

Solitary cold thyroid nodules – a correlation of fine needle aspiration cytology with pentavalent technetium DMSA scanning and radionuclide perfusion scanning

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Abstract

Twenty-five patients with solitary cold thyroid nodules (SCN) were studied by fine needle aspiration (FNA) cytology, radionuclide perfusion scanning (RPS) and pentavalent technetium dimercaptosuccinic acid (99m Tc DMSA) scanning, with an aim to distinguish neoplastic from non-neoplastic nodules. All the patients were operated upon and the nodules were subjected to histopathological examination. 13 of the 25 nodules (52%) were malignant (7 papillary carcinomas, 3 medullary thyroid carcinomas and 1 each of follicular carcinoma, insular carcinoma and clinically anaplastic thyroid tumour). The specificity of DMSA scanning and FNA cytology were 100% and that of RPS 60%. The sensitivity of RPS and DMSA scanning were 80% and 20% and that of FNA cytology (using a broad definition of test-positivity), 100%. Additionally, FNA cytology could morphologically type the majority of neoplasms.

Key words: Papillary carcinoma, insular carcinoma, follicular carcinoma, medullary thyroid carcinoma, anaplastic thyroid tumour.

INTRODUCTION

A variety of investigations are available for the evaluation of solitary cold thyroid nodules (SCN), including radionuclide scintiscanning, ultrasonography and fine needle aspiration (FNA) cytology. On static radionuclide scintiscanning, only the functional status of the nodules can be assessed, whereas radionuclide perfusion scanning (RPS) provides additional information regarding the vascularity of the nodule.¹⁻⁴ New imaging techniques using tumour-seeking radiopharmaceuticals have been developed, e.g. pentavalent technetium dimercaptosuccinic acid (Tc 99m DMSA)⁵⁻⁸ and 131-Iodine metaiodobenzyl guanidine (MIBG).⁹

FNA cytology has been found to be an invaluable modality for the evaluation of SCN, as it not only distinguishes benign from malignant nodules in most of the cases, but also provides accurate morphological diagnosis.⁴ However, FNA cytology may sometimes yield an equivocal picture and in these cases, isotope studies may also not be decisive.⁴

The current study combines the use of FNA cytology, RPS and DMSA scanning for the detection of malignancy in SCN.

MATERIALS AND METHODS

25 out-patients from the surgical department of Lok Nayak Jai Prakash Narain (NJPN) Hospital and the thyroid clinic of the Institute of Nuclear Medicine & Allied Sciences (NMAS), presenting with clinically and scintigraphically proven SCN were taken up for this study. Besides routine investigations, they were subjected to RPS, DMSA scanning and FNA cytology. All 25 patients were then operated upon and a detailed histopathological study of the surgical specimens carried out.

RPS was performed with technetium 99m pertechnetate, using a Siemens ZLC-37 gamma camera, interfaced to an on-line PDP 11/34 computer. 16-20 rapid sequence scintigrams were recorded at the rate of one frame every 30 seconds, to study the perfusion status of the nodule. Hypervascularity was taken to be a positive result and avascularity, a negative result.³ Tc 99m (V) DMSA scanning was done with the same equipment. Scans were obtained at 5 and 30 minutes and at two hours. A persistent accumulation of the radio-tracer in the nodule site was considered to be a positive test.⁵

FNA cytology was done using a 24 gauge

TABLE 1: Final histological diagnosis of 25 cases of solitary cold thyroid nodules

Final Diagnosis	No. of cases
Colloid goitre	7
Colloid goitre with Hashimoto's thyroiditis	3
Adenoma	2
Papillary carcinoma	7
Follicular carcinoma	1
Medullary thyroid carcinoma	3
Insular carcinoma	1
Clinically anaplastic thyroid tumour	1
Total	25

needle attached to a syringe mounted on a syringe-holder. Smears were air-dried, fixed in methanol and stained with May Gmnwald Giemsa (MGG). Two smears in each case were wet-fixed in ethanol for any subsequent special staining technique.

The extent of surgery varied from lobectomy to near-total or even total thyroidectomy, depending on the FNA cytological diagnosis. Debulking thyroidectomies were performed in two cases and block dissection of cervical lymph nodes was done in all cases showing FNA cytological evidence of metastasis. The resected specimens were fixed in formalin and processed for histopathological study.

The sensitivity and specificity of each investigative modality were calculated using a general decision matrix.¹⁰ The results of the

individual investigations were then compared. The pre-test probabilities were derived from the observed incidence of neoplasia and post-test probabilities were calculated using Baye's theorem.¹⁰ The tests were then analysed on the basis of probability statements.

RESULTS

The break-down of the 25 cases based on the final histopathological diagnosis is depicted in Table 1. 13/25 cases (52%) were found to be malignant neoplasms and two were adenomas, yielding a 60% overall incidence of neoplasia.

The localisation pattern seen on DMSA scanning in the 25 cases is shown in Table 2. Persistent localisation of DMSA was seen in only three cases, two cases of medullary thyroid carcinoma (MTC) and one case of clinically

TABLE 2: Tc99m (V) DMSA localisation pattern in SCN (25 cases)

Localisation Pattern	MTC	Other malignancies	Adenoma	Non-Neoplastic
Persistent localisation	2	1*	0	0
Early localisation only	1	1**	0	3
No localisation	0	8	2	7
Total	3	10	2	10

* The case of clinically anaplastic thyroid tumour
 ** A case of papillary carcinoma

TABLE 3: Vascularity of nodule on RPS correlated with final diagnosis (25 cases)

Vascularity	Malignancy	Adenoma	Non-neoplastic
Vascular	11	1	4
Avascular	2	1	6
Total	13	2	10

TABLE 4: Cytodiagnosis of SCN correlated with histodiagnosis (25 cases)

Cytodiagnosis	No.	Histodiagnosis	No.
MALIGNANT			
Papillary carcinoma	5	Papillary carcinoma Papillary carcinoma with Hashimoto's thyroiditis Insular carcinoma with focal papillary areas	
Papillary carcinoma with Hashimoto's thyroiditis	2	Papillary carcinoma with Hashimoto's thyroiditis	
Medullary thyroid carcinoma	3	Medullary thyroid carcinoma	3
Clinically anaplastic thyroid tumour	1	Clinically anaplastic thyroid tumour	1
EQUIVOCAL			
? Extra thyroidal malignancy	1	Cystic Papillary carcinoma	1
Suspicious of neoplasm	5	Follicular carcinoma Follicular adenoma Colloid goitre Colloid goitre with follicular hyperplasia and Hashimoto's thyroiditis	1 2 1 1
Suspicious of follicular neoplasm with Hashimoto's thyroiditis	1	Colloid goitre with follicular hyperplasia and Hashimoto's thyroiditis	1
NON-NEOPLASTIC			
Colloid goitre with Hashimoto's thyroiditis	1	Colloid goitre with Hashimoto's thyroiditis	
Colloid goitre	6	Colloid goitre	
Total	25		25

anaplastic thyroid carcinoma (CATT). One patient each with MTC and papillary carcinoma (PC) and three patients with non-neoplastic nodules revealed early localisation of the radio-tracer (not persisting at 2 hours). None of the non-neoplastic nodules showed a positive test result.

Correlating the vascularity of the nodules on RPS with the final diagnosis (Table 3), it was seen that 12 out of 15 neoplastic nodules were vascular. However, of 13 malignant lesions, 2 were avascular. 4 of 10 non-neoplastic nodules were vascular.

Table 4 depicts the cytodiagnoses correlated with histodiagnoses. In 18 cases, a definitive diagnosis was feasible while in 7 cases, the cytological picture was equivocal. Of the 13 malignant nodules, FNA cytology detected 11 and correctly identified the type of malignancy in 10. FNA cytology also correctly identified 7

of 10 non-neoplastic nodules, labelling the remaining 3 and the 2 adenomas as equivocal.

Cytological and histological features

Smears from colloid goitre showed mild to moderate cellularity with background colloid and monomorphic clusters of follicular cells (Fig. 1). The cases showing moderate cellularity with a prominent acinar pattern or occasional three-dimensional tissue fragments were classified as cytologically equivocal.

The presence of Hashimoto's thyroiditis (HT) in association with neoplastic or non-neoplastic lesions was picked up in 4 out of 5 cases by the presence of a prominent lymphoid population, Hurthle cells, multinucleated giant cells and degenerative changes in follicular cells (Fig. 2).

Of the 7 cases of PC, 6 were correctly diagnosed by FNA cytology. Smears characteristically showed high cellularity with

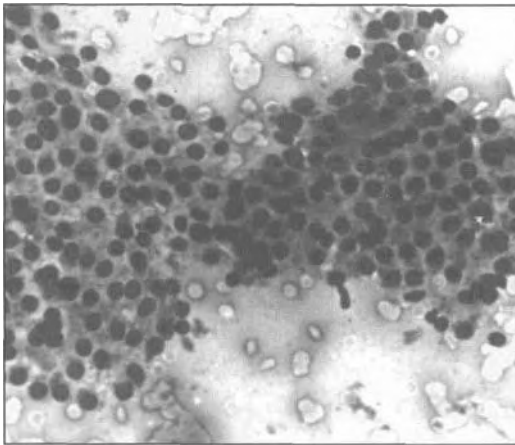


FIG. 1: Clusters of monomorphic follicular cells in a background of colloid. MGG \times 200

papillary clusters, some with vascular core (Fig. 3) and three dimensional tissue fragments. Loose clusters and acinar pattern were seen in addition in 3 cases. Intranuclear cytoplasmic inclusions and dense cytoplasm were seen in 4, and psammoma bodies in 1. Squamous metaplasia (Fig. 4), Hurthle cell change (Fig. 5) and spindle cell change of follicular cells were seen in 5, 3 and 2 cases respectively.

Nuclear grooves were seen in some of the cells in 3 cases (Fig. 6). One case of cystic PC received an equivocal cytological diagnosis owing to marked dilution of cells in the haemorrhagic fluid aspirated. These 7 cases of PC included 1 diffuse sclerosing variant and 1 encapsulated variant (with capsular infiltration). Two of the cases showed histological evidence of HT in the affected as well as contralateral lobe, while 1 case showed HT in the contralateral lobe alone.

Of the 3 cases of MTC, one was a classic MTC and the other two were oxyphil variants of MTC. Aspirates were cellular with round and

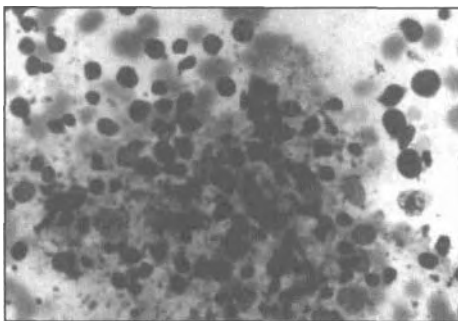


FIG. 2: Follicular cell degeneration and infiltration by lymphoid cells in Hashimoto's thyroiditis. MGG \times 200

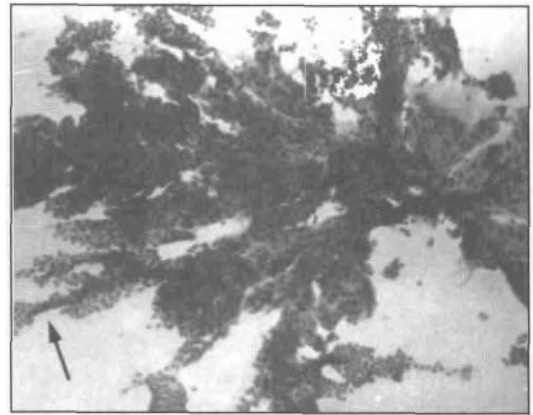


FIG. 3: High cellularity with cells in papillary clusters some with vascular core (arrow). MGG \times 150

spindle cells arranged in dissociated pattern (Fig. 7). The tumour cells in classic MTC had moderate amounts of pink granular cytoplasm and eccentric nuclei. Binucleated and trinucleated cells, focal cellular pleomorphism and focal clustering of tumour cells were seen. The second case showed, in addition, a very prominent population of large cells with abundant deeply staining cytoplasm and pink granules (oxyphilic cells). Focal clustering and papillary patterns were present. Some papillae were populated by small round cells transforming to spindle cells (Fig. 8) and others by oxyphilic cells (Fig. 9). Binucleated and trinucleated cells and cells with bizarre giant nuclei were frequent. The third case showed a completely oxyphilic cell population with focal acinar pattern. No amyloid was seen in the cytological smears of any of these cases. Immunocytochemical study showed the presence of calcitonin in most of the tumour cells in case 1 and some of the cells in cases 2 and 3. Histological study showed an organoid pattern with nests, cords and trabeculae of tumour cells arranged in a connective tissue stroma with a delicate vascular network. In case 2, the small

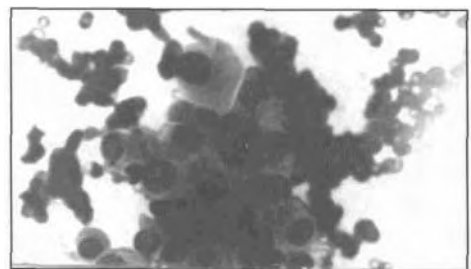


FIG. 4: Metaplastic squamous cells in papillary carcinoma. MGG \times 200

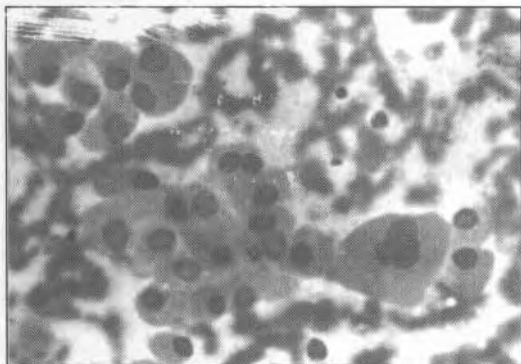


FIG. 5: Hurthle cell change in papillary carcinoma. MGG $\times 200$

round cells merged into areas of oxyphil cell tumour (Fig. 10), while in case 3, the entire tumour showed oxyphilic cells. The papillary pattern seen in the cytological smears was reflected in the histological sections. Amyloid and calcitonin could be demonstrated in histological sections in all three cases.

Both the follicular adenomas and the case of follicular carcinoma (FC) were labelled as equivocal on cytology, owing to sub-optimal cellularity and presence of colloid in the background. Acinar pattern was prominent (Fig. 11) and there was focal clustering and fire-flare activity. Histopathological sections showed capsular and vascular permeation in the case of FC.

Aspirates from CATT showed dissociated as well as adenoid and papillary clusters of follicular cells and many bizarre giant forms with single to multiple nuclei. Mitotic activity was prominent with abnormal mitoses. Bizarre malignant squamous cells and ghost cells were seen. Features of HT were also present. Sections from debulked tumour tissue showed a bizarre malignant squamous cell component alternating with areas of pleomorphic papillary

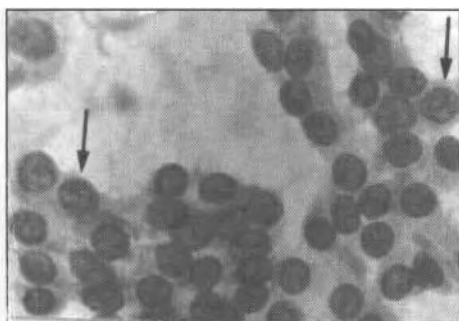


FIG. 6: Nuclear grooves (arrow) in papillary carcinoma. Pap $\times 400$

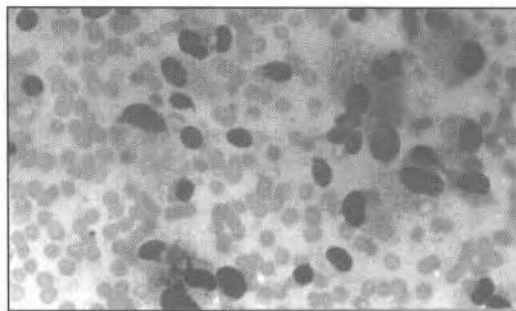


FIG. 7: Dissociated round and spindle cells in medullary thyroid carcinoma. MGG $\times 200$

adenocarcinoma. The presence of HT was confirmed on the sections.

Smears from IC were cellular with monomorphic clustered follicular cells mostly showing dense cytoplasm, fire-flare appearance and focal papillary pattern. FNA cytology from a metastatic lesion in the clavicle also showed the same cytological picture. A misdiagnosis of PC was made in this case. Sections showed an insular (poorly differentiated) thyroid carcinoma, consisting of sheets of small, uniform tumour cells with round to oval nuclei that showed minimal pleomorphism. A focal papillary pattern was present but not prominent. Capsular and vascular permeation were seen.

In the two cases with FNA cytology proven metastatic lymphadenopathy, sections of the block-dissection specimen showed evidence of metastatic carcinoma.

Table 5 shows the decision matrix for statistical analysis and Table 6 shows the calculated sensitivity and specificity of the tests used. It can be seen that FNA (using a broad definition of test-positivity that includes malignant and equivocal cytological reports) as well as RPS had high sensitivity rates, FNA being the more

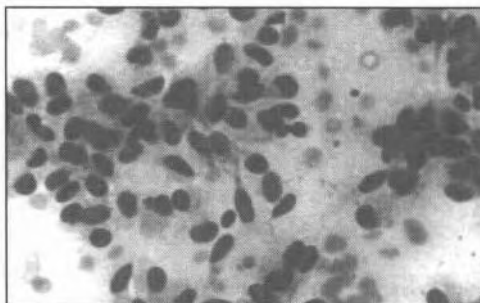


FIG. 8: Papillary clusters of spindle and round cells in medullary thyroid carcinoma. MGG $\times 200$

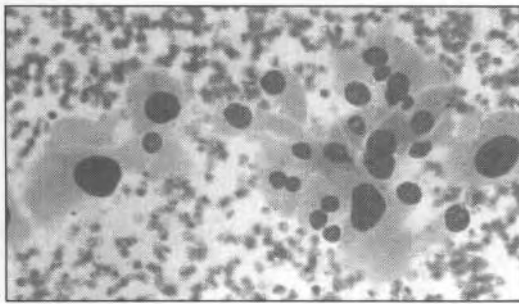


FIG. 9: Papillary clusters of oxyphilic cells in medullary thyroid carcinoma. MGG x 300

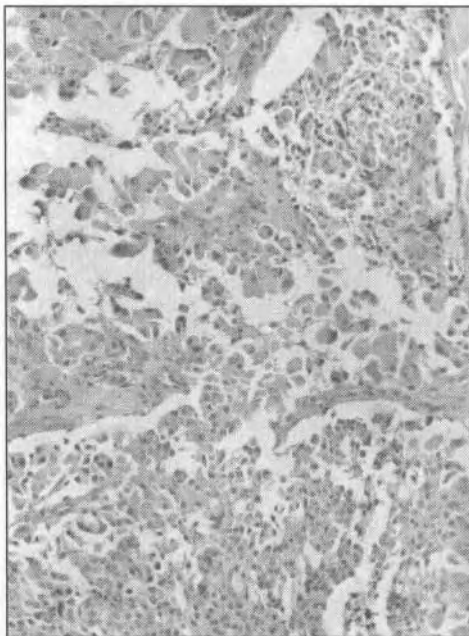


FIG. 10: Small round cell area merging with oxyphilic pattern in medullary thyroid carcinoma. H&E x 150

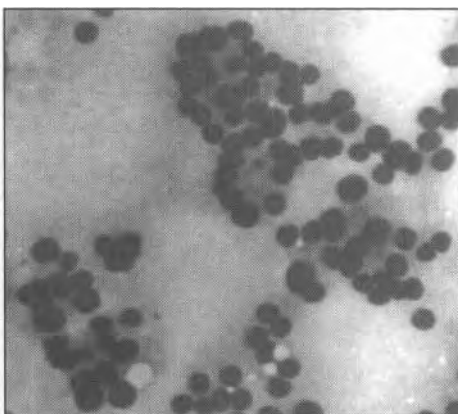


FIG. 11: Acinar pattern in follicular carcinoma. MGG x 200

specific of the two. DMSA scanning, though 100% specific, had a very low sensitivity of only 20%.

DISCUSSION

Reports of malignancy in SCN vary from 10.4% to 44.7%.¹¹⁻¹³ The present study yielded a 52% incidence of malignancy. DMSA scanning had a sensitivity rate of only 20% but the specificity was 100%. Of the three cases that were positive on DMSA scanning, two were MTCs and one a CATT. The exact mechanism of DMSA localisation by MTC is obscure and it has been postulated to be related to microcalcifications in the tumour.⁵ The differences in DMSA localisation pattern (early or persistent localisation) may be due to differences in the extent of microcalcification in the tumour.¹⁴ We are not aware of any detailed study on the DMSA localisation in thyroid tumors other than MTC. The phenomenon of DMSA localisation in CATT is to our knowledge unreported and may require further evaluation in a larger series. ^{99m}Tc (V) DMSA scanning was found to have a specificity of 100% but its sensitivity was only 20%. It is therefore not a useful investigation in the diagnostic workup of SCN but may be useful in cases of suspected MTC.

RPS yielded a satisfactorily high sensitivity rate of 80% which compares well with other studies.¹¹ However the specificity here was only 60% compared to 75-100% reported by other workers. Of the seven cytologically equivocal nodules, RPS labelled all three neoplastic nodules (one adenoma and two carcinomas) as vascular. The two PC's that were negative on RPS were less than 1 cm in size raising the possibility that the resolution capacity of the gamma camera was probably insufficient to demonstrate the type of perfusion in nodules of such small size.

Since its introduction in 1952 FNA cytology¹⁵ has been extensively employed and is today an integral part of the diagnostic workup of nodular thyroid disease. PC was the commonest malignancy in this series. The cytopathology of PC has been well described.¹⁶ Intra-nuclear cytoplasmic inclusions were present in only 51% of our cases as opposed to 83% reported by Kini *et al.*¹⁶ These, however, were also seen in one case of insular carcinoma, and have been reported by other workers in non-papillary neoplasms of the thyroid.¹⁷⁻¹⁹ As Miller *et al.*²⁰ observed, dense cytoplasm, three-dimensional clusters and papillary clusters (with or without vascular core) were characteristic features of PC.

TABLE 5: Decision matrix for calculation of sensitivity and specificity of various diagnostic tests

TEST	Neoplastic thyroid nodule				Non-neoplastic thyroid nodule			
	+ve Test (a)	Equivocal (a or b)	-ve Test (b)	Total (a+b)	+ve Test (c)	Equivocal (c or d)	-ve test (d)	Total (c+d)
FNA cytology	11	4	0	15	0	3	7	10
RPS	12	0	3	15	4	0	6	10
99mTc (V) DMSA Scanning	3	0	12	15	0	0	10	10

Positive test results : Malignant/follicular neoplasm on FNA cytology; vascular on RPS; Persistent localisation on DMSA scanning.

Equivocal test result : Equivocal on FNA cytology.

Negative test results : Non-neoplastic on FNA cytology; avascular on RPS; only early localisation/ no localisation on DMSA scanning.

Sensitivity = $a/(a+b)$: Specificity = $d/(c+d)$

The low incidence (14%) of psammoma bodies (a strong indicator of lymph node metastasis)²⁷ is probably a reflection of the lack of lymph node metastasis in the cases of PC in this study. Psammoma bodies have occasionally been found in non-neoplastic thyroid lesions.²¹⁻²² Interestingly, associated HT was found in two cases of PC. The reported incidence of carcinoma in HT varies from 5% to 22.5%.²³⁻²⁴ However, reports on the incidence of HT in papillary carcinoma are scanty.⁴

The encapsulated variant of PC in our series showed vascular permeation which is at variance with reports of these tumours having an unusually good prognosis. One diffuse sclerosing variant which occurred in the isthmus nodule of a young female showed FNA cytological as well as histological evidence of associated thyroiditis, a common finding in this variant of PC.²⁵⁻²⁶

Cytological features of MTC have been documented.²⁷⁻²⁸ A dispersed cell pattern dominated in classic MTC. Variant forms of MTC have been described.²⁹ The papillary variant needs to be distinguished from PC coexisting

with MTC.²⁹ The oxyphil variant has often been misdiagnosed as Hurthle cell tumour.³⁰

Distinction of follicular neoplasms from follicular hyperplasia was difficult owing to suboptimal cellularity and the presence of colloid in the background. Suen³¹ found it helpful to divide follicular lesions into three cytological groups according to their probability of being malignant.

The combination of pleomorphic adenocarcinoma with squamous cell carcinoma presenting as CATT has not been reported. We have however, encountered one case of papillary carcinoma with squamous cell carcinoma presenting as a CATT.³²

There are scanty reports on the cytology of IC³³⁻³⁴ which behaves more aggressively than differentiated thyroid carcinoma.³³⁻³⁶ A focal papillary pattern led us to misdiagnose it as PC. Some cases of IC have been shown to blend with conventional PC, while others become manifest only in recurrences of what had originally been PC.³⁶

The ideal test is one which offers 100%

TABLE 6: Sensitivity and specificity of various investigations

Test	Sensitivity (Defn. of +ve test)		Specificity (Defn. +ve test)	
	Narrow	Broad	Narrow	Broad
FNA cytology	73.33%	100%	100%	70%
RPS	80%	NA	60%	NA
99mTc(V) DMSA scanning	20%	NA	100%	NA

NA : Not applicable, as there are no equivocal results.

sensitivity and specificity. In spite of the limitations with the small number of cases, the high sensitivity and specificity of FNA cytology has shown it to be a valuable tool in the diagnosis of SCN. The feasibility of accurate morphological typing of the tumour by FNA cytology enables planning of the extent of surgery. A narrow definition of test positivity eliminates false positive diagnosis. A broad definition of test positivity increases the sensitivity (pick up rate) for neoplastic lesions, albeit decreasing the specificity.

A broad definition of test positivity may be preferred by many surgeons so as to not miss any case of malignancy. The outstanding role of FNA however, is in segregating the SCNs that do not require surgery from the ones that do. Using Baye's theorem,¹⁰ when the test is positive, the probability of neoplasia is 100% for FNA cytology (narrow definition) as well as for DMSA. The percentage of missed disease however is 0% for FNA cytology (broad definition) but as high as 54% for DMSA. RPS misses 33% of neoplasms while the percentage of operations done for non-neoplastic disorders is 25%. We consider therefore, that FNA cytology is the best single investigative modality for evaluating SCN.

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