Dear Editor,

We would like to highlight the need to reduce intraoperative frozen section (FS) during diagnostic hemithyroidectomy performed on thyroid nodules with Bethesda III cytology. Thyroid nodules are increasingly diagnosed and subjected to fine needle aspiration cytology. Bethesda III is a cytological category that consists of atypia or follicular lesion of undetermined significance, and carries a 6–30% risk of malignancy. Hemithyroidectomy is commonly performed on Bethesda III nodules to obtain a definitive histological diagnosis. FS during hemithyroidectomy allows some thyroid cancers—predominantly papillary thyroid carcinoma (PTC)—to be diagnosed intraoperatively. Such a diagnosis may prompt the surgeon to perform a total thyroidectomy and/or central neck dissection. However, the routine use of FS on Bethesda III nodules is controversial considering the low probability of a diagnosis of malignancy on FS, and such a diagnosis would not necessarily alter the extent of surgery. Until 2016, we practised FS routinely on Bethesda III nodules followed by total thyroidectomy with or without elective central neck dissection, if thyroid carcinoma was diagnosed on FS—except for papillary thyroid microcarcinomas. In view of recent guidelines recommending hemithyroidectomy without elective central neck dissection to be an acceptable treatment of well-differentiated intrathyroidal papillary carcinomas that are ≤4cm, we reviewed our experience to determine how FS in Bethesda III nodules may be reduced.

After obtaining ethics approval from our institution in Singapore, we studied the preoperative clinical, sonographic and pathologic characteristics associated with the diagnosis of malignancy or suspicion of malignancy on FS in 98 Bethesda III nodules from 98 patients. These patients underwent hemithyroidectomy and FS from our department between 2010 and 2016. Sonographic characteristics were retrieved from the radiologist’s report and suspicion of malignancy, defined by the presence of any of these features—microcalcification, marked hypoechogenicity, taller-than-wider configuration, irregular margin, extrathyroidal extension or abnormal cervical lymph nodes—was considered present if it was so specified by the radiologist. Cytologic atypia was diagnosed when nuclear enlargement, pale or clear chromatin, grooves or pseudoinclusions were seen in various combinations in the follicular cells, but were insufficient for a diagnosis of suspicion of malignancy (Bethesda V) or malignancy (Bethesda VI).

The age of the patients ranged from 16.6–79.7 years (mean 51.7 years). Seventy-two were female (73.5%). On FS, only 4 nodules (4.1%) were diagnosed as malignant (3 papillary and 1 medullary carcinoma), and 4 were suspicious of malignancy (2 papillary and 2 follicular carcinoma). The rest (91.8%) were benign or indeterminate of malignancy. On univariate analysis, the preoperative characteristics associated with a diagnosis of malignancy or suspicion of malignancy on FS were nuclear atypia (P=0.009), microcalcification (P=0.003) and the radiologist’s suspicion of malignancy on sonography (P=0.001). On multivariate logistic regression, only microcalcification (P=0.029) and radiologist’s suspicion of malignancy on sonography (P=0.030) remained significant (Table 1). This is consistent with the understanding that sonographic suspicion is most frequently associated with papillary thyroid carcinoma.

However, even if we only selected Bethesda III nodules with either microcalcification or a radiologist’s suspicion of malignancy for FS, the likelihood of a diagnosis of malignancy on FS would only increase from:

\[
\frac{4}{98} = 4.1\% \quad \Rightarrow \quad \frac{2}{23} = 8.7\% .
\]

Moreover, the size of the 3 PTCs diagnosed on FS were 1.3cm, 2.6cm and 3.5cm pathologically. None demonstrated gross extrathyroidal extension or nodal metastasis intraoperatively. Only 1 tumour diagnosed as malignant on FS, a medullary carcinoma (MTC), showed gross extrathyroidal extension and gross nodal metastases. This would be the only tumour that certainly required a total thyroidectomy and neck dissection. Therefore, FS in our series of Bethesda III nodules would convincingly change the extent of surgery in only 1 out of 98 patients (1.02%). Even in this patient, the fact that his MTC was diagnosed as Bethesda III was unusual. Upon review of the cytology, we found clues of MTC—the most important being the presence of singly dispersed cells misinterpreted as follicular cells. However, the cytology lacked amyloid, and was insufficient for immunohistochemistry. Neither was serum calcitonin or carcinoembryonic antigen available because MTC was not suspected clinically. If it had been, this MTC would probably be diagnosed.
Table 1. Factors predictive of malignancy or suspicion of malignancy on frozen section in thyroid nodules with Bethesda III cytology

| Preoperative characteristics | Frozen section | Benign or indeterminate n=90 | Suspicious or malignant n=8 | Univariate P value | Multivariate odds ratio (95% CI) | Multivariate P value |
|-----------------------------|----------------|-------------------------------|-----------------------------|-------------------|-------------------------------|---------------------|
| Mean age, years (95% CI)    | 52.0 (49.0–55.0) | 48.6 (36.9–60.2) | 0.517 | 0.98 (0.92–1.05) | 0.537 |
| Male, no. (%)               | 22 (24.4) | 4 (50.0) | 0.203 | 4.43 (0.69–28.65) | 0.118 |
| Hoarseness, no. (%)         |                |                              |                |                   | 0.161 |
| Yes                         | 1 (1.1) | 1 (12.5) | 0.161 |
| No                          | 87 (98.9) | 7 (87.5) |
| Unknown                     | 2 | 0 |
| Dysphagia, no. (%)          |                |                              |                |                   | 0.467 |
| Yes                         | 6 (6.8) | 1 (12.5) | 0.467 |
| No                          | 82 (93.2) | 7 (87.5) |
| Unknown                     | 2 | 0 |
| Subjective growth, no. (%)  |                |                              |                |                   | 0.515 |
| Yes                         | 7 (8.0) | 1 (12.5) | 0.515 |
| No                          | 81 (92.0) | 7 (87.5) |
| Unknown                     | 2 | 0 |
| Vocal cord palsy, no. (%)   |                |                              |                |                   | 1.00 |
| Yes                         | 1 (1.1) | 0 | 1.00 |
| No                          | 87 (98.9) | 8 (100) |
| Unknown                     | 2 | 0 |
| Median\(^a\) size in mm\(^b\) (range) | 26.5 (1.0–75.0) | 36.0 (13.0–76.0) | 0.237 | NA |
| Echogenicity, no. (%)\(^c\) |                |                              |                |                   | 0.215 |
| Hypoechoic                  | 38 (52.8) | 5 (100) | 0.215 |
| Isoechoic                   | 12 (16.7) | 0 |
| Neither                     | 22 (30.6) | 0 |
| Unknown                     | 18 | 3 |
| Consistency, no. (%)\(^d\)  |                |                              |                |                   | 0.716 |
| Solid                       | 45 (50.6) | 5 (62.5) | 0.716 |
| Solid-cystic                | 44 (49.4) | 3 (37.5) |
| Neither                     | 0 | 0 |
| Unknown                     | 1 | 0 |
| Internal vascularity, no. (%)\(^e\) | 29 (32.2) | 5 (62.5) | 0.121 |
| Taller-than-wider, no. (%)  | 1 (1.1) | 0 | 0.121 |
| Ill-defined margins, no. (%)\(^f\) | 5 (5.6) | 1 (12.5) | 0.409 |
| Microcalcification, no. (%)\(^g\) | 11 (12.2) | 5 (62.5) | 0.003 | 8.56 (1.25–58.51) | 0.029 |
| Suspicion of malignancy on sonography, no. (%)\(^h\) | 9 (10.0) | 5 (62.5) | 0.003 | 8.56 (1.25–58.51) | 0.029 |
| Nuclear atypia, no. (%)     |                |                              |                |                   | 0.469 |
| Yes                         | 42 (46.7) | 6 (75.0) | 0.009 | 0.60 (0.15–2.40) | 0.469 |
| No                          | 42 (46.7) | 0 |
| Unknown                     | 6 (6.7) | 2 (25.0) |

CI: confidence interval; NA: not applicable
\(^a\) Patient-reported growth in the thyroid nodule
\(^b\) Size was not parametrically distributed
\(^c\) Sonographic features
\(^d\) Based on the radiologist’s report
NA: These characteristics were not incorporated into the multivariate analysis because they were not significant on univariate analysis, but age and sex were included because they are traditional predictors of thyroid malignancy.
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We would like to thank Sister Sow Fong Lee, the chief nurse of the Operating Theatre of Tan Tock Seng Hospital, for facilitating the data collection, and Dr Aruni Seneviratna, a clinical epidemiologist at Tan Tock Seng Hospital, for advice on the statistical analyses performed in this study.

REFERENCES

1. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2017;27:1341-6.

2. Guevara N, Lassalle S, Benaim G, et al. Role of frozen section analysis in nodular thyroid pathology. Eur Ann Otorhinolaryngol Head Neck Dis 2015;132:67-70.

3. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133.

4. Remonti LR, Kramer CR, Letito CB, et al. Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies. Thyroid 2015;25:538-50.

5. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214. Erratum in: Thyroid 2010;20:674-5.

6. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 2007;246:375-81; discussion 381-4.

7. Nixon IJ, Gansly I, Patel SG, et al. Thyroid lobectomy for treatment of well differentiated intrathyroidal malignancy. Surgery 2012;151:571-9.

8. Adam MA, Pura J, Gu L, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. Ann Surg 2014;260:601-5; discussion 605-7.

9. Organizing Committee for the 1st Singapore Differentiated Thyroid Cancer Consensus Meeting. Multidisciplinary care for well-differentiated papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study. J Clin Endocrinol Metab 2015;100:1316-24.

Declarations

This paper was first presented as oral presentations at the ENT World Congress, 2017 and the Asia Pacific Thyroid Congress, 2018. The authors have no funding and conflict of interest to declare.

Acknowledgements

We would like to thank Sister Sow Fong Lee, the chief nurse of the Operating Theatre of Tan Tock Seng Hospital, for facilitating the data collection, and Dr Aruni Seneviratna, a clinical epidemiologist at Tan Tock Seng Hospital, for advice on the statistical analyses performed in this study.