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## Title and Investigators

Optimizing Surgical Management of Thyroid Cancer: Using Surgeon-performed Ultrasound to Predict Extrathyroidal Extension of Papillary Thyroid Carcinoma.

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## Abstract

Our study aims to evaluate clinician-performed ultrasound assessment of papillary thyroid cancer, the most common malignant thyroid disease [1]. Ultrasound has previously been reported to identify extrathyroidal extension of papillary thyroid cancers, a feature that imparts worse prognosis [2, 3]. Conversely, ultrasound may be capable of identifying patients who lack aggressive features and may be good candidates for less extensive operations. Further studies of this modality as performed by surgeons could substantiate whether extrathyroidal extension could be accurately detected on in-office imaging prior to surgery, and thereby influence surgical management. To investigate this issue, we will perform a retrospective cross-sectional study of UCSF patients who have undergone surgeon-performed ultrasound prior to thyroid surgery for papillary thyroid carcinoma. We will review patient charts for patient characteristics and surgical pathology results, examining ultrasonographic data for features such as edge definition and degree of tumor contact with the thyroid capsule, and pathologic features such as the presence or absence of extrathyroidal extension. Sensitivity, specificity, positive and negative predictive values, and statistical significance of the association between ultrasound findings and pathologic findings will be calculated.

## Specific aims

1. To determine the accuracy of tumor contact with the thyroid capsule as identified on clinician-performed ultrasound in identifying extrathyroidal extension.
2. To determine whether any additional features on ultrasound correlate with extrathyroidal extension of tumor.
3. To assess whether the use of clinician-performed ultrasound could be used to change surgical management of patients with papillary thyroid cancer.

## Significance

Thyroid nodules are common, occurring in at least 50% of adults as evaluated by ultrasound and at autopsy [1, 4]. Most are benign, with malignant nodules representing about 10% of all identified nodules and generally having a favorable prognosis. The most common of malignant nodules is papillary thyroid carcinoma (PTC), making up 80% or more of all thyroid cancers [1]. Though the prognosis for PTC is excellent, age, size, extrathyroidal extension, and distant metastasis have been shown to predict worse prognosis [5].

Surgical management varies as surgeons attempt to balance risk of residual or recurrent disease with the morbidity of extensive operations. Total thyroidectomy is usually performed, given the frequency of multifocal disease in PTC and the reduction of local recurrence and facilitation of follow-up that such an operation provides [6]. However, for small cancers without extrathyroidal extension, lobectomy is reasonable [2]. Despite accepted guidelines for follow-up, which allow for good detection of sub-clinical recurrence, the survival rate for PTC has remained unchanged in the last 30 years [6]. Clearly, improved strategies for risk stratification are needed in order to identify those cancers that require more extensive operation, and to minimize the morbidity and mortality of recurrence as well as surgical complications.

Imaging with ultrasound, already frequently done and demonstrated to be an effective tool for evaluation of thyroid disease and cancer staging [3], may be a method of quickly, inexpensively, and effectively identifying patients who might benefit from extensive surgical intervention and those that will do well with more conservative operations. High-resolution ultrasound has been evaluated as a tool for assessing extrathyroidal extension and has been shown to have good predictive value [2, 3]. As extrathyroidal extension has been found in 25% of papillary microcarcinomas >5mm [7], identifying these tumors could have implications for the management of many patients. Previous studies utilized assessment by radiologists or were performed with two-dimensional data. Surgeon-performed ultrasound, which provides real-time, three-dimensional evaluation by the clinician who is managing the patient's disease and planning surgery, may be a more efficient strategy for appraising papillary thyroid cancers in the preoperative setting. Our study assessed the accuracy of clinician-performed ultrasound in identifying extrathyroidal extension with the aim of identifying the role of this test in clinical practice and its potential impact.

## Methods

*Overview of design*

This is a retrospective cross-sectional study of UCSF patients seen by Dr. Lisa Orloff for papillary thyroid cancer over the past 7 years. The ultrasound imaging and report for these patients will be reviewed by a medical student blinded to the stage and features of the cancer. Presence or absence of extrathyroidal extension on pathology will subsequently be recorded. Statistical testing will be done to determine the accuracy of ultrasound findings in identifying extrathyroidal extension.

*Study subjects*

Subjects will be past patients of Dr. Lisa Orloff, the primary thyroid surgeon in the Department of Otolaryngology – Head and Neck Surgery. Using only these patients will minimize variation in ultrasound findings due to differences in technique or skill. These patients span the 7-year period of Dr. Orloff's tenure at UCSF. Inclusion criteria were chosen to identify adults (>18 years old) with FNA-diagnosed papillary thyroid cancer who have undergone operative treatment. We will exclude subjects with incomplete records to improve the quality of analysis; patients whose operation occurred >2 months after ultrasound evaluation, to reduce the likelihood that tumor invasion of the capsule

occurred between the time of imaging and surgery; and patients with an additional thyroid disorder, to rule out the possibility that imaging findings could be influenced by other changes to the thyroid tissue.

*Measurements*

The predictor variable we are assessing is the presence of extrathyroidal extension of the thyroid tumor on preoperative ultrasound. This will be measured by identifying the degree of tumor contact with the thyroid capsule, which will be graded on a 5-point scale (from 0 to 4): 0, 0% of tumor circumference contacts thyroid capsule; 1, 1–25%; 2, 26–50%; 3, 51–75%; and 4, 76–100% [3]. We will also evaluate images for the presence or absence of an intact thyroid capsule, as well as for additional qualitative features that have not previously been described and that may correlate with extrathyroidal extension. Image quality could be affected by machine calibration, clinician technique, or patient body habitus, and we will attempt to minimize this by studying only patients who have been evaluated by Dr. Orloff using her office ultrasound machine. We will record patient BMI in order to ascertain whether this might influence our results. Other confounders include history of another thyroid disorder, which could affect tissue echotexture, and length of time between ultrasound and operation, both of which we will minimize by utilizing relevant exclusion criteria.

The outcome variable is the presence of extrathyroidal extension on surgical pathology. This is a dichotomous outcome determined by the pathologists who evaluate the surgical specimen. Though there may be some potential for confounding with the skill level of the pathologist, we cannot control for different pathologist readings and, as we do in clinical practice, we will use the pathologic diagnosis as the gold standard.

*Statistical issues*

We will calculate descriptive statistics of our study population to assist in assessing generalizability. These descriptors include age (mean and range), gender, BMI, tumor size (mean and range), and frequency of extrathyroidal extension. Our question of interest will be evaluated by calculating the sensitivity, specificity, positive predictive value, and negative predictive value of ultrasound features such as degree of contact between tumor and thyroid capsule, absence of intact capsule identified on ultrasound, and potentially other features that have not previously been described. We will produce an ROC curve displaying the relationship between sensitivity and specificity of ordinal outcomes such as degree of contact between tumor and thyroid capsule. We will also use chi-squared tests to evaluate the statistical significance of the association between the presence of ultrasound features such as tumor contact with the capsule and capsule interruption, and extrathyroidal extension on pathology.

With these tests in mind, we calculated our sample size. In order to evaluate the sensitivity and specificity of ultrasound for extrathyroidal extension, we presumed based on the literature that the incidence of extrathyroidal extension is approximately 40% [2, 3]. Given the importance of specificity in using this test in clinical practice (we want to be sure there is indeed no extrathyroidal extension if we were to change practice to more conservative surgery as a result), we would like our confidence interval to be narrow

(0.1) and our confidence level to be high (99%, alpha=0.01), especially as we would like to build on prior evidence from other groups. Using these values, we would need 639 subjects/group. Given that our subjects are limited to the patients in our current records, we may not have this number. A wider confidence interval of 0.15, still with alpha=0.01, would require 284 subjects/group, potentially a more feasible number.

We also hypothesize that ultrasound identification of contact greater than a certain amount (e.g., >50%) between the tumor and thyroid capsule predicts extrathyroidal extension on pathology. The null hypothesis is therefore that there is no association between tumor contact with thyroid capsule on ultrasound imaging and extrathyroidal extension on pathology. A chi-squared test is used to calculate statistical significance between the dichotomous predictor and outcome. In these calculations we assume a standard alpha and beta of 0.05 and 0.20. (Even if we'd prefer to use a smaller alpha in order to minimize the chances of making a type I error, since we may be reducing the aggressiveness of treatment for patients based on these results, the number of subjects we'd need for our sensitivity and specificity calculations is much larger than the number required for this analysis, and will therefore likely provide us with the ability to reduce alpha further, regardless of the alpha value we assume here. Since we would be changing practice from current accepted practice based on our results, making a type II error would not be as problematic as a type I, and we can keep beta at the standard level.) To determine our effect size we used data from a prior study [2] that showed that the incidence of positive pathology with ultrasound identification of >50% tumor-capsule contact, or a "positive" test, was 0.63, and the incidence of positive pathology with a "negative" ultrasound was 0.37, giving a difference of about 0.25 (we round down to overestimate the number of subjects needed). Using these parameters, we require 69 subjects/group.

Given the varying sample size estimates across the study, a sample size of 284 subjects per group will be sufficient to test all hypotheses in the study.

## Administrative

*Quality Control and Personnel*

All ultrasound imaging has been performed by Dr. Orloff according to her standard technique, using her in-office ultrasound machine. All data gathering will be done by a single medical student blinded to the disease characteristics of the patient, with all ultrasound review performed prior to the review of surgical pathology.

*Timetable*

All data has been previously obtained in the course of standard patient care. Data can therefore be collected from existing records, and data collection will take place over approximately 1 month in mid-September to mid-October of 2012.

*Ethical considerations:*

Subjects included in this study do not require any further intervention and do not have their care affected in any way. Patient data has already been collected as part of the

standard work-up and treatment for papillary thyroid cancer, and no identifying information will be used.

**References**:


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