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ORIGINAL ARTICLE

Value of repeat ultrasound-guided fine-needle aspiration in thyroid nodule with a first benign cytologic result: Impact of ultrasound to predict malignancy

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Abstract This study aimed to investigate the value of repeat ultrasound-guided fine-needle aspiration (FNAC-US) in benign thyroid nodules and determine the ultrasound (US) predictors of malignancy in this group of nodules. The authors studied 35 of 143 nodules with initially benign cytological result who underwent serial re-biopsy (FNAC-US). By means of surgery, malignancy histology results were confirmed in 10 (28.5%) cases (G1) versus 25 (71.5%) benign nodules (G2). The clinical, lab, scintigraphyc, and US features were compared between the two groups to predict malignancy in thyroid nodules with initially benign cytological result. The cytological finding of 28/35 nodules were change to indeterminate cytology (Bethesda system category III or IV) at second and/or ≥third cytological study. In this group of 28 cases, 23 (82.1%) was identified until the third procedure. The interval between first and third re-biopsy was 13 months (median). There were no differences in age, gender, thyrotropin (TSH) levels, thyroid auto-antibodies, or thyroid dysfunctions. The scintigraphy showed cold nodule in 80% of G1 versus 78.9% of G2 (NS). Sonographic studies showed malignant suspected US features in G1: microcalcifications, central flow, hypoechogenicity, and border irregularity. This study suggests repeating FNAC-US in nodules with first benign cytologic result and suspicious US features of malignancy for at least two times (until the third FNAC) in about 13 months horizon.

Keywords Thyroid nodule · Fine-needle aspiration cytology · Ultrasound · Thyroid cancer

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Introduction

The value of repeated thyroid nodule fine-needle aspiration cytology (FNAC) during follow-up is still controversial and most society's guidelines indicate that benign lesions may be followed yearly by ultrasound (US) only. FNAC is still considering the gold standard for evaluating thyroid nodules [1]. However, FNAC has some limitations in thyroid nodule diagnosis, such as false negative (FN), false positive and/or inadequate results. The reported FN rate of FNAC ranges from 1.3 to 11.5% in several studies [2–5]. The majority of patients with thyroid nodule can be managed conservatively and it justifies the effort to select better candidates for thyroidectomy [5, 6].

It is recommended that all benign thyroid nodules be followed with only US examinations 6–18 months after the initial benign FNAC. If nodule size is stable (<50% change in volume or <20% increase in at least two nodule dimensions in solid nodules or in the solid portion of mixed cystic-solid nodules), the interval before the next follow-up clinical examination or US may be longer (every 3–5 years) [1].

The repeat FNAC is not considering for nodules with initially benign cytologic result in spite of clinical or lab features, scintigraphyc or US parameters at baseline. There is no consensus for the need to repeat cytology after an initial benign result, despite the reported minimal 1% rate

of FN results [5]. Some authors advise a follow up FNAC in all patients [5, 7, 8]; others suggest repeat FNAC only for patients who develop clinically suspicious findings [6, 9–11]. In according to Mehanna et al. [12] the probability of a benign thyroid nodule being accurately diagnosed as benign from a single FNAC is 90%. However, the accuracy of diagnosis increases significantly to 98% if two separate aspirates were performed on different occasions.

Illouz et al. [7] retrospectively studied the cytologic and histological results of 119 nodules surgically treated. The repetition of FNAC reveals a relevant number of cancers which were missed by the first FNAC (10/44 surgically treated suspicious or malignant in repeated FNAC during follow up). They recommended three adequate FNAC to decrease the number of FN results.

A recent data suggests ultrasound characteristics of malignancy rather than growth as a criterion for repeat FNAC in the case of nodules with an initial benign cytological result [13]. This study enrolled 895 thyroid nodules, 102 (11.4%) presented suspicious US parameters. The second FNAC revealed malignancy in 18 (17.6%) nodules, including 20% (2/10) of those showing growth and 17.4% (16/92) that did not. Seventy-six (9.6%) of 793 nodules without suspicious characteristics presented growth. Only one case of malignancy was diagnosed by repeat FNAC.

Kwak et al. [14] showed a higher risk of malignancy in patients with suspected US features in a thyroid nodule with initially benign cytologic results. The risk of malignancy was lower for negative (0.6%) versus positive US suspected features (20.4%) in a thyroid nodule with benign cytologic results. Of 122 surgically treated thyroid nodules in this group, 23 (18.8%) were malignant. They conclude that repeat FNAC should be performed for initially benign thyroid nodule with suspicious US features.

It is estimated that cytology indicative of papillary thyroid carcinoma (PTC) is associate with younger age, male gender, higher thyrotropin (TSH) values (even in normal ranges: >1.8 mU/ml), thyroid auto-antibodies (TAb) and solitary nodularity [15, 16]. The accuracy of these clinical aspects, US or scintigraphyc features in distinguishing benign from malignant thyroid nodule with initially benign cytologic result is not well-established.

The benefits and criteria for re-biopsy of benign thyroid nodule at first FNAC and positive US needs more comprehension and may help the surgical decision in these specific cases and to avoid unnecessary aggressive treatments. This study aimed to investigate the value of repeat ultrasound-guided fine-needle aspiration (FNAC-US) in benign thyroid nodules and determine the ultrasound (US) predictors of malignancy in this group of nodules. The clinical and scintigraphyc parameters of malignancy in thyroid nodules with initially benign cytological results is still analyzed in a long-term follow up period.

Materials and methods

Design and study population

The study was approved by the institutional review board and no competing financial interests exist by authors. The authors retrospectively studied the data from 143 patients submitted to total or partial thyroid surgery between 1998 and 2008 at the University of Campinas General Hospital, São Paulo, Brazil, an area of iodine sufficiency. This study included 35 thyroid nodules diagnosed as benign at first FNAC-US evaluation and underwent follow-up (annual serial re-biopsy) study showed a malignancy histology result in 10 (28.5%) cases (G1) versus 25 (71.5%) benign nodules (G2). All patients preoperatively diagnosed with a thyroid nodule by US or by clinical examination, underwent FNAC-US and were assessed retrospectively for clinical, US, and scintigraphyc variables to prediction of malignancy in this group. The mean follow up was 53.9 ± 50.7 months. The most common surgical indication was indeterminate cytology plus newly suspect ultrasound features during follow up (Table 1).

Clinical and lab parameters

The clinical variables were age and gender. There was a female predominance into two groups (benign versus malignant nodules) (Table 2). The lab variables enrolled baseline TSH and free thyroxin (FT4) serum concentrations. The TSH and FT4 were dosed through chemiluminescent analyzer, sandwich technique, range from 0.4 to 4.5 UI/ml and 0.9 to 1.8 ng/ml, respectively. The thyroid autoimmunity was defined by elevated serum levels of antithyroid peroxidase (TPOAb, reference value <35 μ UI/ml) and antithyroglobulin antibodies (Tg-Ab, reference value <49 IU/ml) determined by immunometric assays.

Thyroid disorders were classified as follows in normal thyroid function (TSH and FT4 values within the reference

Table 1 Criteria for surgical treatment of 35 nodules with initially benign cytological result by FNAC-US according to final histology result

Surgical criteria	Benign	Malign	Total
Clinical/compressive symptoms	02 (8%)	–	02 (5.7%)
FNAC + Scintigraphy–Cold nodule	09 (36%)	03 (30%)	12 (34.2%)
FNAC suspect (indeterminate)	06 (24%)	02 (20%)	08 (22.9%)
FNAC suspect + US features	08 (32%)	05 (50%)	13 (37.2%)
Total	25 (100%)	10 (100%)	35 (100%)

FNAC fine-needle aspiration cytology, *FNAC-US* fine-needle aspiration cytology guided ultrasound, *US* ultrasound

Table 2 Clinical and lab aspects of 35 patients with initially benign cytological result of fine-needle aspiration cytology (FNAC) of thyroid nodule during the follow up according to final histology result

Variables	Benign	Malignant	Total	*P*-value
Nodules (*n*)	25	10	35	–
Age (months)	47.72 ± 13.11	46.80 ± 14.02	47.46 ± 13.17	1.00
Gender (Female)	22/25	8/10	30/35	0.61
Nodule (number)/patient	1.56 ± 1.15	1.50 ± 1.26	1.54 ± 1.17	0.76
Nodule size (cm)	3.04 ± 1.72	1.55 ± 0.58	2.59 ± 1.52	0.003
TSH (mU/ml) [median]	1.11	1.67	1.14	0.57
FT4 (mU/ml) [median]	1.30	1.28	1.29	0.38
TAb positively (*n*)	5/20	1/9	6/29	0.63
Auto-immune disease (*n*)	6/21	1/10	7/31	0.37
Normal thyroid function	18/25	6/10	24/35	0.61
Hyperthyroidism	5/25	2/10	7/35	0.84
Hypothyroidism	2/25	2/10	4/35	0.32

values); autoimmune thyroid disease (AITD) (euthyroid with high TAb); overt hypothyroidism (elevated TSH with reduced free T4 levels); thyrotoxicosis (or hyperthyroidism): low TSH and elevated FT4 (Table 2).

Cytological and scintigraphyc features

Cytological analysis was based on Bethesda classification system [16]. All of slides from FNAC result were re-analyzed by an expert cytopathologist of the pathology department (P.S.M) in order to confirm the results. After obtaining the previous pathology reports the cytologist reviewed them and reclassified the cases using the Bethesda system according to the microscopic features which were described on the existing pathology reports. This review of slides was blind to outcomes in all cases. The FNAC result was classified into six categories: unsatisfactory (I), benign (II), follicular lesion of undeterminate significance (III), follicular neoplasm (IV), suspicious of malignance (V), and malignant (VI). Benign cytologic findings included colloid nodules, adenomatous hyperplasia, lymphocytic thyroiditis, and Graves disease. The indeterminate category (III and IV) includes follicular lesion, Hurtle Cell tumor, and atypical presentation which could not exclude malignancy. Follicular neoplasm demonstrated follicular architecture, overlapped nuclei, high cellularity, scant colloid, and no nuclear features of PTC. The FNAC result was considered suspicious for PTC when demonstrated papillary or follicular architecture with overlapped nuclei and nuclear characteristics such as nuclear enlargement, border irregularity, intranuclear inclusions, and/or nuclear grooves. The unsatisfactory sample was defined as the absence of at least six follicular cell groups, each one containing 10–15 cells derived from at least two aspirates of a nodule according to the American Thyroid Association (ATA) guidelines. The interval between first and repeat aspiration was more than 90 days (to avoid nuclear atypia related to aspiration). Malignancy result was confirmed by means of thyroid surgery.

The relevance of cold nodule was evaluated using a ^{99m}Tc-pertechnetate (Tc) scans. Twenty minutes after an intravenous injection of 10 mCi (370 MBq) of ^{99m}Tc, the images were obtained on a computerized scintillation camera equipped with a low-energy, high-resolution, parallel hole collimator, according to validated protocol used at the institution [17], with the nodules being reported as cold, warm, or hot.

Sonographic parameters and FNAC-US

Real-time US was performed and supervised by a radiology team with experience in thyroid imaging at the institution. It was not possible to control the numbers of professionals enrolled in FNAC procedures and the interpersonal or intrapersonal reproducibility of the FNAC during the follow up period. Internal components of the nodule were defined as solid, mixed, or cystic. US analyses for masses with mixed components were evaluated on the basis of internal solid components. The FNAC was performed systematically in nodules $\geq$1 cm in diameter. US features defined size and suspicious parameters of malignancy [1] as following: hypoechogenicity, microcalcifications, border irregularity, and central flow by Doppler study. The presence of one of these parameters defined the nodule as positive at US findings (suspicious malignant nodule) being the FNAC study indicated in nodule <1 cm diameter [1]. If a nodule did not show suspicious features it was classified as probably benign (negative US findings). When a nodule was detected, FNAC-US was performed using a 22-gauge needle without local anesthesia. If the aspirate was

hemorrhagic a 25-gauge needle was used. Aspiration was expressed on frosted-end glass slides, air-dried, and stained using Papanicolaou's method [18]. For each sample, at least three slides were obtained for cytological analysis. The follow up FNAC was repeated systematically after 12–18 months, in the case of nodules with suspicious US characteristics, irrespective of growth, and in the cases when the nodule showed significant growth (volume increase ≥50%, showing an increase in diameter ≥20%, and with at least two of the measurements ≥2 mm) during the same period. The surgery criteria was based on the clinical (compressive and laboratory complications), image and cytological approach.

The nodule size and presence of other nodules within the thyroid were also noted and classified into single/solitary versus multinodular goiter. In this group (multinodular goiter), the most suspect nodule was included into study.

Statistical analysis

The data was analyzed by χ^2 test or Fisher's exact test for categorical variables and Mann–Whitney test for the quantitative variables of two groups ($P < 0.05$). Statistics were performed using SPSS, version 13.0.

Results

There was a 28.5% prevalence of malignancy (10/35) in thyroid nodule with initially benign cytology. There were no differences in mean age and female gender predominance between the two groups. The serum TSH, FT4, auto-immune disease, and thyroid state function were not correlated to malignancy in these nodules (Table 2). The blind review of the slides by an expert cytologist obtained 10.9% less diagnoses of III or IV Bethesda categories, reclassified as benign (II) result which was confirmed by means of surgery.

Of 35 nodules with initially benign cytological result, a posterior future non-benign FNAC result was obtained in 28 (80%) and confirmed in 10 (28.5%) cases in long-term follow up by means of surgery (Fig. 1). The cytological finding of 28/35 nodules were change to indeterminate cytology (category III or IV from Bethesda system) at second and/or ≥third cytological study. In this group of 28 cases, 23 (82.1%) was identified until the third procedure. PTC was detected in 9/35 (25.7%) malignant cases (four follicular variant and five, classical histology), and one follicular carcinoma of these 35 surgically treated nodules with initially benign cytology result. The mean interval between initial and the third re-biopsy was 24.90 ± 28.20 (median: 13) months. Seven patients underwent surgery even if they were persistently benign at repeated FNAC due to the clinical symptoms ($n = 1$), compressive symptoms ($n = 2$) and cold nodule (scintigraphyc result) associated to suspect US features ($n = 4$).

Sonographic evaluation showed a larger mean size in benign nodules ($P = 0.003$) (Table 2). Solitary nodules were not at increased risk (AOR 0.95, 95% CI 0.49–1.83, $P = 0.89$). The growth size tumor over than 20% neither cold nodule at scintigraphyc study were not determinant for malignancy ($P = 0.57$ and 0.95, respectively). The scintigraphy showed cold nodule in 80% of G1 versus 78.9% of benign lesions (G2) ($P = 1.00$). There were no false-positives and all malignant cases undergoing surgery were found to be malignant (Fig. 1).

Sonographic studies showed positive US in malignant group (G1): microcalcifications, central flow, hypoechogenicity, and

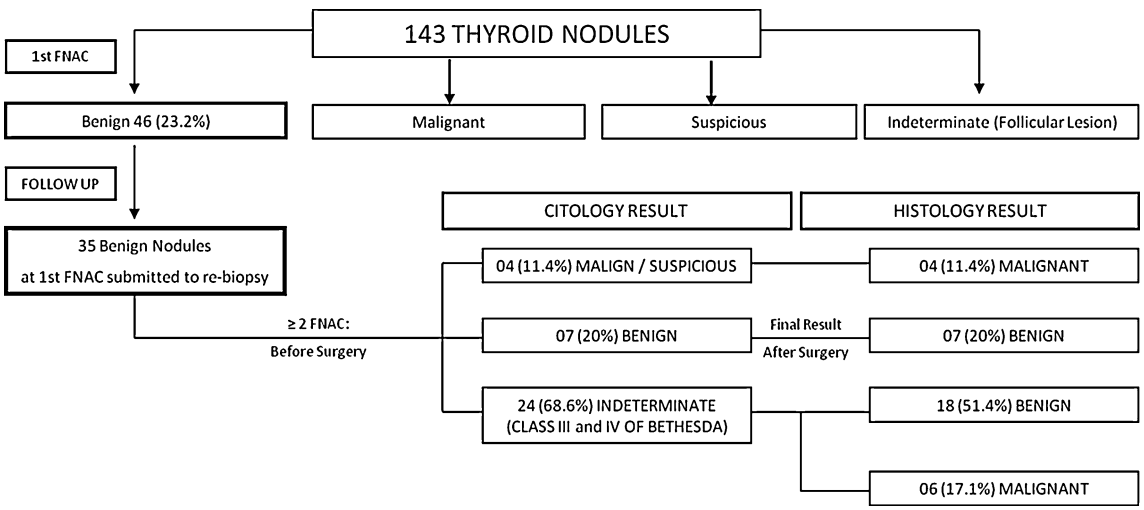

Fig. 1 Follow up of thyroid nodules with initially benign cytological result and histology correlation by means of surgery after serious re-biopsies (Fine-Needle Aspiration Cytology [FNAC]) in a single center

Table 3 Ultrasound parameters of malignance in the 35 nodules with initially benign cytological result by Fine-Needle Aspiration Cytology (FNAC) according to final histology result

Variables	Benign (%) (25)	Malignant (%) (10)	Total (35)	*P*-value
Microcalcifications	4/23 (17.4%)	7/10 (70%)	11/33 (33.3%)	0.014
Macrocalcifications	6/23 (26.1%)	1/10 (10%)	07/33 (21.2%)	0.95
Border irregularity	5/24 (20.8%)	6/10 (60%)	11/34 (32.3%)	0.036
Hypoechogenicity	8/24 (33.3%)	8/10 (80%)	16/34 (47%)	0.023
Size $\geq$ 2 cm	18/23 (78.3%)	4/10 (40%)	22/33 (66.7%)	0.028
Internal flow	1/16 (6.3%)	5/9 (55.5%)	6/25 (24%)	0.001
Absent flow	11/16 (68.8%)	0/9	11/25 (44%)	<0.001

border irregularity (Table 3). The internal flow by Doppler study was the strongest predictor of malignancy ($P < 0.001$) followed by microcalcifications, hypoechogenicity, and border irregularity. The absent of flow was an important criteria of benignity detected in almost 70% of benign thyroid nodules (G2) in this study (Table 3).

Discussion

Malignancy in thyroid nodules with initially benign cytology result showed a smaller size and suspect sonographic features during a mean 5 years follow up period. The scintigraphy was not useful to the differentiation of two groups. The number and nodule position were not predictive of malignancy. No clinical or lab parameter was significant in this study. This data indicates that repeating FNAC in patients with first benign cytologic result for at least two times (until the third FNAC) in about 13 months horizon could improve the diagnosis rate of malignant tumors and should be performed for thyroid nodules that have suspicious US features, even if the initial cytologic results indicate that it is a benign lesion.

The first benign FNAC could not exclude malignancy in all thyroid nodules. A definitive malignant diagnosis was present in 10/143 surgically treated nodules with initially benign cytologic result. Thus, considering the cytological results of the first FNAC, the malignancy rate achieved was 28%, whereas after re-puncture this value improved to 35%, increasing the diagnostic accuracy by 7%. The data from Kwak et al. [14] showed 23/122 malignant cases of surgically treated nodules benign at first presentation, mean interval between first and follow up FNAC of 15.6 months, similar to Illouz et al. [7] (11/119 surgically treated initially benign thyroid nodules) and to the results.

Some recent investigations showed larger median benign tumors over 2 cm of diameter [14, 15, 19] similar to the results. A retrospective analysis of more than ten thousand FNACs, demonstrated that repeated thyroidal FNACs yielding benign diagnoses increased the accuracy in 8% (from 90 to 98%) [8]. The re-biopsy reduces the rate of FN diagnosis from an average of 5.2% to <1.3% in nodules with initially benign cytological result [10].

Some studies have tried to document the natural history of benign tumors such as these. Alexander et al. [20] followed 268 patients with 330 US-guided FNAC benign thyroid nodules over a mean interval of 20 months. The repeating FNAC detected 1 malignant case of 74 nodules, a poorly differentiated PTC. Shin et al. [21] found nine malignancies in the 187 cases (4.8%) by repeat US-FNAC. Of 44 patients in the re-aspiration group, six malignancies were identified (13.6%). Orlandi et al. [22] studied 799 satisfactory FNAC from 302 patients (14–84 years.) followed for 2–12 years undergoing annually FNAC analysis. They conclude that in the absence of suspicious clinical changes and with at least three FNAC confirming the cytologic diagnosis of benignity, the follow-up of nodules by FNAC could be discontinued.

Van Roosmalen et al. [6] described the results and costs of two management strategies of routine follow-up FNAC in 576 nodules initially read as benign. In one of these strategies, follow-up FNAC was systematically repeated (Group I approach), and in the other hand, the follow-up FNAC was repeated only when clinical symptoms had been developed (Group II approach). The FNAC diagnosis according to Group I approach remained benign on follow-up biopsy in 96.2%, was altered to follicular neoplasm in 3% (7/235), and was suspicious for malignancy in 0.8% (2/235). When following Group II approach, the follow-up FNA was not "benign" in 7% (4/57). Cost-consequence analysis showed no benefit in routine follow-up FNAC after initially benign FNA readings. Routine follow-up FNAC in patients whose initial cytology result was benign has a low diagnostic upgrading value and is relatively costly. They concluded that in patients whose initial FNAC is benign, it is recommend the FNAC be repeated only if clinically suspicious signs or complaints develop.

Other investigators have also reported cases of carcinomas arising within benign nodules [23, 24]. Baloch et al. [24] studied the role of repeat FNAC in the evaluation of thyroid nodules initially classified as "nondiagnostic" due to limited cellularity or as "indeterminate for neoplasm".

The prevalence of malignancy was 50/101 (49%) of surgically treated nodules. There were no false-positives and all malignant cases undergoing surgery were found to be malignant, in according to the results. The presented data suggests that resection should not be performed in cases with repeat benign cytology even when that showed suspicious US findings. All the cases with repeat benign cytology were benign on surgical follow-up.

The risk of malignancy seems to be higher in patients with positive US features in a thyroid nodule with initially benign cytologic results by Kwak et al. [14]. The likelihood of having a benign thyroid nodule with suspicious US features was lower (79.6%) versus negative US features (99.4%). The risk of malignancy for initially benign thyroid nodules at FNAC with an increase in size at follow-up US was slightly higher (1.4%), but they did not demonstrate the specific US feature enrolled to thyroid malignancy. In another series from Kwak et al. [25], the repeat aspiration revealed "suspicious for malignancy" or "malignancy" results in 15 (93.8%) of 16 thyroid cancers with "benign" results on initial aspirate and US suspect findings.

The adequate interval to repeating FNAC is not well-established in medical literature. It was observed the increasing diagnosis of malignancy until the third re-biopsy in about one-to-two-years (median interval of 13 months) horizon in benign thyroid nodule at first FNAC, similar to recent literature [9, 12, 14, 21]. Flanagan et al. [9] studied 402 patients who underwent thyroid surgery during a 22-month period. The use of one repeat FNAC increased the sensitivity for malignancy from 81.7 to 90.4% and decreased the false-negative rate (17.1–11.4%).

In according to the results and corroborated by Rosario et al. [13], ultrasound parameters were superior as a criterion for repeat FNAC when compared to nodule growth. In fact, nodule growth is known to have a low positive predictive value for malignancy [20, 21].

It is important to cite some limitations of this study. Doubtless, the fact of FNAC-US was not carried for the same person of radiology team at the institution added to the unlikely control of the interpersonal or intrapersonal reproducibility of the FNAC during the follow up period represents a true limitation. However, the supervision of the achievement of the procedure by radiologists' members of the Radiology department minimizes the probable errors. This study demonstrated that 80% of nodules were benign at the first cytological exam became indeterminate or malignant at the second or third evaluations. However, in expert hands in about 40% of patients with histological diagnosis of thyroid carcinoma were defined benign at the first cytological exam. A bias may be that this study could not include all nodules examined in the same period of time submitted to FNAC and only some part of surgically treated nodules were included. In particular, it may be that benign nodules at repeated cytological exams and not undergoing surgery were not included in this study. However, this study reflects the real clinical practice in day care of patients with thyroid nodule and the difficult pitfalls in their management. Prospective studies are required to define the role of this risk prediction in refining clinical management of the larger patient population.

In conclusion, thyroid malignancy detected after first benign cytology showed a smaller size and suspects US features. The scintigraphy, clinical, or lab parameters were not useful to the differentiation of two groups. This study showed that the first benign FNAC could not exclude malignancy in all thyroid nodules and suggests to repeat FNAC in nodules with first benign cytologic result and positive US parameters for at least two times (until the third FNAC) in about 13 months horizon, to obtain a higher diagnosis accuracy. These findings enhance the current limited predictive armamentarium and can assist to guide surgical decision making.

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