Value of specimen radiographs in diagnosing multifocality of thyroid cancer

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Background: Specimen radiography has been used widely to evaluate the complete excision of calcified breast lesions but has not been evaluated for thyroid cancer.

Methods: Specimen radiographs were evaluated retrospectively to identify additional cancers that were demonstrated only as calcifications. Receiver operating characteristic curve analysis was performed to compare the combination of specimen radiography and ultrasonography versus ultrasonography alone for detecting multifocality.

Results: Some 122 thyroid cancer specimens were obtained from 122 patients between January and April 2008. Specimen radiography detected 27 cancers (18.5 per cent) not detected by ultrasonography. Diagnoses were changed after evaluation of specimen radiographs in three of these patients. The area under the curve of the combination of specimen radiography and ultrasonography was significantly higher than that of ultrasonography alone (P = 0.005).

Conclusion: Specimen radiography is a potentially useful tool for diagnosing cancer type and predicting the extent of thyroid cancer.

Introduction

High-frequency ultrasonography is a useful diagnostic method for local staging as well as for diagnosing non-palpable small thyroid nodules. Several studies have suggested that ultrasonographic features, including microcalcifications, absent ‘halo’ sign, marked hypoechogenicity, extraglandular extensions, irregular or microlobulated margins, heterogeneous echo textures and shapes that are taller than wide, can predict various thyroid malignancies. Of these, microcalcifications have been shown to be the most specific to papillary thyroid cancer. In most patients with thyroid cancer, near-total or total thyroidectomy is recommended. However, thyroid lobectomy alone may be sufficient in a patient with a thyroid cancer that is a small, low-risk, isolated, intrathyroidal papillary carcinoma in the absence of cervical nodal metastases. Although ultrasonography can detect a thyroid cancer manifested as a microcalcification without an associated mass, it may still have detection limitations.

Therefore, thyroid lobectomy may be insufficient based on preoperative ultrasound images.

Specimen radiography has been used widely to evaluate the complete excision of calcified breast lesions, but has not been evaluated for the thyroid gland. The present study investigated the added diagnostic value of specimen radiography in detecting additional cancer foci in patients with proven or suspected papillary cancer of the thyroid.

Methods

The institutional review board approved this study, and required neither patient approval nor informed consent for the review of images and records.

Study population

From January to April 2008, operative specimens were obtained from consecutive patients who underwent thyroid surgery after diagnosis of papillary carcinoma.
following fine-needle aspiration biopsy, including those with suspected papillary carcinoma. Patients who had undergone previous thyroid or neck surgery and those undergoing hemithyroidectomy were excluded.

**Imaging by ultrasonography and specimen radiography**

Ultrasonography was performed with a 7–15-MHz linear-array transducer (HD1 3000 or 5000; Philips Medical Systems, Bothell, Washington, USA) or a 5–12-MHz linear-array transducer (iU22; Philips Medical Systems). Using both machines, compound imaging was performed in all patients. Real-time ultrasonography was performed by one of two radiologists with 7 and 11 years of experience in thyroid imaging. The scanning protocol in all patients included both transverse and longitudinal real-time imaging of the thyroid, with the use of a picture archiving and communications system to review all patient data. Sonographic interpretations were entered prospectively into a computer database for clinical use. Microcalcifications revealed by ultrasonography were defined as hyperechoic punctuate foci with or without acoustic shadowing, excluding dense round calcification or condensed colloid showing a comet tail artefact. The location, size, multiplicity and ultrasonographic features of thyroid nodules were recorded.

After surgery, specimen radiographs were obtained using the Lorad®/Hologic Selenia FFDM system (Lorad/Hologic, Danbury, Connecticut, USA), which was a dedicated mammography unit during the study period. The system, based on a detector with amorphous selenium, used a direct-capture, 70-µm pixel device and yielded a 2560 × 3328 matrix image with an 18 × 24-cm paddle. The system was set to allocate 16-bit images and store them at 12 bits. Routine views of thyroid specimens were obtained (focal spot size 0·3 mm). These images were displayed on a pair of high-resolution, 5-megapixel LCD monitors (MFGD 5621HD®; Barco, Buluth, Georgia, USA) that were part of the review workstation (Selenia Softcopy Workstation™; Lorad/Hologic) with soft-copy reading software (MeVis BreastCare®; MeVis Medical Solutions, Bremen, Germany).

Calcifications on specimen radiographs were classified by the longest dimension as microcalcification (equal or less than 1 mm), macrocalcification (more than 1 mm), or mixed calcifications (when both microcalcifications and macrocalcifications were present in thyroid cancers). The morphology of thyroid calcifications was evaluated and classified as punctuate, eggshell, dystrophic, amorphous or pleomorphic. These subdivisions were based on morphological analysis of breast calcifications shown on mammographic images. A calcification was described as punctate when it was smaller than 0·5 mm; eggshell when it was located on the surface of a sphere; and dystrophic when it was coarse, irregular or ‘lava shaped’, and larger than 0·5 mm. Calcification was described as amorphous when it was too small or hazy in appearance to give a more specific classification and pleomorphic when it varied in size and shape; pleomorphic calcification was generally less than 0·5 mm in diameter and more conspicuous than amorphous calcification.

**Fig. 1** Frequency of calcifications on specimen radiographs from 146 cancers detected by ultrasonography
Histopathology

All patients underwent total or near-total thyroidectomy with central neck node dissection. Surgical specimens were fixed in 10 per cent formalin and cut at 3-mm intervals. All suspicious lesions and surrounding tissues were embedded in paraffin wax and stained with haematoxylin and eosin for histological examination. Five pathologists, who did not have any information about the ultrasound images and specimen radiographs, evaluated the specimens. The locations of each section were labelled and recorded in the pathology reports. The presence of calcification, including dystrophic calcification or psammoma body and cancer multiplicity, was determined from pathological reports.

Correlation between ultrasonography, specimen radiography and pathological findings

Specimen radiographs were evaluated initially by one radiologist in comparison with ultrasound images and records and pathological reports. All specimen radiographs, ultrasound and pathological images, and records were then evaluated by two radiologists, a pathologist and a surgeon in radiopathological conferences that were held weekly between May 2008 and December 2008. In these meetings, a consensus was reached regarding the radiographic features of specimen radiographs in comparison with ultrasound and pathological images. When calcifications observed on radiographs could not be explained by initial pathology reports and images, the specimen was reviewed again by a specialist thyroid pathologist who had not evaluated the initial specimen. Finally, specimen radiographs were analysed retrospectively as follows: thyroid cancers detected by ultrasonography were correlated with specimen radiographs, and thyroid gland calcifications not detected by ultrasonography were analysed and correlated with histopathological findings.

Statistical analysis

The sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of ultrasonography in detecting multiple thyroid cancers were calculated. The ability of specimen radiographs to
identify an additional cancer and changes in pathological diagnosis that were demonstrated only as calcifications was calculated. Receiver operating characteristic (ROC) curve analysis was performed to compare the ability of the combination of specimen radiography and ultrasonography versus ultrasonography alone to detect multifocality. Statistical significance was assumed at $P < 0.050$. Statistical analysis was performed using MedCalc® (Medisoftware, Mariakerke, Belgium).

**Results**

From January to April 2008, operative specimens were obtained for 126 consecutive patients who underwent thyroid surgery after diagnosis of papillary carcinoma following fine-needle aspiration biopsy, including 13 patients with suspected papillary carcinoma. After excluding four hemithyroidectomy specimens, 122 patients undergoing total (62 patients) or near-total (60) thyroidectomy with
central neck node dissection formed the basis of the study. These 122 patients (102 women and 20 men) had a mean age at initial treatment of 48 (range 17–79) years.

Of 46 patients with multifocal papillary thyroid cancer confirmed by histopathology, 22 patients had bilateral disease and 24 had unilobar multiple cancers. Exact mass density as seen on ultrasonography was not found on specimen radiographs. Calcification visibility within the mass, however, was more easily identified on specimen radiographs than by ultrasonography. Preoperative staging ultrasonography detected multifocality in 20 patients (two cancers in 17 patients, three cancers in two and four cancers in one). Specimen radiography detected multiplicity in a further 14 patients. Multiplicity was not detected by either modality in 12 patients.

Ultrasonography detected 146 cancers before surgery. Of these, it detected calcifications in 78. Specimen radiography detected calcifications in 105 cancers, including calcifications related to 27 cancers (18.5 per cent, 27 of 146) not detected by ultrasonography (Fig. 1). Calcifications related to the 105 ultrasound-detected cancers had varying appearances on specimen radiographs. The most common pattern related to the cancer was punctate microcalcification (Fig. 2). Radiographic analysis for each specimen took around 5 min.

Of the 27 specimens with calcifications that were seen solely on radiographs (Fig. 3), 16 were associated with cancer foci. The pathological diagnosis changed after evaluation of specimen radiographs in three of these specimens. An initial diagnosis of two multifocal papillary carcinomas was changed to diffuse sclerosing variant of papillary carcinoma (DSVPC), a diagnosis of single papillary microcarcinoma was changed to DSVPC (Fig. 4) and a diagnosis of two multifocal follicular variants of papillary carcinoma was changed to DSVPC. Of the 16 patients with additional cancer foci detected solely by radiography, 14 had a single cancer and two had multifocal thyroid cancers on preoperative ultrasonography. Diagnoses of single cancers were therefore changed to multifocal cancers in 14 of 27 patients after correlation with specimen radiographs. Four patients showed no definite calcification but colloid crystals were present on pathological review. After the consensus meetings, colloid crystals were considered as specific radiographic features that appeared as subtle, faint amorphous calcifications on specimen radiographs. Even after revising the pathology, no pathological features correlated with the punctate calcifications seen on seven specimen radiographs.

Of the 122 patients with thyroid cancer, 57 had a single cancer 1 cm or smaller on preoperative ultrasonography.
thyroid microcalcifications seen by ultrasonography repre-
sent psammoma bodies, which are laminated, basophilic, 
spherical concretions that are characteristic of papillary 
carcinoma\(^\text{11,15}\). Although high-frequency ultrasonography 
is a useful diagnostic method for the evaluation of thyroid 
nodules, it may have limitations in documenting calci-
fications, especially microcalcifications. To discriminate 
malignant from benign thyroid nodules, several stud-
ies have reported various calcification patterns\(^{6–10,14,16}\).
Although a malignant nodule may have both coarse calcifi-
cations and microcalcifications\(^\text{15}\), calcifications within the 
 solitary mass can indicate malignancy\(^7\). Microcalcifications 
have been reported to be the most specific for papillary 
cancer\(^6,8,10\).

Ultrasonography has been the most widely used tool 
for the evaluation of local stage before surgery\(^17–19\). 
However, detecting a breast cancer that is solely manifested 
as a microcalcification on mammography is difficult on 
ultrasonography\(^\text{20}\). Mammography is the most sensitive 
technique for detecting microcalcification in breast tissue 
and postoperative specimen radiographs have been used 
widely to evaluate the complete excision of calcified 
breast lesions\(^\text{12}\). Unfortunately, preoperative radiography 
of thyroid glands cannot be achieved using mammographic 
techniques because thyroid glands cannot be compressed 
lke the breast. The only way to confirm microcalcifications 
in thyroid glands detected by ultrasonography has been to 
find a psammoma body on pathological examination\(^\text{15}\). 
There have been no studies of specimen radiography of 
the thyroid gland.

Specimen radiography of 27 specimens with calcifica-
tions revealed 16 cancer foci not seen on ultrasonography, 
changed the diagnosis from a single cancer to multifocal 
cancers in 14 patients, and changed the pathological diag-
nosis to DSVPC in three patients. DSVPC of the thyroid 
gland is a rare variant of papillary thyroid carcinoma. Sev-
eral investigators have reported sonographic features of 
DSVPC in thyroid glands to be diffuse scattered microcalci-
fications with underlying heterogeneous hypoechogetic-
ity on ultrasonography\(^\text{21–23}\). Scattered microcalcifications 
seen on ultrasonography are well correlated with psam-
moma bodies on histopathological review\(^\text{21}\). In this study, 
three patients in whom the diagnosis changed from sin-
gle or multiple papillary carcinomas to DSVPC showed 
diffuse or regional scattered microcalcifications in the thy-
roid gland. Before correlation with specimen radiographs, 
pathologists were not concerned with scattered microcalci-
fications. After carefully reviewing specimen radiographs 
and correlating them with pathological findings, a pathol-
gist specializing in thyroid histology diagnosed DSVPC in 
three patients. Specimen radiographs may therefore help 
pathologists diagnose histological thyroid cancer. Patients 
with DSVPC should be treated aggressively and fol-
lowed closely\(^\text{24,25}\). Therefore, specimen radiography still 
has value in diagnosing DSVPC accurately, even when 
performed after surgery.

In most patients with thyroid cancer, near-total or total 
thyroidectomy is recommended to remove the primary 
cancer completely, facilitate postoperative treatment with 
radioactive iodine, permit accurate long-term surveillance 
for disease recurrence, and minimize the risk of disease 
recurrence and metastatic spread\(^1\). However, patients who 
undergo near-total or total thyroidectomy need to take 
thyroid hormones for the rest of their lives. Although 
there is controversy about the extent of surgery when 
treating low-risk patients\(^\text{26}\), lobectomy alone has been 
recommended in patients with small (less than 1 cm), 
intrathyroidal, node-negative and low-risk cancer\(^1\).

A papillary thyroid microcarcinoma (PTMC) is defined 
by the World Health Organization as a tumour of 
1.0 cm or less in diameter\(^\text{27}\). Although most small thyroid 
cancers are low grade and respond well to radioiodine 
therapy, some have metastatic potential and recur\(^\text{28–30}\). 
PTMC has an incidence of lymph node metastasis of 
3.1–18.2 per cent and a locoregional recurrence rate of 
up to 20 per cent\(^\text{31–33}\). In the study period, PTMC 
comprised about half of excised thyroid cancers because 
many Korean patients selected surgery rather than follow-
up\(^\text{34,35}\). Considering the high frequency of surgery for 
PTMC in Korea, the detection of multifocality is a critical 
issue in deciding the extent of thyroid surgery\(^1\). In the 
present study, of 57 patients with a single thyroid cancer 
that was 1 cm or smaller on preoperative ultrasonography, 
11 had multifocality on pathological examination, eight 
with unilobar and three with bilobar disease. Specimen 
radiography detected multiplicity in six patients.

This study has several potential limitations. Calcifica-
tions seen on specimen radiographs in seven patients could 
not be documented pathologically, even after meticulous 
review. These were regarded as benign lesions because 
there were no additional cancer foci or psammoma bodies. 
Specimen radiographs cannot be acquired before surgery, 
and therefore have no value in helping surgeons deter-
mine the extent of surgery. Initial pathology reports 
were recorded by five pathologists, and the specimen was 
reviewed again by a different pathologist (S.W.H.) spe-
cializing in thyroid pathology when initial reports could 
not explain the images. Interobserver variability in the 
histological diagnosis\(^\text{36–38}\) is a potential limitation of this 
study. Finally, most of the additional cancers detected were 
incidental microcarcinomas that did not necessarily have 
an impact on patient management.

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The present study highlights the need to develop diagnostic modalities before surgery that can reliably identify thyroid calcifications more sensitively than high-resolution ultrasonography and thus influence surgical strategy.

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References


