

Differential Diagnosis of Nodular Goiter by Means of Aspiration Biopsy Cytology —Results in recent five years—

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ABSTRACT

A series of the aspiration biopsy cytology (ABC) was conducted on 1092 patients with nodular goiter, and the accuracy of diagnosis obtained preoperatively by the ABC method was studied using 277 cases firmly diagnosed by the surgical operations. As to determination whether a nodule is benign or malignant, 5.5% was noted as false positive, 11.8% as false negative, the overall accuracy being 92.1%. Upon diagnosis by ABC, much of them were mutually misdiagnosed between papillary proliferation and papillary carcinoma of epithelial cells partially observed in adenomatous goiter, showing the most part to be false positive and false negative. Occult carcinoma was predominated in the false negative cases. In general, although a question remains in a little more false negative cases, ABC itself indicates a high diagnosability with no expected complications. Specially as to malignant nodules, it was superior in nontraumatic determination of histological types, being able to determine the mode of operation already at the stage of examinations for outpatients.

Thyroid is one of the small organs in the body showing various lesions most frequently. Although modules are observed same in appearance, they are much different in nature being benign, malignant, hyperplastic, retrogressive, inflammatory, etc. Accordingly the basis of right treatments is to correctly diagnose the respective nodules. Up to date nodular goiter used to be diagnosed mainly by palpation supplemented by cervical xeroradiography, scintigraphy, etc. Recently ultrasonic diagnosis, CT scan, and other clinical imaging techniques being developed, an epoch-making improvement has been made on diagnosis of modules, i.e., to find out how far in what shape a module exists, etc., however, still a qualitative diagnosis to see whether it is benign or malignant has not been sufficiently developed. It means, differentiation of nodules depends much on the physicians' ex-

periences and perception. The authors have since long been trying to induce this diagnosis by ABC to obtain the more objective ways of nodule differentiation. In past 5 years numerous cases were studied to find out usefulness and the limits of ABC. Now most of those in question have been experienced, therefore, the results are reported below.

MATERIALS AND METHODS

ABC was applied to 1092 patients with nodular goiter visited the Second Surgery Ward of the University Hospital of Hiroshima, from August 1982 to July 1986 for 60 months, either of them having received the initial examination only before surgery. Referring to 277 cases showing the both diagnoses before the operation by ABC and after resection by histopathological tests, both results were studied in compari-

son as to the diagnosability by ABC, misdiagnoses and their reasons. The specimens were collected using the suction unit equipped with a 23G Cathelin's needle (5 cm) and a 10 ml disposable syringe (Cameco, Sweden). Smears were stained with MGG stain, and cells in the specimens were examined according to the criterion of Löwhagen¹⁶. Determinations were made in reference to the microscopic findings of smear and simple statement on cervical tumor at outpatient only. A nodule was punctured twice from different portions, and determined from two smears prepared. Meanwhile, in case when nodule was a cyst, centrifuged residue of the liquid content was used as smear.

RESULT

Table 1 shows the consequence from the preoperative diagnosis by ABC to the postoperative definite diagnosis with 277 cases. In the table the term 'follicular adenoma' upon diagnosis by ABC has been used in the meaning of benign goiter with nearly no colloid showing the repeated microfollicular pattern as stated by Löwhagen¹⁶, which is a little different from the so-called follicular adenoma used in usual histopathological classifications⁹. The authors

see to it that follicular adenoma is hardly differentiable from follicular carcinoma by ABC⁹, but in this series of study tried to differentiate it having nuclear diameter of the cell as a tentative standard¹¹, i.e., that larger in the mean nuclear diameter than 14 μm (about 2 times larger than that of red blood cells in the background) was determined as carcinoma and that smaller than the same as adenoma. Furthermore, the term 'colloid goiter' in the table includes both adenomatous goiter as stated in the histological diagnosis and a part of follicular adenoma (that easily causes cystic changes containing much colloid). They are the designations conventionally used, as both of them show findings by ABC quite similar with each other making it hardly differentiated. Naturally all of those determined malignant by ABC (140 cases) had been surgically operated, and those determined as follicular adenoma (48 cases) also were resected taking possible false negative cases into consideration. In addition, surgical operations were applied to 28 patients noted to have calcification upon cervical xeroradiography although being determined benign by ABC (colloid goiter and Hashimoto's thyroiditis), 30 patients with large and hard nodules, and 31 patients who

Table 1

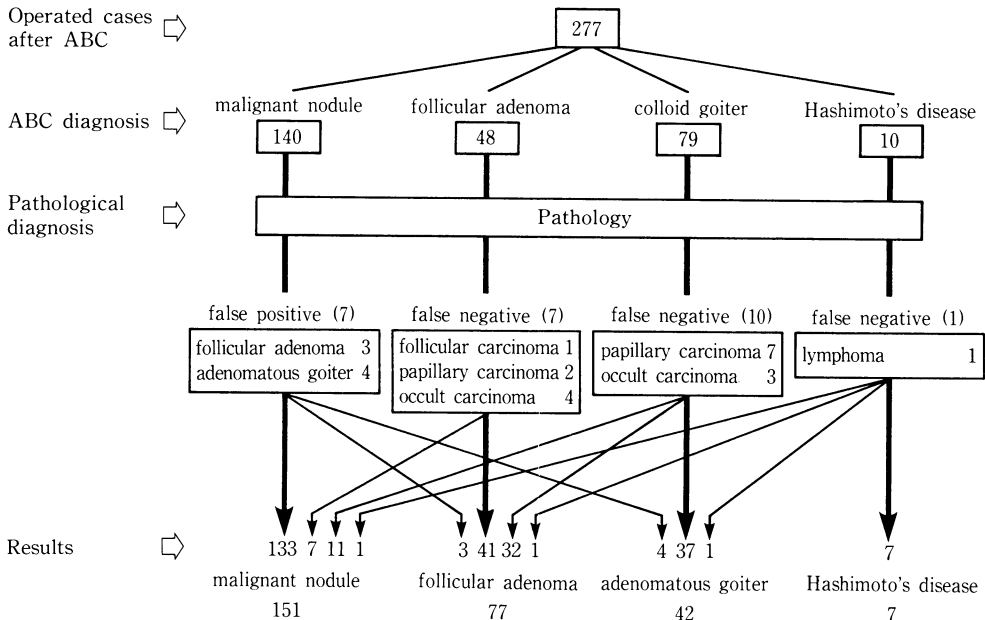


Table 2

benign nodules (126)	follicular adenoma	77
	adenomatous goiter	42
	Hashimoto's thyroiditis	7
malignant nodules (151)	papillary carcinoma	115
	follicular carcinoma	8
	medullary carcinoma	7
	anaplastic carcinoma	6
	adenosquamous carcinoma	1
	occult carcinoma	7
	lymphoma	7

wanted to have surgery by themselves. Table 2 shows details of those histopathological diagnoses referring to the resected cases.

i) Diagnostic accuracy of ABC

From the above the diagnostic accuracy on thyroid nodules referring to benign and malignant cases are noted to be as follows:

False positive = {No. of benign cases diagnosed as malignant (7)}/
{No. of benign cases in total (126)} × 100 = 5.5 (%)

False negative = {No. of malignant cases diagnosed as benign (18)}/
{No. of malignant cases in total (151)} × 100 = 11.8 (%)

Overall accuracy = {No. of cases in total (277) - No. of cases misdiagnosed (25)}/{No. of cases in Total (277)} × 100 = 92.1(%)

ii) Details of 7 false positive cases

There were 4 cases with papillary patterns noted in tissue of adenomatous goiter diagnosed as papillary carcinoma. Next, there were 3 cases of follicular adenoma determined to be malignant, which however included 2 cases of 'over-reading' their papillary patterns slightly noted in distribution of follicles. (It was thought to be carcinoma but actually it wasn't.) Another case was oxyphilic adenoma consisted of large cells diagnosed as follicular carcinoma.

iii) Details of 18 false positive cases

Contrary to the false positive cases as above, there were 7 cases of papillary carcinoma determined as adenomatous goiter, together with 7 cases of occult carcinoma failed to notice, both of them being the major part of misdiagnosis. As to the former it was common in every case that carcinoma consisted of small cells with less cytoplasm containing no intranuclear inclusion

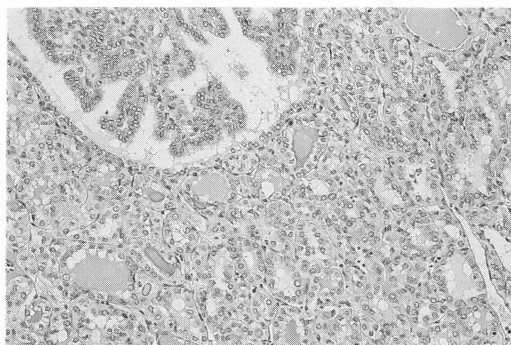


Fig. 1. Histology of "papillofollicular" carcinoma showing focal papillary proliferation in the follicular pattern.

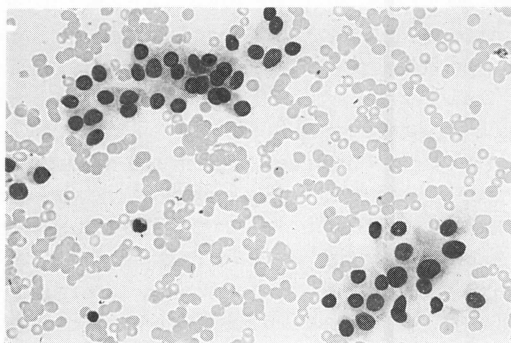


Fig. 2. Microfollicular pattern mimicking follicular adenoma was derived from same nodule shown in Fig. 1

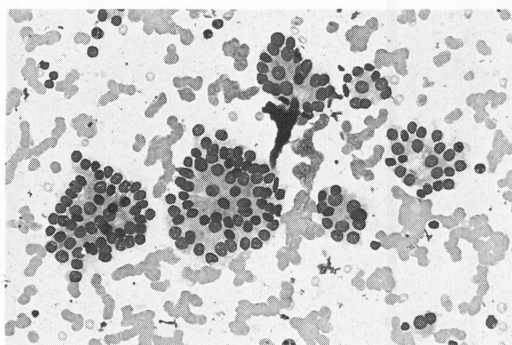


Fig. 3. This is a case of follicular carcinoma apparently looks like "fetal" type adenoma

body. As to the latter either one was found coincidentally during operations of benign nodules or in the specimens thus enucleated, all of which belonged to papillary carcinoma in their histol-

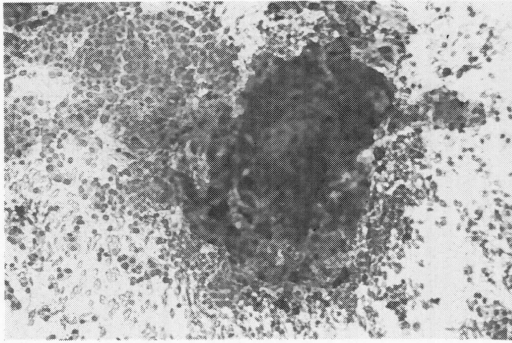


Fig. 4. Large cell cluster of adenomatous goiter, mimicking papillary carcinoma because of high cellularity and relatively abundant cytoplasm

ogy. Furthermore, there were 2 cases of papillary carcinoma, and 1 case of follicular carcinoma, both diagnosed as follicular adenoma. The former, being a type of carcinoma showing both papillary and follicular patterns, is considered to be misdiagnosed because a part with strong follicular proliferation was suctioned by chance upon puncture. (Fig. 1 and 2). The latter was the case of follicular carcinoma hardly determinable by ABC showing no heteromorphism on cells (Fig. 3). Those 3 cases stated above being diagnosed as 'adenoma' caused no practical hazard to 'overlook carcinoma', as either of them was surgically operated according to the initial plan. There was a case of lymphoma diagnosed as Hashimoto's thyroiditis, which was a misdiagnosis because of numerous lymphocytes in smear being well differentiated. Fig. 6 shows 7 cases of occult carcinoma schematized, wherein 5 of them were found coincidentally on the ipsilateral lobe during the surgical operation of benign nodules, while 2 of them were found as small lesions in the excised benign nodules.

iv) Tissue types of malignant nodules identifiable by ABC (Usually tissue types are determined with pathological specimens. How far it would be possible to determine it correct with ABC was studied.)

It was roughly successful in 'differential diagnosis for benign and malignant cases', but occasionally some of the tissue types were classified in a wrong way, including 3 cases of misdiagnosis between follicular carcinoma and papillary carcinoma (the former was misdiagnosed as the latter and vice versa), 2 cases of

the same between anaplastic carcinoma and papillary carcinoma, and 2 cases of the same between medullary carcinoma and papillary carcinoma respectively, and 1 case of adenosquamous carcinoma misdiagnosed as anaplastic carcinoma, 8 cases in total. There were 137 cases determined correctly as malignant by ABC (Table 1), which means that at a ratio of 94.2% the determination of tissue type by ABC well corresponded with that diagnosed with the paraffined specimens.

v) Application frequencies of ABC and their accuracies

Out of 277 cases in Table 1, 41 cases were repunctured later due to 'less numbers of cells', or 'short of the information for determination', etc., upon which, however, 18 cases of carcinoma were picked up.

DISCUSSION

This series of the study for ABC was made subject to the 'nodules palpable', therefore, 'detection of occult carcinoma' was essentially impossible. In future, improvement of determination on false negative cases related to this point should have to depend on a certain precise ultrasonic apparatus to be introduced. As reported by some researchers^{8,10}, it is hard to determine follicular adenoma out of well differentiated follicular carcinoma, therefore, even according to the author's way of differentiation by nuclear diameter 3 false positive cases and 1 false negative case were noted. A misdiagnosis of papillofollicular carcinoma (according to the criterion it belongs to papillary carcinoma) was caused by a suction from the part of follicular pattern due to unprecise microscopy manipulated, wherein a part of the papillary patterns was confirmed upon remicroscopy of two smears to every corner. In this series of the study misdiagnoses were predominated in those between adenomatous goiter and well differentiated papillary carcinoma. It is said to be differentiable by further studies on volumes of cytoplasm in epithelial cells (that with more cytoplasm is carcinoma), and volumes and properties of colloid (that with less colloid being ropier is carcinoma)¹⁶. Practically, however, even upon reexamination taking these points into account, more than a half of those misdiagnosed can hardly be differentiated (Figs. 4 and

Table 3

Author (Reference)	Cases Operated after ABC	Malignant	False negative	False positive	Suspected to be malignancy* ³ (Actually malignant)	Examined for occult carcinoma or not
Einharn	(4) 177* ¹	52	4/ 52(7.7%)	0	19(13)	undescribed
Löwhagen	(8) 412	96	9/ 96(9.6)	0	123(24)	undescribed
Shnürer	(12) 284	28	1/ 28(3.6)	0	7(12)	undescribed
Friedman	(7) 265* ²	52	1/ 52(1.9)	1/ 213(0.5%)	0	undescribed
Miller	(10) 147	45	2/ 45(4.4)	1/ 102(1.0)	42(8)	6(out of statistics)
Chu	(2) 109	28	2/ 28(7.1)	2/ 81(2.5)	0	2(out of statistics)
Colacchio	(3) 80	23	3/ 23(13.0)	4/ 57(7.0)	0	undescribed
Varhang	(15) 264	68	16/ 68(23.5)	0	74(26)	undescribed
Togon	(14) 514	202	36/202(17.8)	21/ 312(6.7)	0	10(in statistics)
Radetic	(11) 2190	248	78/248(31.4)	9/1942(0.5)	252(82)	Partly in statistics
Present series	277	151	18/151(11.8)	7/ 126(5.5)	0	7(in statistics)

*¹ Including that open biopsied

*² Including that open biopsied and that with recurrence case

*³ Including that with follicular neoplasm

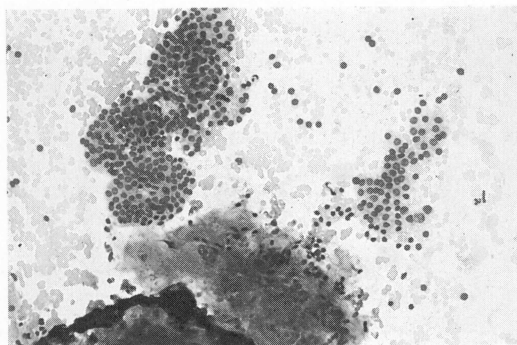


Fig. 5. Well differentiated papillary carcinoma of the thyroid without intranuclear occlusion, apparently showing papillary proliferation of adenomatous goiter.

5), which should have to be studied further in future. As stated already under RESULTS, 89 outpatients diagnosed as colloid goiter or Hashimoto's disease by ABC under observations were surgically operated due to the above stated reasons, out of which 10 cases of carcinoma and 1 case of lymphoma (Table 1) were detected. It indicates the fact that the physicians in the outpatients' ward should not hesitate to give surgical operations whenever a certain abnormality is noted on those in the course of precise follow-up. Specially, out of 7 cases with papillary carcinoma successfully picked up from those diagnosed as colloid goiter preoperatively, 4 cases were detectable upon microcarcification of

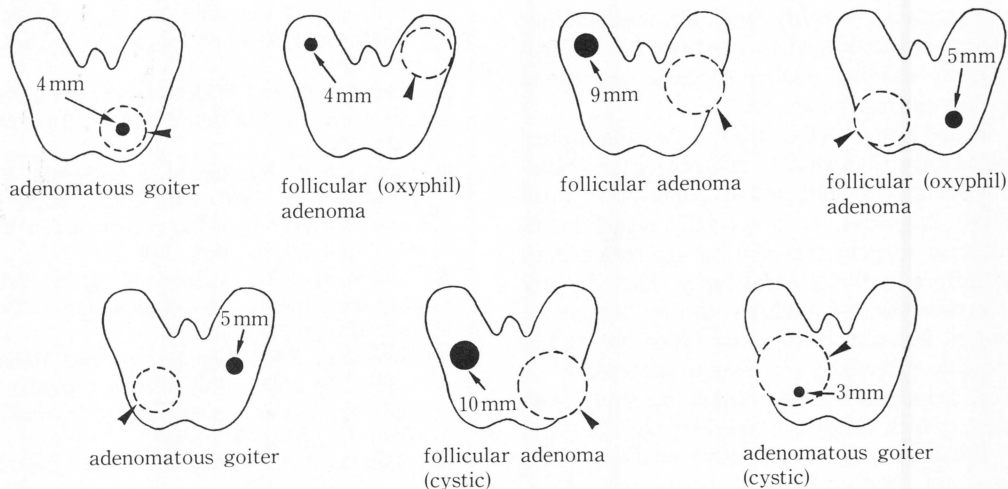


Fig. 6. Locality and size (major axis) of occult carcinoma cases (arrow) Dotted circles show another benign nodules (arrow head)

the xeroradiography, which is remarkable as a step to supplement defects of ABC. Furthermore, when sufficient findings were unobtainable by the initial tests of smears, repunctures should have to be tried by all means to find out the respective malignancy.

Table 3 shows various reports referring to the results of ABC for nodular goiter. It must be taken into consideration in comparison of those 6 reports^{4,8,10,12,15} that less numbers of misdiagnosis are noted therein as the result having those hardly determined included in the 'suspected malignancy'. In addition, most of the overseas reports do not refer to the cases of occult carcinoma, intentionally excluding them out of statistics^{2,10}, therefore, their accuracy should have to be estimated somewhat lower. Furthermore, some report included those easily diagnosable as local recurrence in the population of statistics⁷. Generally taking those matters into consideration, the authors' result can be by no means inferior to their studies.

Referring to complications occurred upon execution of ABC, there was nothing notable except a few cases of mild blood stains remained on the neck, and 2 cases with strong cough attacks upon puncture of trachea by mistake. It has been reported that seeding or implantation of tumor cells may rarely occur even by means of ABC using a thin needle^{6,13}, which however was not confirmed to be because of puncture in the author's study. There is a case of implantation occurred around the wound after surgery of malignant nodule, which however has no evidence to determine that caused by preoperative puncture. As such implantation is noted only when carcinoma is infiltrated into surrounding tissues, it is considered to be caused more frequently by seeding during surgical operations than that during puncture.

As stated above, ABC itself shows the higher diagnosability than that of the presently available methods, although not so superior in false negative diagnoses. It is specially beneficial in the thyroid surgery wherein the operation plan much differs by histological types that not only a determination of nodules to be benign or malignant but also histological types are highly identifiable. Recently in Japan increasing of medical expenses has been taken up as a social problem, which obliges to consider the medicine from the phase of cost effective analysis. ABC being simple and economical can be one of the most effective ways of examination from this point of view.

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