***Methods*** (includes patient population, procedures, and data analysis), ***Results***, and ***Conclusions***. The abstract should contain the data to support the key findings or conclusions of the study. The trial registration number for randomized clinical trials must be included at the end of the abstract. The first time an abbreviated term is used, spell it out in full and follow with the abbreviation in parentheses – for example: ultrasound (US).

TEXT: Original Scientific Reports should be arranged in sections titled Introduction, Material and Methods, Results, and Discussion.

1. Introduction: conveys the background and purpose of the report
2. Material and Methods
3. Results & Discussion

When required by the nature of the report, manuscripts that do not follow this specific format may be accepted.

ACKNOWLEDGEMENTS: A brief statement should acknowledge individuals, other than authors, who were of direct help in the reported work or if the work was supported by a federal or commercial grant. All acknowledged persons should give their written consent to being named in the manuscript. This consent is to be uploaded upon manuscript submission.

REFERENCES: Reference citations in the text should be identified by numbers in brackets (e.g. [4]). Number the references in order of their first appearance in the text (not alphabetically). Once a reference is cited, all subsequent citations should be to the original number. References may not appear in your Reference List unless they have been cited in the text or tables. Manuscripts that have been accepted for publication or are in press may be listed as references, but the Journal does not reference unpublished data and personal communications. Use the form for references adopted by the U.S. National Library of Medicine, as in Index Medicus. For each reference, show inclusive page ranges (e.g., 7-19).

In references to journal articles, please include (1) surname and initials (without periods) of the first three authors and et al for all others, (2) the year in parentheses, (3) title of article. (4) abbreviated Journal name, (5) volume number, and (6) inclusive page numbers, in that order. An example follows:

1. Honda T, Nozaki M, Isono N, et al (2001) Endoscope-assisted facial fracture repair. World J Surg 25:1075-1083

In references to books, please include (1) surname and initials (without periods) of the first three authors and et al. for all others, (2) chapter title, if any, (2) chapter title, if any, (3) the year in parentheses, (4) editor(s), if any, (5) title of book, (6) publisher, (6) city of publication, and (7) inclusive page numbers. Volume and edition numbers, and name of translator should be included when appropriate. Examples follow:

1. Harlan BJ, Starr A, Harwin FM, Anesthesia for cardiac surgery (1996) In: Illustrated Handbook of Cardiac Surgery, Springer-Verlag, New York, p. 6-12

2. Jones MC, Smith RB, Treatment of gastric cancer (1976) In: Ford TL (ed) Cancer of the Digestive System, Springer-Verlag, Berlin, p. 140-154

TABLES:

- All tables are to be numbered using Arabic numerals
- Tables should always be cited in text in consecutive numerical order
- For each table, please supply a table heading
- The table title should explain clearly and concisely the components of the table
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body

ARTWORK:

Electronic Figure Submission

- Supply all figures electronically
- Indicate what graphics program was used to create the artwork
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MS Office files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files
- Save and name your figure files with “Fig” and the figure number (e.g., Fig1.eps)

Line Art

- Definition: Black and white graphic with no shading
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size

- All lines should be at least 0.1 mm (0.3 pt) wide
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi

Halftone Art

- Definition: Photographs, drawing, or paintings with fine shading, etc.
- If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.
- Halftones should have a minimum resolution of 300 dpi

Combination Art

- Definition: a combination of halftone and line art (e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.)
- Combination artwork should have a minimum resolution of 600 dpi

Color Art

- Color art is free of charge for online publication
- If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.
- If the figures will be printed in black and white, do not refer to color in the captions.
- Color artwork should be submitted as RGP (8 bits per channel).

Figure Lettering

- To add lettering, it is best to use Helvetica or Arial (san serif fonts)
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2-3mm (8-12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions into your illustrations

Figure Numbering

- All figures are to be numbered using Arabic numerals
- Figure parts should be denoted by lowercase letters (a, b, c, etc.)
- Figures should always be cited in text in consecutive numerical order
- If an appendix appears in your manuscript and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures, "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Figure Captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.

- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption

Figure Placement and Size

- When preparing your figures, size figures to fit in the column width.
- For most journals the figures should be 39 mm, 84 mm, 129 mm, or 174 mm wide and not higher than 234 mm.

Accessibility (in order to give people of all abilities and disabilities access to the content of your figures, please make sure of the following)

- All figures have descriptive captions (blind users could then use a text-to-speech software or a text-toBraille hardware)
- Patterns are used instead or in addition to colors for conveying information (color-blind users would then be able to distinguish the visual elements)
- All figure lettering has a contrast ratio of at least 4.5:1

MULTIMEDIA MANUSCRIPT SUBMISSION:

- A Multimedia manuscript is an article with imbedded video material. Up to 3 videos per manuscript submission will be accepted. All standard instructions for Audio, Video, and Animations should be followed for Multimedia Manuscript Submissions.
- The content of these files must be identical to that reviewed and accepted by the editors of *World Journal of Surgery*
- All narration should be in English.
- Generally, the video clip is used to support the technique description. Additional data regarding the results of the procedure described should be included with the manuscript.

ELECTRONIC SUPPLEMENTARY MATERIAL:

Submission

- Supply all supplementary material in standard file formats.
- Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.
- To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

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Text and Presentations

- Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.
- A collection of figures may also be combined in a PDF file.

Spreadsheets

- Spreadsheets should be converted to PDF if no interaction with the data is intended.
- If the readers should be encouraged to make their own calculations, spreadsheets should be submitted as .xls files (MS Excel).

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- Specialized formats such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

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- It is possible to collect multiple files in a .zip or .gz file.

Numbering

- If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.
- Refer to the supplementary files as "Online Resource", e.g., "... as shown in the animation (Online Resource 3)", "... additional data are given in Online Resource 4".
- Name the files consecutively, e.g. "ESM_3.mpg", "ESM_4.pdf".

Captions

- For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

- Electronic supplementary material will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

- The manuscript contain a descriptive caption for each supplementary material
- Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)

ABBREVIATIONS, DRUG AND PRODUCT NAMES, DIGITS: Please use the standard abbreviations and units listed in Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers, Sixth Edition (Reston, Va., Council of Biology Editors, 1994). The first time an abbreviated term is used, spell it out in full and follow with the abbreviation in parentheses – for example: ultrasound (US).

Generic names for drugs and chemicals should be used the first time the drug or chemical is mentioned in the text and, preferably, thereafter. The first reference to a drug or chemical in the text should be followed by the manufacturer name, city, state or province, and country – and, if you wish, the trade name – in parentheses.

Please express digits as numerals except when they are the first word in a sentence. Decimals should be written in North American format. Express units of measurement in the metric system whenever possible, and abbreviate them when used with numbers.

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Statement of Human and Animal Rights: **http://www.springer.com/authors?SGWID=0-111-6-608309-0**

REVIEW AND ACTION

The editorial staff will examine the manuscripts and will customarily send them to appropriate experts. Authors will be notified as to the acceptability of a manuscript as rapidly as possible. All manuscripts will be put through iThenticate, an online plagiarism detection tool comparing the manuscript against

previously published scientific work in other journals. If any misconduct is detected, the editorial office will contact the author(s) concerning next steps and actions.

AFTER ACCEPTANCE

Upon acceptance of your article, the corresponding author will receive an email with a link to the special Author Query Application at Springer's web page where he/she can indicate whether they wish to order Springer Open Choice*, offprints, etc. Once the Author Query Application has been completed, the manuscript will be processed and the proofs will be sent to the corresponding author.

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AUTHOR PROOFS

After a submission is accepted and processed through production, a proof of the article is made available to the corresponding author. The purpose of the proof is to check for typesetting or conversion errors and the completeness and accuracy of the text, tables and figures. It is particularly important to check the proofs for accurate spelling of the author's names. It will be impossible to change an incorrectly spelled author's name after publication. Substantial changes in content, e.g., new results, corrected values, title and authorship, are not allowed without the approval of the Editor-in-Chief. Please note that the corresponding author will only receive one proof for review. Revised proofs are provided only upon request of the corresponding author. The article will be published online after receipt of the corrected proofs. This is the official first publication citable with the DOI (Digital Object Identifier). After online publication, further changes can only be made in the form of an Erratum, which will be hyperlinked to the article. After release of the printed version, the article can also be cited by issue and page numbers.

CONSENSUS STATEMENT ON SUBMISSION AND PUBLICATION OF MANUSCRIPTS

(Published in the June 2001 issue of *World Journal of Surgery*, page A7)

Increasing problems of duplicate and fraudulent submissions and publications have prompted the editors of surgical journals, including *World Journal of Surgery*, to support these overall principles of publication:

Duplicate Submission and Publication

In general, if a manuscript has been peer-reviewed and published, any subsequent publication is duplication. Exceptions to this general rule may be:

a) Prior publication in meeting program abstract booklets or expanded abstracts such as those published by the Surgical Forum of the American College of Surgeons or Transplantation Proceedings. However, these must be referenced in the final manuscript.

b) A manuscript which extends an original database (a good rule might be expansion by 50% or more) or which analyzes the original database in a different way in order to prove or disprove a different hypothesis. Previous manuscripts reporting the original database must, however, be referenced.

c) Manuscripts which have been published originally in non-English language journals, provided that the prior publication is clearly indicated on the English language submission and referenced in the manuscript. In some circumstances, permission to publish may need to be obtained from the non- English language journal.

For example, any submission duplicating material previously published in full in "Proceedings" or book chapters is considered duplicate unless the exceptions in (a) above apply. Similarly, manuscripts dealing with subgroups of data (i.e., patients) that have previously been analyzed, discussed and published as a larger group are considered duplicate unless (b) above applies.

The Internet raises special concerns. If data have previously appeared on the Internet, submission of those data for publication is considered duplication. If Internet publication follows journal publication, the journal publication should be clearly referenced. Some journals may provide early Internet publication of accepted peer reviewed papers which are subsequently published in that journal. This does not constitute duplication if both manuscripts are identical and covered by the same single copyright.

Fraudulent Publication
The following activities are examples of fraudulent publication practices:

a) Willful and knowing submissions of false data for publication.
b) Submission of data from sources not the author's (or authors') own.
c) Falsely certifying that the submitted work is original and has not been submitted to, or accepted by, another journal.
d) Sponsoring or vouching for a manuscript containing data over which the sponsor has no control or knowledge.
e) Allowing one's name to appear as an author without having contributed significantly to the study.
f) Adding an author's name to a manuscript to which he/she has not contributed, or reviewed or agreed to in its current form.
g) Flagrant omission of reference to the work of other investigators which established their priority.
h) Falsification of any item on the copyright form.
i) Failure to disclose potential conflict of interest with a sponsoring agency.

While not intended as an all-inclusive document, these examples and guidelines should alert authors to potential problems that should be avoided when they are considering submission of a manuscript to a peer-reviewed journal.

Surgery Journal Editors Group Consensus Statement on the Adoption of the COPE Guidelines
We, the undersigned member journals of the Surgery Journal Editors Group (SJEG), in the furtherance of integrity in surgical and scientific publication, agree to adopt the guidelines established by the Committee on Publication Ethics (COPE)[1]. The COPE guidelines represent a means of addressing a variety of ethical

concerns, including duplicate publication and authorship misconduct issues, which have, unfortunately, become more prevalent. This statement is being simultaneously published in the respective journals of the members of the Surgery Journal

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American Journal of Surgery Kirby I Bland, MD

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Annals of Surgical Oncology Charles M Balch, MD

Annals of Thoracic Surgery L Henry Edmunds Jr, MD

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BJS

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Surgical Laparoscopy, Endoscopy & Percutaneous Techniques, Maurice E Arregui, MD, Carol Scott-Conner, MD, PhD

The American Surgeon

J David Richardson, MD

World Journal of Surgery John G Hunter, MD

Zentralblatt für Chirurgie

Hans Lippert, MD, Ulrich Hopt, MD, Karl-Walter Jauch, MD

[1]*COPE Committee on Publication Ethics. http://publicationethics.org/guidelines*

CONSENSUS STATEMENT ON SURGERY JOURNAL AUTHORSHIP – 2006

In the majority of clinical and research studies submitted to surgery journals for possible publication, many individuals participate in the conception, execution, and documentation of each of those works. However, recognition of work in the form of authorship has varied widely. This consensus statement is being issued to clarify and define the criteria for surgical journal authorship.

The following guidelines should be used to identify individuals whose work qualifies them as authors as distinct from those who are contributors to the work under consideration. All persons designated as authors should qualify for authorship, and all those who qualify should be so credited.

A. Authorship Criteria

Individuals claiming authorship should meet all of the following 3 conditions:

Authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data;

Authors participate in drafting the article or revising it critically for important intellectual content; and

Authors give final approval of the version to be submitted and any revised version to be published.

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Allowing one's name to appear as an author without having contributed significantly to the study or adding the name of an individual who has not contributed or who has not agreed to the work in its current form is considered a breach of appropriate authorship.

Acquisition of funding, collection of data, contributing cases, or general supervision of the research group, of itself, or just being the Chair of the department does not justify authorship if the above criteria are not fulfilled.

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The order of authorship on the byline should be a joint decision of the co-authors. Authors should be prepared to explain the order in which authors are listed.

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When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above and editors will ask these individuals to complete journal-specific author and conflict of interest disclosure forms. When submitting a group-author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name.

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All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include: individuals who allowed their clinical experience (i.e., cases) to be included, a person who provided purely technical help, writing assistance, or a department Chair who provided only general support. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as “clinical investigators” or “participating investigators,” and their function or contribution should be described - for example, “served as scientific advisors,” “critically reviewed the study proposal,” “collected data,” or “provided and cared for study patients.”

Because readers may infer their endorsement of the data and conclusions, all persons listed as contributors must give written permission to be acknowledged.

E. In Conclusion

This consensus statement is intended as a basic guide for authors. In the interest of promoting the highest ethics in surgical publishing and the surgical sciences, we ask that authors take these criteria into careful consideration when submitting a manuscript to a peer-reviewed surgical journal. This statement is being

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