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► **To cite this version:**

Jon Oxley, Chandan Sen. Errors rates in reporting prostatic core biopsies. *Histopathology*, 2011, 58 (5), pp.759. 10.1111/j.1365-2559.2011.03794.x . hal-00626291

HAL Id: hal-00626291

<https://hal.science/hal-00626291>

Submitted on 25 Sep 2011

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Errors rates in reporting prostatic core biopsies

Journal:	<i>Histopathology</i>
Manuscript ID:	HISTOP-02-10-0091.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	22-Apr-2010
Complete List of Authors:	Oxley, Jon; Southmead Hospital, Cellular Pathology Sen, Chandan; Southmead Hospital, Cellular Pathology
Keywords:	prostate, error, screening



view

Errors rates in reporting prostatic core biopsies.

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Abstract

Aims: To evaluate the false negative and false positive error rates both in a screening and non-screening population.

Methods and Results: A total of 4192 prostatic biopsies were reported in a six year period by 15 consultant histopathologists, two of whom had an interest in uropathology and were deemed specialists (JO and CS). All biopsies were reviewed prior to the multidisciplinary team (MDT) meeting.

The overall false negative rate was 1.7% (screening 2.1%, non-screening 1.5%). The overall false positive rate was 0.5%; (screening 0.9%, non-screening 0.4%). These error rates varied amongst pathologists with a false negative rate ranging from 0 to 9.3% and a false positive rate ranging from 0 to 3.8%.

Conclusion: The false negative rate was three times greater than the false positive rate showing that detecting significant pathology is far greater in the negative biopsies. More errors occurred in the screening population than the non-screened population. The consultants making the most errors were non specialists but the specialists also made false negative errors, suggesting that just using specialist reporting alone would not have eradicated errors.

Key words: Prostate biopsy, prostate cancer, false negative and false positive

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Introduction:

The under and over diagnosis of prostatic adenocarcinoma on needle core biopsies is one of the most frequent problems in pathology practice. The increasing use of PSA as a screening tool in recent years has led to an increase in the number of prostate needle biopsies. This has led to an increasing number of specimens which contain only a few atypical glands or a very small focus of adenocarcinoma, which can be easily missed or misinterpreted [1,2] leading to a false negative or false positive diagnosis.

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Foci suspicious for adenocarcinoma are seen in 3-5% of needle biopsy specimens [3,4,5] and in 40-50% of rebiopsies cancer is detected [4,6,7,8] (even men with serum PSA less than 4 ng/ml had a 33% risk of cancer on rebiopsy.) As a result men with a suspicious diagnosis should be rebiopsied regardless of serum PSA levels. The diagnosis of even very small foci of adenocarcinoma in prostatic needle biopsy tissue is important because there is often no correlation between the amount of tumour seen on needle biopsy and the amount of tumour present in the radical prostatectomy [2,9].

The false negative rate is difficult to measure as a wholesale review of all negative biopsies is laborious but targeted audits have shown an error rate of between 1% [10] and 4% [11] with a recent paper stating 2.4% [12] but this was dependant on the protocol used. Berney et al looked at cases diagnosed between 1990-6 and found that there was a false positive rate of 3% in core biopsies and considerably higher in TURPs [13] but this is not a reflection of today's practice as little immunohistochemistry was performed during this era. A better indicator comes from the European Randomised Screening Program of Prostate Cancer (ERSPC) Study which has reported a false positive rate of

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1.2 % in a screening population [11] but once again the rate in a non-screened population remains unclear.

Histopathologists are a key part of the MDT approach to treating cancer. Their role is to review any relevant histology or cytology and to correct any inaccuracies, when either new information is available or an error is detected. It is well recognised that errors are an inevitable part of histopathology [14]. However, the consequences can be minimised if these errors are detected by pathology review before any treatment has occurred. Previous studies have used a selected audit to calculate false negative and false positive rates [11] or they have reviewed negative biopsies from patients who had subsequent biopsies showing cancer [12]. Neither of these methods can truly reflect the actual error rates as neither looks at all biopsies originally diagnosed as benign. This study uses the MDT review process as a way of measuring error rates as we implemented a complete review of all biopsies prior to the MDT. Previous studies have also shown a variation in error rates between centres [11], thought to be due to the presence or absence of pathologists with special interest in uropathology, and this study also looks at variation in error rate between consultants.

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Materials & Methods:

Patient Selection:

Southmead Hospital [in Bristol](#) is one of the centres involved in a prostate cancer screening study. This means that we receive biopsies from both a pure screening population and a more heterogeneous population typical of most centres in the UK. All

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the screening patients had PSA levels less than 20 ug/ml. The remaining patients had PSA levels ranging from less than 20 to more than 500 ug/ml and represented either a symptomatic population of men or those who had been PSA screened at their request by their general practitioner. All screening patients had 10 core biopsies whilst the non-screened population had between 6 and 12 ultrasound guided core biopsies, unless there was an extremely high clinical index of suspicion of cancer when fewer cores were taken.

Processing and Reporting of Biopsies:

These core biopsies were submitted as left and right cores with separate cores from the right and left apex in the majority of patients. They were subjected to routine processing and examined after haematoxylin and eosin staining on three levels. Spare sections of each level was kept for immunohistochemistry if it was required. Over the six year period from April 2002- April 2008 the biopsies were reported by 15 consultant pathologists (two of whom had a special interest in uro pathology, JO and CS). There was informal consultation between the consultants but cancers were not formally double reported. All cases were classified into five categories; benign, atypical changes not amounting to high grade PIN, high grade PIN (HGPIN), suspicious for malignancy and prostatic adenocarcinoma. This classification system had been agreed amongst the histopathologists from the various centres taking part in the screening study. A standard proforma, based on the Royal College of Pathologists minimum dataset [15], was completed for each case of prostatic adenocarcinoma.

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Review of biopsies:

Historically, the urology MDT meeting reviewed only prostatic cores that had been diagnosed as containing adenocarcinoma but from January 2002 we started reviewing all the biopsies taken. The prostatic biopsies were reviewed prior to the weekly MDT meeting by CS or JO. To establish a definitive diagnosis for lesions suspicious of adenocarcinoma or to confirm a diagnosis of adenocarcinoma, deeper levels were examined and immunohistochemistry performed wherever necessary. Any disagreement or discrepancy was discussed with the reporting pathologist and a consensus was reached.

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A supplementary report was issued if this consensus differed from the original report.

The pathology database was searched for the word "supplementary" in order to identify cases for this audit.

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Definition of false negative and false positive errors:

All cases reported as benign, atypical changes not amounting to HGPIN and HGPIN that were changed on review to either suspicious for malignancy or adenocarcinoma were considered to be false negative errors.

The false negative rate was the number of errors divided by the number of sets of cores originally reported as benign, or atypical changes not amounting to HGPIN or HGPIN, multiplied by 100.

All cases reported as adenocarcinoma that were changed to suspicious, or HGPIN, or atypical changes not amounting to HGPIN or benign were considered as false positive errors. The false positive rate was the number of these errors divided by the number of sets of cores originally reported as adenocarcinoma, multiplied by 100.

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Results

In the six year period, 4192 biopsies from 3441 patients were reported. Of these there were 1141 biopsies from 925 patients from the screening study and 3051 biopsies from 2516 patients from a non- screening population. The various categories after review for all the patients and separately for both the screened and non-screened patients are shown in Table 1. The diagnostic category was changed in 146 (3%) cases (Table 2).

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FALSE NEGATIVE BIOPSIES:

Overall thirty two cases were changed to adenocarcinoma on review (Table 2), but five cases were changed from suspicious for malignancy to cancer on review. These five biopsies all had very small volumes of tumour and the changes were considered to reflect differences in thresholds for calling cancer rather than errors *per se* and were not included in the error rate calculations. Of the 27 other cases 22 had originally been reported as benign, 5 as HGPIN. Reviewing the slides from these cases revealed that most had very small foci of adenocarcinoma in a single core which had been missed / overlooked by the reporting pathologist. 26 cases had less than 5% tumour; 5 cases had between 10 and 20%. (One of these had been signed out in error as benign whilst the others were missed) and 1 case had 30% tumour. The latter case had a pseudohyperplastic morphology of adenocarcinoma which had been interpreted as benign (Figure 1). The Gleason score was 3+3 = 6 in 24 of these cases, 3+4 =7 in two cases and 4+4=8 in one case.

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Fourteen cases were upgraded to suspicious for adenocarcinoma . Of these 12 had originally been reported as benign, 1 as atypia not amounting to HGPIN and 1 as HGPIN.

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Eleven of these cases had subsequent biopsies; 7 of these showed adenocarcinoma, 1 suspicious for malignancy, 1 showed HGPIN and two were benign.

The overall false negative rate was 27 cases of cancer plus 14 cases of suspicious divided by 2367 (as the total number of biopsies which were reported as neither suspicious nor cancer before the review) multiplied by 100 = 1.7% (see Table 3).

FALSE POSITIVE BIOPSIES:

In nine cases the diagnosis of cancer was changed, 3 to suspicious, 1 to HGPIN and 5 to benign. In the five cases changed to benign, three were interpreted as atrophic, one as post radiation changes, and one as Cowper's glands (Figure 2). The post radiation case changed to benign had had a TURP with cancer in it previously and the management would not have changed. The other four did not have repeat biopsies. The case changed to HGPIN had immunohistochemistry performed and this showed a basal layer. This patient had a subsequent biopsy that showed HGPIN only. The three cases changed to suspicious had only very few glands showing malignant features and were thought to be insufficient to be diagnostic. All these patients had subsequent biopsies – two showed cancer and one showed HGPIN.

The overall false positive rate was 9 cases of cancer changed divided by 1680 (as the total number of biopsies which were reported as cancer before the review) multiplied by 100 = 0.5% (see Table 3).

ERROR RATES: OVERALL AND PER CONSULTANT

Five consultants reported less than 60 biopsies and made no errors. The number of biopsies and the time period over which the pathologist reported the cores was recorded.

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Southmead Hospital is typical of many centres in the UK with many staffing changes and over the period of the study 15 pathologists reported the core biopsies.

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Eight pathologists made either false negative or false positive errors and this data is shown in table 3. The false negative rate varied from 0% to 9.3%, whereas the false positive rate varied from 0 to 3.8%. Consultant 10 had the highest false negative rate but made no false positive diagnoses, which was probably due to only reporting 44 cancers in the time period. Consultant 5 had a high false negative and false positive rate. Both the error rates were higher in the screened patients in comparison to the non-screened patients (Table 3).

Discussion

The definition of a false negative error in prostatic core biopsies is open to a degree of interpretation as previous studies have audited just benign diagnoses [11,12] but patients with HGPIN or atypia not amounting to HGPIN should also be included as these patients would not be automatically offered a repeat biopsy and as a result the diagnosis of cancer would have been missed. We have also included those cases not only changed to cancer but also to suspicious for malignancy as the majority of these patients had an early repeat biopsy which showed cancer. We excluded those patients whose biopsies were changed from suspicious to cancer on review as we felt this was not a true error but a reflection of thresholds for individual consultants to call cancer [11] and these patients would have been offered a repeat biopsy anyway, which was likely to have shown cancer.

We have previously published a single year audit which used the definition of those cases changed from benign to cancer and this showed a false negative error rate of 0.6% [16] but this larger audit used a broader definition and as a result found a higher rate of 1.7%. Kronz et al studied 3,251 biopsy cases seen in consultation and identified 87 (2.7%)

patients with missed lesions including HGPIN, of which 32 (1%) had prostatic adenocarcinoma [10]. This figure is probably an underestimation, as only selected biopsies were submitted for consultation. These errors would have changed patient management in 0.5% of all the patients. Van der Kwast et al reviewed 127 sets of prostatic needle biopsies with a benign outcome randomly selected from 7 centres participating in the ERSPC [11]. The authors identified variation between the reviewing pathologists with either a 4% or a 10% false negative rate. This variation was partly due to the threshold each pathologist had for diagnosing prostate cancer when only small numbers of abnormal glands were present [11]. In a recent publication, Wolters et al reported an overall false negative biopsy rate of 2.4% (1.1% for adenocarcinoma and 1.3% for ASAP) by reviewing 196 biopsies in a prostate cancer screening setting [12].

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All of the false negative biopsy rates reported in these studies are based on review of material from a screening population or a consultation practice. In our study, the false negative rate in the screening population was 2.1% which is similar to that reported in these studies. The false negative rate in the non-screened population was 1.5% whereas the overall rate was 1.7%. The difference in rates reflects the higher rate of cancers and the lower rate of suspicious in the non-screened population in comparison to the screened patients. Also the non-screening cancers were likely to be a larger volume and less easily missed.

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The definition of false positive used by most authors [11,13] is those cases changed from cancer to a non-cancer diagnosis simply because the cancer cases were audited. We have used this definition to enable comparison, but have not included those cases changed

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from suspicious to benign, which could be argued were also significant changes (though none occurred in this study). We found that overall this was 0.5% but once again the screening population had a higher rate of 0.9% compared with the non-screened group of 0.4%. Other authors have found a rate of between 1.2% and 3% [11,13] but the higher rate was in a non-contemporary series. The decrease in false positive cases from the period studied by Berney et al and our study or the ERSPC data would suggest there has been a combination of greater use of immunohistochemistry as well as training of pathologists in uropathology. This is also reflected in the litigation figures for prostate pathology which show that false negative claims have increased whilst false positive claims have decreased over the past decade [17].

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The main difference between this study and the other series reported in literature is that it encompasses a longer period of time and consequently includes a much larger number of biopsies. It is, to date, the largest series of prostatic biopsies which have been reviewed in literature and is an ongoing project. We felt it was imperative to examine our MDT review data following the recent recommendation by The National Institute for Clinical Excellence (NICE), that all negative cores be discussed at the MDT, but without the slides being formally reviewed. [18]. At the present time, we are aware that very few centres review the negative biopsies prior to the MDT (personal communication). Our study highlights that the probability of detecting significant pathology on review is far greater in the negative biopsies. The false positive cases were due to misinterpretation, where the exact cause could be identified and rectified by becoming familiar with the morphology of these misleading pitfalls. The false negative diagnoses, on the other hand,

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were predominantly errors of oversight, where small foci of carcinoma were either not seen at all, or not identified as being cancer. It is clear that these errors are more difficult to rectify by further education and training.

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This study has also revealed a significant variation in the error rates between pathologists.

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The consultants with the three highest error rates were all senior pathologists with greater than 60 years experience between them. The majority of false negative diagnoses were

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due to missed lesions and it could be argued that these pathologists suffered from

overconfidence or distractions or time pressures, whilst more junior colleagues had been

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exposed to core biopsies during their training and took longer and more care examining

them. Reporting the radical prostatectomy specimens was done by either CS and JO and

not seeing these may have been detrimental to the training of the general pathologists,

although many district general hospitals report core biopsies but not radical

prostatectomy specimens. Wolters et al suggest that screening one level at high power

would have detected this type of error but we suggest that it is a combination of knowing

when to examine a focus at high power and when not to, as often the malignant focus

may only be in one level. Minimising errors is critical to patient safety and this study has

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demonstrated that this can be done via review prior to the MDT but this is a costly

method and most departments would be very unwilling to implement this. As the

negative biopsies are less than 50% of the workload and as the positive cores are already

reviewed, the increase in workload would not be too onerous. We estimate that reviewing

the negative cores took us 1 to 2 hours per week. Some departments double report the

Deleted: The majority of departments review the malignant cores for the MDT prior to the patient receiving treatment as advised by NICE [18]. If this is done then all the false positive errors we detected would have been detected, if the reviewer was experienced. Unfortunately most errors in prostate cores appear to be missed lesions and these would not be detected in any department implementing the NICE guidance. One

malignant diagnoses but there are reported errors even with this system [19]. Another

method being adopted by centres is specialist reporting and indeed the pathologists with a specialist interest had some of the lowest rates but the specialists made mistakes, but at no more than 1.4% false negative rate and neither made false positive errors. Certainly it could be related to the number of biopsies seen per month, with the consultant with the highest false negative rate only reporting 2 per month but the converse is not true as the consultant reporting over 10 a month also had a high false negative rate. Southmead Hospital has now moved to complete specialist reporting but we are continuing to review all biopsies and will repeat this audit in the future.

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In conclusion, errors are detected at the review prior to the MDT meeting and reviewing the negative cores detects more clinically relevant errors than reviewing the cancer diagnoses. Current strategies of specialist reporting and double reporting cancers will decrease error rates but we feel a review of all biopsies is the only reliable method.

Acknowledgements

We would like to thank our colleagues and the screening study for allowing us to use this data and the screening histopathology subgroup for using the classification of non-cancer diagnoses.

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Figure 1: Pseudohyperplastic carcinoma misdiagnosed as benign (a) H&E x200 (b) Immunohistochemistry for high molecular weight keratin (34BE12)

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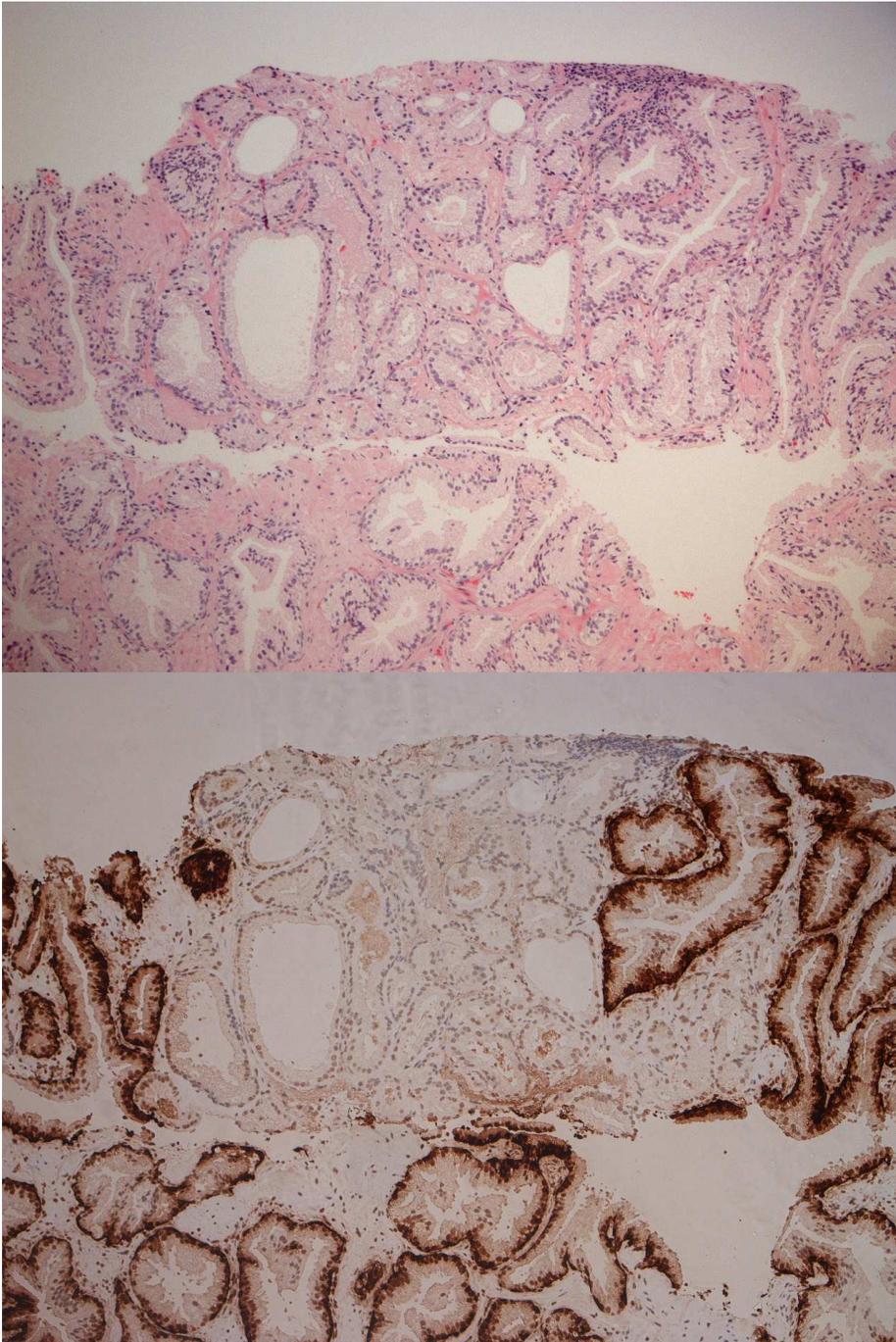
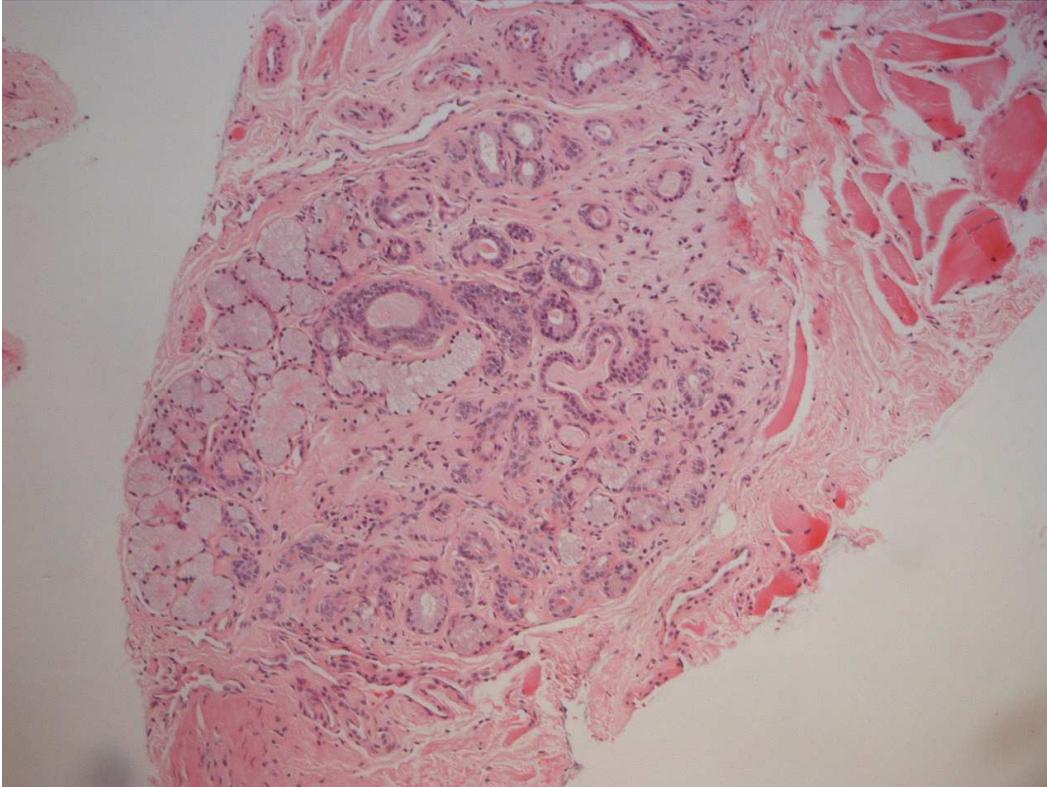


Figure 2: Cowper's glands misdiagnosed as adenocarcinoma. (Original magnification x200)



Review

Table 1 : Diagnosis in 4192 prostatic biopsies following review and divided into screened and non screened cases.

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Diagnosis	OVERALL		SCREENED		NON-SCREENED	
	Number	%	Number	%	Number	%
inadequate	14	0.3	6	0.5	8	0.3
benign	1790	42.7	546	47.9	1244	40.8
atypia	58	1.4	31	2.7	27	0.9
HGPIN	484	11.5	155	13.6	329	10.8
suspicious	135	3.2	54	4.7	81	2.7
cancer	1703	40.6	349	30.6	1354	44.4
<u>TCC</u>	4	0.1	0	0	4	0.1
lymphoma	4	0.1	0	0	4	0.1
TOTAL	4192	100.00	1141	100.00	3051	100.00

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TCC = transitional cell carcinoma

Table 2: Data showing the changes of diagnosis after biopsies were reviewed (a) Overall (4192 biopsies) (b) Screening (1141 biopsies) (c) Non Screening (3051 biopsies), **Yellow highlight = false negative, blue highlight = false positive**

OVERALL							
	Review diagnosis	benign	atypia	HGPIN	Suspicious	cancer	TOTAL
<i>Original diagnosis</i>							
benign		x	7	76	12	22	117
atypia		0	x	5	1	0	6
HGPIN		3	0	x	1	5	9
suspicious		0	0	0	X	5	5
cancer		5	0	1	3	x	9
TOTAL		8	7	82	17	32	146

SCREENING							
	Review diagnosis	benign	atypia	HGPIN	Suspicious	cancer	TOTAL
<i>Original diagnosis</i>							
benign		x	5	27	8	7	47
atypia		0	x	1	0	0	1
HGPIN		1	0	X	1	0	2
suspicious		0	0	0	x	1	1
cancer		0	0	1	2	x	3
TOTAL		1	5	29	11	8	54

NON-SCREENING							
	Review diagnosis	benign	atypia	HGPIN	suspicious	cancer	TOTAL
<i>Original diagnosis</i>							
benign		X	2	49	4	15	70
atypia		0	X	4	1	0	5
HGPIN		2	0	X	0	5	7
suspicious		0	0	0	X	4	4
cancer		5	0	0	1	X	6
TOTAL		7	2	53	6	24	92

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Rates highlighted in red are greater than the overall rate. Consultants 1 and 3 had a special interest in uropathology.

We are grateful for the comments from the referee and have tried to answer specific points as detailed below.

Referee: 1

Comments to the Author

Oxley et al here report on the error rate in a large series of prostate biopsies. Every biopsy in this series of 4192 cases was reviewed by one of two experts in uropathology. This is a huge task and the results are interesting. The false negative rate was more than 3 times as high as the false positive rate which is in line with our general experience. The author's conclusion that false positive rate can be reduced by education while false negative rate is probably more difficult to minimise is sound. However, the recommendation that "this highlights the importance of reviewing the biopsies reported as negative in the first instance" is not realistic in most laboratories. This would mean that all specimens are read by two pathologists which would double the diagnostic work.

The negative results are less than half the number of cores – the positive biopsies are already reviewed in most labs so it would in fact only increase the workload by less than a quarter – but we accept that this will be extra work, but in the same way that negative cervical smears are double checked we think this needs to be best practice and certainly adopted in any screening program. We estimate that it took us an extra 1 – 2 hours to do this – and we have added this in the discussion. Value for money it is clear that reviewing the negative cores is better than the positive cores. Also if the negative cores are changed to cancer then subsequent biopsies would not occur - decreasing the lab workload.

The authors have extended the definition of false negative to include cases that after review are reported as suspicious, which may be reasonable. It is more difficult to understand why they did not use the corresponding definition of false positive. A misinterpretation of an evidently benign lesion as suspicious for cancer may cause a considerable stress on the patient and despite multiple repeat biopsies it is impossible to definitely get rid of a suspicion of malignancy. In the current study, a modified definition of false positive would however not change the results as there were no cases originally reported as suspicious that were changed to benign on review.

The definition of false positive has not been changed as we are comparing the figures with previous studies who have used this definition. We accept that patients who are labeled suspicious but are benign are problematic and we have added a comment on this in discussion

[If we had included then it would very slightly have *decreased* the error rate as the definition would also have to include all biopsies originally reported as either suspicious or cancer – so although none were changed from suspicious the 9 cases of cancer changed would be divided by $1680 + 123$, changing the error rate from 0.54 to 0.49.]

It seems that the major cause of false negative biopsies is that certain pathologists rush through the specimens and overlook significant pathology. Thus, the problem is largely personal rather than systematic, which is my experience as well. Are there other possibilities to handle this rather than reviewing all cases again? It does not seem rational to let certain colleagues do a very fast and suboptimal work and then do the same work once again just to compensate for their neglect.

We make NO suggestion that they rushed their work – but distractions were probably a factor. Clearly working in a distraction free environment is critical but very hard to obtain. When approached these consultants stated that they reported these with care but clearly missed lesions. It is easy to suggest that they rushed their work but we think it is probably more complex than this.

How were the study results received by the colleagues? Did it have any consequences on an individual level? One may also wonder if someone who has a high error rate on prostate biopsies may have a similar error rate on other specimens.

This audit only looked at prostate cores as these have been identified as problem areas. The colleagues with high rates were specialists in other areas – (including some considered as national experts). Previous authors have found error rates of around 1% in general reporting.

Reviewing all cases would indeed be a very large undertaking – the results of such a review are in progress at another Bristol hospital and may give this data.

Thus, the solution may not necessarily be to exclude these persons from diagnosing prostate biopsies.

Colleagues with high rates were keen to stop this work as we moved to specialist reporting as their interests and skills were in other fields.

How were the cases with changed diagnoses traced? Is there a search function in the reporting system in Bristol that allows search of cases where the diagnostic category has been changed? Or were the cases registered prospectively?

The pathology database was searched for the word "supplementary" which was added to all extra reports. This will be added to methods.

The terms specialist vs non-specialist are not self-explaining. We understand after reading the ms that the authors uses specialist to refer to someone with a special interest in uropathology. However, in some countries it may also be understood as someone who has finished the specialization in pathology as opposed to a trainee or resident. Thus, I suggest that when the terms are introduced the first time (i.e. in the abstract), it is stated clearly that a senior pathology with special interest in uropathology is meant.

Altered as indicated.

The use of the nomenclature biopsy, biopsy set, set of cores and cores could be more consistent. In international literature biopsy is often used to designate a set of biopsy cores taken in one session while core refers to a single biopsy core. In the first paragraph of the result section, the authors first use sets of cores and then cores only, when set is probably meant (3051 cores). Similarly, in Tab 3, the term cores is used in the column headings, while set of cores (or biopsies) is probably meant.

Altered as indicated

The main message is the rate of false positive and negative. It would make sense if this was presented clearly in the results section (under false positive and negative, respectively) with both % and n/n to allow the reader to quickly see how the rates were calculated.

Altered as indicated

Would it be possible to somehow highlight the cases in Table 2 that are counted as false positives and false negative, respectively? It would be easier for the reader to get an overview of the error rate.

Altered as indicated

The manuscript could do with some brushing up. The first time Southmead Hospital is mentioned, the city name Bristol is not given. On the other hand, it is mentioned several times later in the text. It should be given when first mentioned, but not anymore. Similarly, some statements are repeated several times, such as the fact that 2 of 15 pathologists had a special interest in uropathology, There are other examples in the Discussion.

Altered as indicated

MINOR COMMENTS: All altered as indicated

MDT should be written out in the abstract.

British pathologists are probably familiar with NICE but for others a short explanation would be helpful.

Introduction, p.2: units missing for PSA <4 (ng/ml)

Results, p. 4 under False negative biopsies: Please clarify what These in the second sentence refers to (probably the 5 cases mentioned in the second part of the first sentence).

In several places some words are missing which makes the sentences difficult to understand:
Results, p. 4: The various categories after review for the all the... Results, p. 5 under Error rates:
The number of sets of cores and the over what period... Discussion, p. 5, first paragraph: which
was likely to shown cancer Discussion, p. 7, second paragraph: The consultants with the three
highest rates... (error rates probably meant)

Some blank spaces between words seem to be missing in the text and in the ref list.

For Peer Review

Errors rates in reporting prostatic core biopsies.

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Abstract

Aims: To evaluate the false negative and false positive error rates both in a screening and non-screening population.

Methods and Results: A total of 4192 prostatic biopsies were reported in a six year period by 15 consultant histopathologists, two of whom had an interest in uropathology and were deemed specialists (JO and CS) All biopsies were reviewed prior to the multidisciplinary team (MDT) meeting.

The overall false negative rate was 1.7% (screening 2.1%, non-screening 1.5%). The overall false positive rate was 0.5%; (screening 0.9%, non-screening 0.4%). These error rates varied amongst pathologists with a false negative rate ranging from 0 to 9.3% and a false positive rate ranging from 0 to 3.8%.

Conclusion: The false negative rate was three times greater than the false positive rate showing that detecting significant pathology is far greater in the negative biopsies. More errors occurred in the screening population than the non-screened population. The consultants making the most errors were non specialists but the specialists also made false negative errors, suggesting that just using specialist reporting alone would not have eradicated errors.

Key words: Prostate biopsy, prostate cancer, false negative and false positive

Introduction:

The under and over diagnosis of prostatic adenocarcinoma on needle core biopsies is one of the most frequent problems in pathology practice. The increasing use of PSA as a screening tool in recent years has led to an increase in the number of prostate needle biopsies. This has led to an increasing number of specimens which contain only a few atypical glands or a very small focus of adenocarcinoma, which can be easily missed or misinterpreted [1,2] leading to a false negative or false positive diagnosis.

Foci suspicious for adenocarcinoma are seen in 3-5% of needle biopsy specimens [3,4,5] and in 40-50% of rebiopsies cancer is detected [4,6,7,8] (even men with serum PSA less than 4 ng/ml had a 33% risk of cancer on rebiopsy.) As a result men with a suspicious diagnosis should be rebiopsied regardless of serum PSA levels. The diagnosis of even very small foci of adenocarcinoma in prostatic needle biopsy tissue is important because there is often no correlation between the amount of tumour seen on needle biopsy and the amount of tumour present in the radical prostatectomy [2,9].

The false negative rate is difficult to measure as a wholesale review of all negative biopsies is laborious but targeted audits have shown an error rate of between 1% [10] and 4% [11] with a recent paper stating 2.4% [12] but this was dependant on the protocol used. Berney et al looked at cases diagnosed between 1990-6 and found that there was a false positive rate of 3% in core biopsies and considerably higher in TURPs [13] but this is not a reflection of today's practice as little immunohistochemistry was performed during this era. A better indicator comes from the European Randomised Screening Program of Prostate Cancer (ERSPC) Study which has reported a false positive rate of

1.2 % in a screening population [11] but once again the rate in a non-screened population remains unclear.

Histopathologists are a key part of the MDT approach to treating cancer. Their role is to review any relevant histology or cytology and to correct any inaccuracies, when either new information is available or an error is detected. It is well recognised that errors are an inevitable part of histopathology [14]. However, the consequences can be minimised if these errors are detected by pathology review before any treatment has occurred.

Previous studies have used a selected audit to calculate false negative and false positive rates [11] or they have reviewed negative biopsies from patients who had subsequent biopsies showing cancer [12]. Neither of these methods can truly reflect the actual error rates as neither looks at all biopsies originally diagnosed as benign. This study uses the MDT review process as a way of measuring error rates as we implemented a complete review of all biopsies prior to the MDT. Previous studies have also shown a variation in error rates between centres [11], thought to be due to the presence or absence of pathologists with special interest in uropathology, and this study also looks at variation in error rate between consultants..

Materials & Methods:

Patient Selection:

Southmead Hospital in Bristol is one of the centres involved in a prostate cancer screening study. This means that we receive biopsies from both a pure screening population and a more heterogeneous population typical of most centres in the UK. All

the screening patients had PSA levels less than 20 ug/ml. The remaining patients had PSA levels ranging from less than 20 to more than 500 ug/ml and represented either a symptomatic population of men or those who had been PSA screened at their request by their general practitioner. All screening patients had 10 core biopsies whilst the non-screened population had between 6 and 12 ultrasound guided core biopsies, unless there was an extremely high clinical index of suspicion of cancer when fewer cores were taken.

Processing and Reporting of Biopsies:

These core biopsies were submitted as left and right cores with separate cores from the right and left apex in the majority of patients. They were subjected to routine processing and examined after haematoxylin and eosin staining on three levels. Spare sections of each level was kept for immunohistochemistry if it was required. Over the six year period from April 2002- April 2008 the biopsies were reported by 15 consultant pathologists (two of whom had a special interest in uropathology, JO and CS). There was informal consultation between the consultants but cancers were not formally double reported. All cases were classified into five categories; benign, atypical changes not amounting to high grade PIN, high grade PIN (HGPN), suspicious for malignancy and prostatic adenocarcinoma. This classification system had been agreed amongst the histopathologists from the various centres taking part in the screening study. A standard proforma, based on the Royal College of Pathologists minimum dataset [15], was completed for each case of prostatic adenocarcinoma.

Review of biopsies:

Historically, the urology MDT meeting reviewed only prostatic cores that had been diagnosed as containing adenocarcinoma but from January 2002 we started reviewing all the biopsies taken. The prostatic biopsies were reviewed prior to the weekly MDT meeting by CS or JO. To establish a definitive diagnosis for lesions suspicious of adenocarcinoma or to confirm a diagnosis of adenocarcinoma, deeper levels were examined and immunohistochemistry performed wherever necessary. Any disagreement or discrepancy was discussed with the reporting pathologist and a consensus was reached. A supplementary report was issued if this consensus differed from the original report. The pathology database was searched for the word "supplementary" in order to identify cases for this audit.

Definition of false negative and false positive errors:

All cases reported as benign, atypical changes not amounting to HGPIN and HGPIN that were changed on review to either suspicious for malignancy or adenocarcinoma were considered to be false negative errors.

The false negative rate was the number of errors divided by the number of sets of cores originally reported as benign, or atypical changes not amounting to HGPIN or HGPIN, multiplied by 100.

All cases reported as adenocarcinoma that were changed to suspicious, or HGPIN, or atypical changes not amounting to HGPIN or benign were considered as false positive errors. The false positive rate was the number of these errors divided by the number of sets of cores originally reported as adenocarcinoma, multiplied by 100.

Results

In the six year period 4192 biopsies from 3441 patients were reported. Of these there were 1141 biopsies from 925 patients from the screening study and 3051 biopsies from 2516 patients from a non- screening population. The various categories after review for all the patients and separately for both the screened and non-screened patients are shown in Table 1. The diagnostic category was changed in 146 (3%) cases (Table 2).

FALSE NEGATIVE BIOPSIES:

Overall thirty two cases were changed to adenocarcinoma on review (Table 2), but five cases were changed from suspicious for malignancy to cancer on review. These five biopsies all had very small volumes of tumour and the changes were considered to reflect differences in thresholds for calling cancer rather than errors *per se* and were not included in the error rate calculations. Of the 27 other cases 22 had originally been reported as benign, 5 as HGPIN. Reviewing the slides from these cases revealed that most had very small foci of adenocarcinoma in a single core which had been missed / overlooked by the reporting pathologist. 26 cases had less than 5% tumour; 5 cases had between 10 and 20%. (One of these had been signed out in error as benign whilst the others were missed) and 1 case had 30% tumour. The latter case had a pseudohyperplastic morphology of adenocarcinoma which had been interpreted as benign (Figure 1). The Gleason score was 3+3 = 6 in 24 of these cases, 3+4 =7 in two cases and 4+4=8 in one case.

Fourteen cases were upgraded to suspicious for adenocarcinoma . Of these 12 had originally been reported as benign, 1 as atypia not amounting to HGPIN and 1 as HGPIN.

Eleven of these cases had subsequent biopsies; 7 of these showed adenocarcinoma, 1 suspicious for malignancy, 1 showed HGPIN and two were benign.

The overall false negative rate was 27 cases of cancer plus 14 cases of suspicious divided by 2367 (as the total number of biopsies which were reported as neither suspicious nor cancer before the review) multiplied by 100 = 1.7% (see Table 3).

FALSE POSITIVE BIOPSIES:

In nine cases the diagnosis of cancer was changed, 3 to suspicious, 1 to HGPIN and 5 to benign. In the five cases changed to benign, three were interpreted as atrophic, one as post radiation changes, and one as Cowper's glands (Figure 2). The post radiation case changed to benign had had a TURP with cancer in it previously and the management would not have changed. The other four did not have repeat biopsies. The case changed to HGPIN had immunohistochemistry performed and this showed a basal layer. This patient had a subsequent biopsy that showed HGPIN only. The three cases changed to suspicious had only very few glands showing malignant features and were thought to be insufficient to be diagnostic. All these patients had subsequent biopsies – two showed cancer and one showed HGPIN.

The overall false positive rate was 9 cases of cancer changed divided by 1680 (as the total number of biopsies which were reported as cancer before the review) multiplied by 100 = 0.5% (see Table 3).

ERROR RATES: OVERALL AND PER CONSULTANT

Five consultants reported less than 60 biopsies and made no errors. The number of biopsies and the time period over which the pathologist reported the cores was recorded.

Eight pathologists made either false negative or false positive errors and this data is shown in table 3. The false negative rate varied from 0% to 9.3%, whereas the false positive rate varied from 0 to 3.8%. Consultant 10 had the highest false negative rate but made no false positive diagnoses, which was probably due to only reporting 44 cancers in the time period. Consultant 5 had a high false negative and false positive rate. Both the error rates were higher in the screened patients in comparison to the non-screened patients (Table 3).

Discussion

The definition of a false negative error in prostatic core biopsies is open to a degree of interpretation as previous studies have audited just benign diagnoses [11,12] but patients with HGPIN or atypia not amounting to HGPIN should also be included as these patients would not be automatically offered a repeat biopsy and as a result the diagnosis of cancer would have been missed. We have also included those cases not only changed to cancer but also to suspicious for malignancy as the majority of these patients had an early repeat biopsy which showed cancer. We excluded those patients whose biopsies were changed from suspicious to cancer on review as we felt this was not a true error but a reflection of thresholds for individual consultants to call cancer [11] and these patients would have been offered a repeat biopsy anyway, which was likely to have shown cancer.

We have previously published a single year audit which used the definition of those cases changed from benign to cancer and this showed a false negative error rate of 0.6% [16] but this larger audit used a broader definition and as a result found a higher rate of 1.7%. Kronz et al studied 3,251 biopsy cases seen in consultation and identified 87 (2.7%)

patients with missed lesions including HGPIN, of which 32 (1%) had prostatic adenocarcinoma [10]. This figure is probably an underestimation, as only selected biopsies were submitted for consultation. These errors would have changed patient management in 0.5% of all the patients. Van der Kwast et al reviewed 127 sets of prostatic needle biopsies with a benign outcome randomly selected from 7 centres participating in the ERSPC [11]. The authors identified variation between the reviewing pathologists with either a 4% or a 10% false negative rate. This variation was partly due to the threshold each pathologist had for diagnosing prostate cancer when only small numbers of abnormal glands were present [11]. In a recent publication, Wolters et al reported an overall false negative biopsy rate of 2.4% (1.1% for adenocarcinoma and 1.3% for ASAP) by reviewing 196 biopsies in a prostate cancer screening setting [12]. All of the false negative biopsy rates reported in these studies are based on review of material from a screening population or a consultation practice. In our study, the false negative rate in the screening population was 2.1% which is similar to that reported in these studies. The false negative rate in the non-screened population was 1.5% whereas the overall rate was 1.7%. The difference in rates reflects the higher rate of cancers and the lower rate of suspicious in the non-screened population in comparison to the screened patients. Also the non-screening cancers were likely to be a larger volume and less easily missed.

The definition of false positive used by most authors [11,13] is those cases changed from cancer to a non-cancer diagnosis simply because the cancer cases were audited. We have used this definition to enable comparison, but have not included those cases changed

from suspicious to benign, which could be argued were also significant changes (though none occurred in this study). We found that overall this was 0.5% but once again the screening population had a higher rate of 0.9% compared with the non-screened group of 0.4%. Other authors have found a rate of between 1.2% and 3% [11,13] but the higher rate was in a non-contemporary series. The decrease in false positive cases from the period studied by Berney et al and our study or the ERSPC data would suggest there has been a combination of greater use of immunohistochemistry as well as training of pathologists in uropathology. This is also reflected in the litigation figures for prostate pathology which show that false negative claims have increased whilst false positive claims have decreased over the past decade [17].

The main difference between this study and the other series reported in literature is that it encompasses a longer period of time and consequently includes a much larger number of biopsies. It is, to date, the largest series of prostatic biopsies which have been reviewed in literature and is an ongoing project. We felt it was imperative to examine our MDT review data following the recent recommendation by The National Institute for Clinical Excellence (NICE), that all negative cores be discussed at the MDT, but without the slides being formally reviewed. [18]. At the present time, we are aware that very few centres review the negative biopsies prior to the MDT (personal communication). Our study highlights that the probability of detecting significant pathology on review is far greater in the negative biopsies. The false positive cases were due to misinterpretation, where the exact cause could be identified and rectified by becoming familiar with the morphology of these misleading pitfalls. The false negative diagnoses, on the other hand,

were predominantly errors of oversight, where small foci of carcinoma were either not seen at all, or not identified as being cancer. It is clear that these errors are more difficult to rectify by further education and training.

This study has also revealed a significant variation in the error rates between pathologists. The consultants with the three highest error rates were all senior pathologists with greater than 60 years experience between them. The majority of false negative diagnoses were due to missed lesions and it could be argued that these pathologists suffered from overconfidence or distractions or time pressures, whilst more junior colleagues had been exposed to core biopsies during their training and took longer and more care examining them. Reporting the radical prostatectomy specimens was done by either CS and JO and not seeing these may have been detrimental to the training of the general pathologists, although many district general hospitals report core biopsies but not radical prostatectomy specimens. Wolters et al suggest that screening one level at high power would have detected this type of error but we suggest that it is a combination of knowing when to examine a focus at high power and when not to, as often the malignant focus may only be in one level. Minimising errors is critical to patient safety and this study has demonstrated that this can be done via review prior to the MDT but this is a costly method and most departments would be very unwilling to implement this. As the negative biopsies are less than 50% of the workload and as the positive cores are already reviewed, the increase in workload would not be too onerous. We estimate that reviewing the negative cores took us 1 to 2 hours per week. Some departments double report the malignant diagnoses but there are reported errors even with this system [19]. Another

method being adopted by centres is specialist reporting and indeed the pathologists with a specialist interest had some of the lowest rates but the specialists made mistakes, but at no more than 1.4% false negative rate and neither made false positive errors. Certainly it could be related to the number of biopsies seen per month, with the consultant with the highest false negative rate only reporting 2 per month but the converse is not true as the consultant reporting over 10 a month also had a high false negative rate. Southmead Hospital has now moved to complete specialist reporting but we are continuing to review all biopsies and will repeat this audit in the future.

In conclusion, errors are detected at the review prior to the MDT meeting and reviewing the negative cores detects more clinically relevant errors than reviewing the cancer diagnoses. Current strategies of specialist reporting and double reporting cancers will decrease error rates but we feel a review of all biopsies is the only reliable method.

Acknowledgements

We would like to thank our colleagues and the screening study for allowing us to use this data and the screening histopathology subgroup for using the classification of non-cancer diagnoses.

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Figure 1: Pseudohyperplastic carcinoma misdiagnosed as benign (a) H&E x200 (b) Immunohistochemistry for high molecular weight keratin (34BE12)

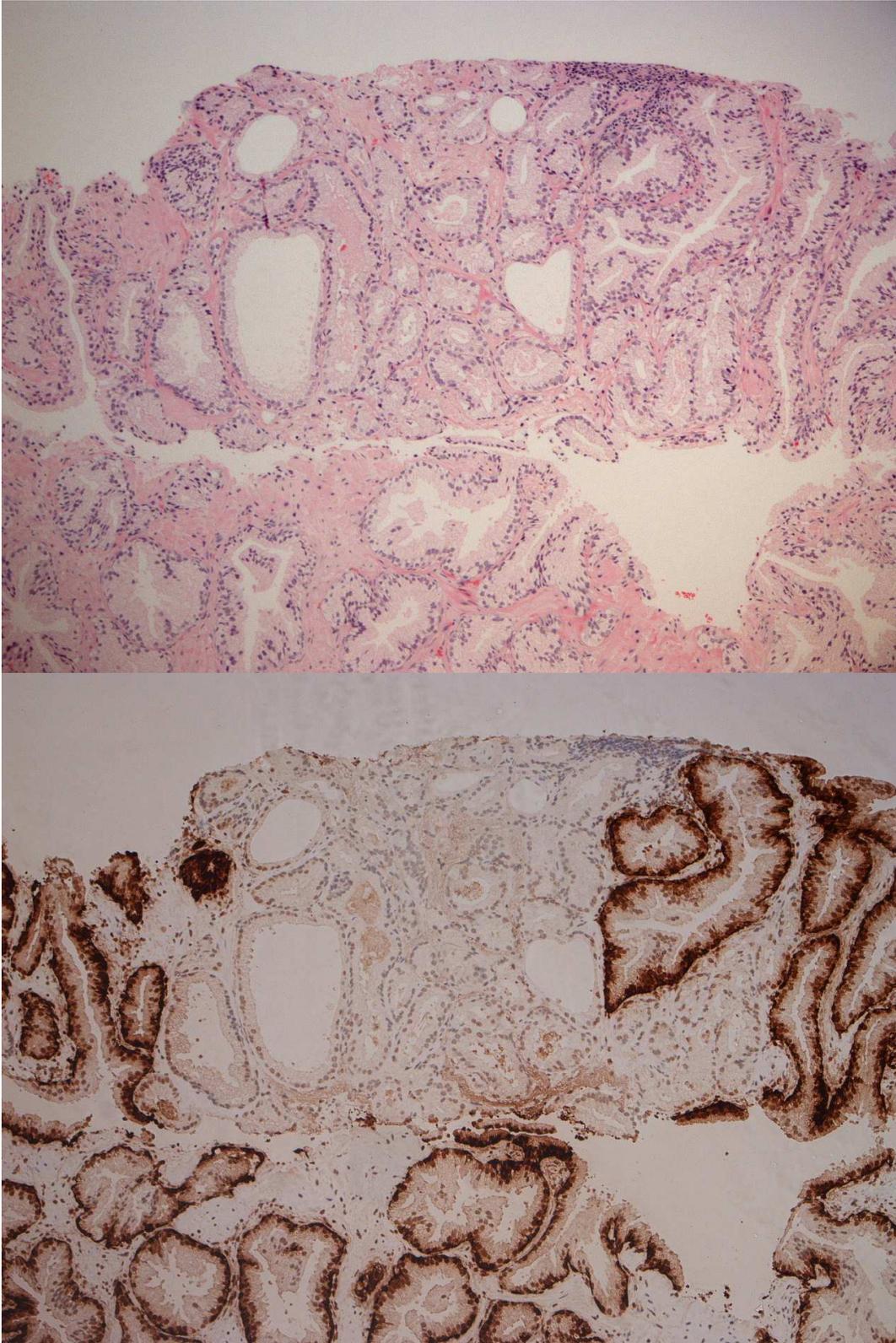
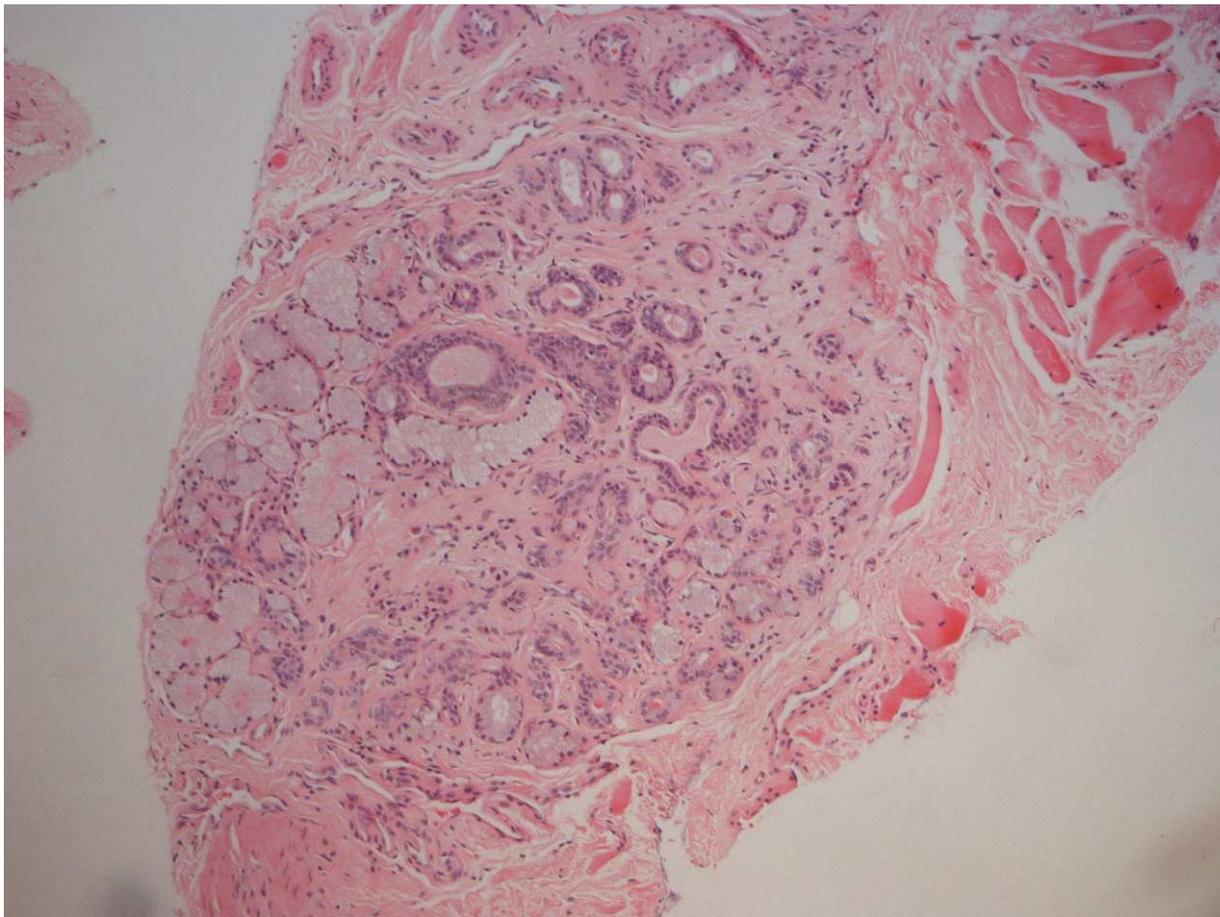


Figure 2: Cowper's glands misdiagnosed as adenocarcinoma. (Original magnification x200)



view

Table 1 : Diagnosis in 4192 prostatic biopsies following review and divided into screened and non screened cases.

Diagnosis	OVERALL		SCREENED		NON-SCREENED	
	Number	%	Number	%	Number	%
inadequate	14	0.3	6	0.5	8	0.3
benign	1790	42.7	546	47.9	1244	40.8
atypia	58	1.4	31	2.7	27	0.9
HGPIN	484	11.5	155	13.6	329	10.8
suspicious	135	3.2	54	4.7	81	2.7
cancer	1703	40.6	349	30.6	1354	44.4
TCC	4	0.1	0	0	4	0.1
lymphoma	4	0.1	0	0	4	0.1
TOTAL	4192	100.00	1141	100.00	3051	100.00

TCC = transitional cell carcinoma

Table 2: Data showing the changes of diagnosis after biopsies were reviewed (a) Overall (4192 biopsies) (b) Screening (1141 biopsies) (c) Non Screening (3051 biopsies). **Yellow highlight = false negative, blue highlight = false positive**

OVERALL						
<i>Review</i>						
<i>diagnosis</i>	benign	atypia	HGPIN	Suspicious	cancer	TOTAL
<i>Original</i>						
<i>diagnosis</i>						
benign	x	7	76	12	22	117
atypia	0	x	5	1	0	6
HGPIN	3	0	x	1	5	9
suspicious	0	0	0	X	5	5
cancer	5	0	1	3	x	9
TOTAL	8	7	82	17	32	146
SCREENING						
<i>Review</i>						
<i>diagnosis</i>	benign	atypia	HGPIN	Suspicious	cancer	TOTAL
<i>Original</i>						
<i>diagnosis</i>						
benign	x	5	27	8	7	47
atypia	0	x	1	0	0	1
HGPIN	1	0	X	1	0	2
suspicious	0	0	0	x	1	1
cancer	0	0	1	2	x	3
TOTAL	1	5	29	11	8	54
NON –SCREENING						
<i>Review</i>						
<i>diagnosis</i>	benign	atypia	HGPIN	suspicious	cancer	TOTAL
<i>Original</i>						
<i>diagnosis</i>						
benign	X	2	49	4	15	70
atypia	0	X	4	1	0	5
HGPIN	2	0	X	0	5	7
suspicious	0	0	0	X	4	4
cancer	5	0	0	1	X	6
TOTAL	7	2	53	6	24	92

Table 3: Number of biopsies reported by each pathologist and error rate per pathologist and for the group overall. Also shown is data for the screening and non-screening patients. (Rates highlighted in red are greater than the overall rate. Consultants 1 and 3 had a special interest in uropathology.)

Consultant	total number	number per month	false negative			false positive		
			number of biopsies originally reported as benign, atypia or HGPIN	Number of errors	rate %	number of biopsies originally reported as cancer	Number of errors	rate %
1	1403	19.8	791	2	0.3	575	0	0.0
2	645	10.4	357	12	3.4	271	4	1.5
3	499	7.8	277	4	1.4	198	0	0.0
4	399	5.6	222	3	1.4	165	1	0.6
5	285	8.1	161	8	5.0	105	4	3.8
6	221	7.6	133	3	2.3	86	0	0.0
7	180	6.9	95	1	1.1	74	0	0.0
8	139	5.4	84	0	0.0	53	0	0.0
9	137	9.1	69	0	0.0	59	0	0.0
10	135	2.2	86	8	9.3	44	0	0.0
11	57	5.7	35	0	0.0	22	0	0.0
12	49	24.5	29	0	0.0	16	0	0.0
13	28	9.3	16	0	0.0	9	0	0.0
14	13	6.5	10	0	0.0	3	0	0.0
15	2	2	2	0	0.0	0	0	0.0
Overall	4192	58.2	2367	41	1.7	1680	9	0.5
Screened	1141	15.8	747	16	2.1	344	3	0.9
Non-Screened	3051	42.4	1620	25	1.5	1336	6	0.4

false negative %error rate = biopsies detected as cancer or suspicious for cancer/biopsies originally reported as benign,atypia,HGPIN x100

false positive %error rate = biopsies detected as not cancer/biopsies originally reported as cancer x100