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Frozen section analysis in the post-Bethesda era

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ABSTRACT

Background: The utility of frozen section (FS) for indeterminate thyroid nodules is controversial. In 2009, the Bethesda System for Reporting Thyroid Cytopathology was established to further subcategorize indeterminate fine-needle aspiration results (follicular lesions, FL) into Bethesda category 3 (BC3) and Bethesda category 4 (BC4). We hypothesize that FS will have less utility in the evaluation of BC3 lesions when compared to BC4.

Materials and methods: A total of 479 patients who underwent thyroid lobectomy from January 2008 to July 2014 were retrospectively reviewed. Patients without appropriate Bethesda categorization were excluded. A total of 135 patients (65 FL, 45 BC3, 25 BC4) comprised the study groups. The sensitivity and specificity of FS within these three categories were determined.

Results: In the FL group, 6 of 65 patients were found to have thyroid cancer. Three were identified on frozen section (FS) resulting in a sensitivity and specificity of 50% and 100%, respectively. Thus, FS changed the operation in 3 of 65 cases (4.6%). In the BC3 group, 5 of 45 patients were found to have cancer. One was identified on FS resulting in a sensitivity and specificity of 20% and 100%, respectively. Thus, FS changed the operation in 1 of 45 patients (2.2%). In the BC4 group, 4 of 25 patients were found to have cancer. Two were identified on FS resulting in a sensitivity and specificity of 50% and 100% respectively. Thus, FS changed the operation in 2 of 25 patients (8%).

Conclusions: There is improved utility of FS in BC 4 patients as 8% avoided reoperation. However, this benefit hinges on surgeon practice regarding the management of differentiated thyroid cancer >1 cm and <4 cm.

Introduction

Thyroid nodules are a common finding in the general population with an incidence of 4% to 10%. Although most nodules are benign, approximately 5% are found to be malignant.[1-3] Fine-needle aspiration (FNA) plays a pivotal role in distinguishing benign from malignant thyroid nodules given its availability, safety, and diagnostic capabilities. Though excellent for many thyroid cancers, FNA is often lacking in the diagnosis of follicular thyroid cancer or follicular variants of papillary thyroid cancer as it cannot clearly identify obligatory histologic features of follicular cancer such as capsular or vascular invasion. Given these shortcomings, the indeterminate FNA diagnosis of "follicular lesion" was frequently made which then required an excisional biopsy to firmly establish a histologic diagnosis. Historically, before the initiation of the

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Bethesda Classification for Reporting Thyroid Cytopathology, approximately 20% of these "follicular lesions" were thought to be malignant.[4,5] As a result, intraoperative frozen section (FS) has been used in an attempt to help guide surgical decision making. Many articles have evaluated its utility, impact on intraoperative decision making, and cost effectiveness with mixed results. Critics cite FS limitations such as artifact, cellular distortion from freezing, sampling errors, and overall lack of impact on decision-making.[6-13] However, some investigators deem FS to be useful and a helpful guide to determining the required extent of resection, thus, decreasing the need for reoperation.[14-17] Posillico *et al.* found frozen section to alter surgical management in 62% of patients and found frozen section of value for determining the extent of thyroidectomy in patients with Bethesda category 3 (BC3).[18] Although there are clearly limitations, the fact remains that many surgeons do indeed send frozen sections to assist with intraoperative decision making.

The vast majority of articles investigating the utility of frozen section, in the setting of indeterminate follicular lesions, have been before the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) which was published in 2009. With the use of the Bethesda System for FNA classification, indeterminate follicular findings have been grouped into two categories: Follicular lesion of undetermined significance (BC 3) and suspicious for follicular neoplasm or follicular neoplasm (BC4). With this specific subcategorization of FNA results, indeterminate follicular lesions are no longer placed in a more encompassing group. There is an implied risk of malignancy of 5% to 15% within the BC3 category as well as a 15%-30% risk in the BC4.[19] We hypothesize that frozen section will have less utility in the evaluation of BC3 lesions when compared to BC4 lesions due to improved cytological categorization in the post-Bethesda era. Based on this hypothesis, the goal of this study was to determine the utility of frozen section in the post-Bethesda era.

Methods

After institutional review board approval, a retrospective review of a prospectively collected database was performed of all patients undergoing a thyroid lobectomy in the Endocrine Surgery Division at the University of Michigan from January 2008 to July 2014. Each patient's record was reviewed for demographic information, nodule size, pre-operative fine need aspiration classification, and final pathology. In the post-Bethesda Era (2011-2014), cytology was classified according to the six categories of the Bethesda System for Reporting Thyroid Cytopathology. All preoperative FNA samples were interpreted and categorized by pathologists at the University of Michigan. Patients lacking appropriate Bethesda categorization in the preoperative cytology report, with contralateral lobe disease necessitating a total thyroidectomy regardless of frozen-section result, as well as thyroid lobectomy cases that did not include a frozen section were excluded. One surgeon in the group routinely performed frozen section on indeterminate nodules. Four surgeons selectively used frozen section based on patient comorbidities, patient preference, or concerning preoperative imaging characteristics. Thyroid frozen sections were performed by the Department of Pathology and interpreted by board-certified pathologists. Patients in the pre-Bethesda era (2008-2011), with a preoperative FNA diagnosis of follicular lesion (FL) who received a thyroid lobectomy with frozen section, were identified as the FL group. In 2011, the BSRTC was implemented at our institution, and the previously used FL diagnosis was changed to follicular lesion of undetermined significance/atypia of undetermined significance (FLUS; BC3) and follicular neoplasm/suspicious for follicular neoplasm (FN/SfFN; BC4). Patients with a preoperative FNA diagnosis of BC3 or BC4, who received a thyroid lobectomy with frozen section, were also identified and placed within their respective groups. Pre-operative cytology was then compared to frozen section as well as final histopathology results. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of frozen section within these categories were then analyzed.

Results

From January 2008 to July 2014, 135 patients met the inclusion criteria and comprised the study group. Sixty-five patients were found before the use of BSRTC and 70 patients after the start of BSRTC (65 FL, 45 BC3, and 25 BC4). Demographic data and surgical findings are shown in Tables 1-3 and Figure.

In the pre-Bethesda follicular lesion group (FL), the average nodule size on final histopathology was 2.4 cm. Six of the 65 patients were found to have thyroid cancer within the sampled nodule on final histopathology. Three of the cancers were papillary, two were follicular carcinoma, and one was a follicular variant of papillary thyroid cancer. Of the six patients with cancer, frozen section correctly identified three cases (two papillary thyroid cancer, one follicular thyroid cancer) providing a sensitivity of 50%, specificity of 100%, PPV of 100%, and NPV of 95%. Thus, frozen section changed the operation in three of 65 follicular lesion patients (4.6%) by prompting the surgeon to perform a completion thyroidectomy at the time of the initial operation. There were no falsely positive frozen sections in the follicular lesion group. In addition, incidentally found micropapillary cancer was identified on final histopathology in seven of the 65 cases (10.8%) averaging 3.3 mm in size. In all seven cases of incidentally found micropapillary cancer, the previously biopsied nodule determined to be a follicular lesion was benign. Frozen section identified the micropapillary thyroid cancer in one of the seven cases. No patients received a completion thyroidectomy at the time of frozen section or following final histopathology as the result of micropapillary carcinoma.

Table 1 – Demographics of patient groups.

Demographics	FL	BC3	BC4
Male	18	13	7
Female	47	32	18
Age (mean)	45.9	46.6	45.6