Ann Surg Oncol (2019) 26:4439–4444
https://doi.org/10.1245/s10434-019-07618-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Preoperative Computed Tomography Changes Surgical Management for Clinically Low-Risk Well-Differentiated Thyroid Cancer

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ABSTRACT

Background. In the current guidelines for differentiated thyroid cancer (DTC), computed tomography (CT) of the neck has a limited role. The authors hypothesized that adding CT to the workup of clinically low-risk DTC size 4 cm or smaller changes the surgical management for a portion of patients due to detection of clinically significant lymph node metastases not located by ultrasound of the neck.

Methods. A prospective cohort of DTC patients at an academic referral center between 2012 and 2016 was reviewed. All the patients with fine-needle aspiration cytopathology results suspicious for malignancy or malignant tumor (Bethesda category 5 or 6, respectively) underwent CT before surgery. Clinically low-risk DTC patients were selected if they had a tumor diameter of 4 cm or less and no evidence for local invasion or suspicious lymph nodes seen on ultrasound. Outcomes focused on alteration of the surgical plan based on CT and correlation with pathology.

Results. The CT findings for 25 (22.5%) of 111 patients with clinically low-risk DTC led to a change in surgical management. Of these 25 patients, 16 (14.4% of the entire cohort) benefited due to the removal of clinically significant lymph node disease not seen on ultrasound. Categorization of the group that had a change in management showed that 6 (85.7%) of 7 lateral neck dissections and 10 (55.6%) of 18 central neck dissections (CND) harbored metastatic nodes larger than 2 mm.

Conclusions. In the group with clinically low-risk DTC, CT changed surgical management for a substantial number of the patients with clinically significant nodal disease not detected by ultrasound. This highlights the fact that in certain practice settings, adding CT to the preoperative staging may be favorable for the detection of nodal metastasis.

The incidence of differentiated thyroid carcinoma (DTC) has risen substantially in recent decades.[1] Because most of these cancers are considered low-risk DTC with almost universal 10-year disease-specific survival, de-escalation of treatment is being pursued.[2–4] Currently, the extent of surgical treatment is determined by preoperative staging. If deemed clinically "low risk," the patient is considered for treatment with hemithyroidectomy rather than total thyroidectomy as previously suggested.[5,6] Findings have shown ultrasonography (US) of the neck to be accurate in the assessment of the thyroid gland itself, especially in detecting small thyroid nodules and possible extrathyroidal extension (ETE).

Ultrasonography also can detect suspicious lymph nodes that are not found on physical examination.[7–10] However, the data are inconsistent on whether US is the optimal imaging method for detecting clinically relevant lymph node metastases. Contrast-enhanced computed tomography (CT) of the neck might have additional value in detecting lymph node metastases and invading disease in areas less well visualized by US.[5,11–14]

First Received: 9 December 2018;
Published Online: 3 October 2019

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The presence of macrometastatic lymph node disease or invasive disease implies more extensive surgery in lateral and/or central neck compartments and possible radioactive iodine remnant ablation (RAI). Nevertheless, the role of CT defined by the 2015 American Thyroid Association (ATA) Management Guidelines for Adult Patients With Thyroid Nodules and Differentiated Thyroid Cancer is limited.[15] It states that CT is recommended only as an adjunct to US for patients with clinical or US evidence of lymph node metastases or locally invasive tumors.

We hypothesized that adding CT of the neck to the preoperative workup of clinically low-risk DTC will change surgical management for a significant portion of patients with lymph node metastases that may be clinically relevant but not detected on US.

MATERIALS AND METHODS

Patient Selection

We used prospectively collected data from a high-volume tertiary care referral center. All adult patients with fine-needle aspiration (FNA) cytopathology suspicious for thyroid malignancy or malignant tumor (Bethesda category 5 or 6, respectively) who underwent surgical treatment for DTC in the general surgery department between 1 January 2012 and 31 December 2016 received a standard preoperative CT of the neck with iodine contrast.

For this study, patients were retrospectively selected as clinically low risk if they had a thyroid mass up to 4 cm in diameter (T1a-2) without evidence for local invasion or lymph nodes metastases (N0) based on physical examination and neck US.[16] Patients with incomplete US reports (defined as no mention of lymph node status in the neck) or non-iodine contrast CT were excluded from the study analysis. In this center, biopsy of suspicious lymph nodes was not routinely performed preoperatively.

Change in Surgical Plan

During the workup for all the patients, the surgeon noted the surgical management plan in the patients' electronic medical records after the initial consultation and review of FNA and US findings, then subsequently ordered a preoperative CT scan of the neck for each patient. Once the CT scan was completed, the surgeon logged into each patient's medical record whether a change in the surgical management plan (i.e., addition of neck dissection) was made or not. The surgical planning was based on the American Thyroid Association guidelines current at that time.

A compartment-orientated neck dissection was performed based on the location of suspicious lymph nodes found on imaging. Central neck dissection (CND), the removal of all lymph nodes from the central neck compartment (level 6), was performed if lymphadenopathy was seen on imaging. When suspicion for lymph node metastasis on imaging was mild our dubious, ipsilateral removal of only the mildly suspected nodes (limited CND) was planned. A lateral neck dissection (LND) was planned if imaging showed suspicious lymph nodes in the lateral neck (levels 1–5), and this was always combined with at least an ipsilateral CND. The surgeon's intraoperative judgment for the central neck compartment could change the planned procedure, although for analysis purposes, this was not regarded as a change in management based on CT.

Interpretation of Radiology

Different radiologists, either at the tertiary referral hospital or at external diagnostic imaging clinics, performed the US as per usual care. Interpretation of the US was based on the radiology reports. The CT was assessed by both the surgeon and a dedicated head and neck radiologist, and interpretative inconsistencies were resolved by discussion. Highly suspicious nodes in a patient with known thyroid malignancy were defined as nodes that had a combination of the following attributes: avid enhancement, cystic change, punctate calcification, central necrosis, peripheral ill definition, and presentation at a high-risk location such as low-level 3, level 4, level 6, and the retropharynx. Mildly suspicious nodes were those with mild or faint enhancement in a high-risk location.

Histopathology

The results of preoperative changes in planned surgical strategy were correlated with pathologic analyses of the resected lymph nodes. A change in surgical plan was considered true-positive if significant metastatic lymph node disease (i.e., at least 5 metastatic lymph nodes or any metastatic lymph node larger than 2 mm) was within the compartments that warranted the surgery. False-positive results were assigned to the surgical plan if micrometastatic lymph nodes (i.e., fewer than 5 metastatic lymph nodes each $\leq$ 2 mm) or no metastatic lymph nodes were found in the compartments that underwent surgical resection based on the preoperative CT.

Statistical Analysis

Clinical baseline features were compared between all the patients. Parametric data are presented as mean $\pm$ standard deviation (SD), and non-parametric data are

presented as median (interquartile range [IQR]). Independent-samples *t* tests were used to calculate the significance of parametric data. Mann–Whitney *U* tests were used for non-normally distributed variables. Chi square tests were used for categorical variables. A *p* value lower than 0.05 was considered significant. Statistical analyses were performed using SPSS version 24 (IBM Corporation, Armonk, NY, USA). The Institutional Research Ethics Board approved this study.

RESULTS

During the inclusion period of the study, 199 patients with a diagnosis of differentiated thyroid cancer (Bethesda 5 or 6) underwent surgery at the tertiary referral hospital. Of these patients, 48 were excluded due to incomplete US reports, which lacked information regarding cervical lymph node status, and 40 were excluded because they did not have low-risk DTC. Consequently, 111 patients with clinically low-risk DTC were included for analyses.

The mean age of the patients was 48.0 ± 14.6) years, and 89 (80.2%) of the patients were women (Table 1). The data showed 13 patients (11.7%) with a positive family history for DTC and 4 patients (3.7%) with a history of radiation exposure to the neck. Of the 111 patients, 83 (74.8%) had proven thyroid malignancy (Bethesda 6) on FNA, and 28 (25.2%) had suspicion of malignancy (Bethesda 5). The patients with a change in surgical plan based on preoperative CT did not differ significantly in any of the preoperative baseline characteristics from the group without a change in management (Table 1).

Changes in Surgical Plan Based on CT

As shown in Table 1, 25 patients (22.5%) had a change in surgical plan based on CT findings. Of these 25 patients, 2 (8%) had a primary tumor smaller than 1 cm (T1a stage), and 23 (92%) had a primary tumor 1–4 cm in size (T1b-T2 stage).

Table 2 focuses on the patients with a change in surgical plan based on CT findings. An LND was indicated for seven patients (6.3% of the entire cohort) with suspicion of metastatic disease in the lateral neck not noted in the initial clinical and US assessment (Fig. 1). Six (85.7%) of these seven patients were found to have pathologic macrometastatic lateral neck disease. The average number of lymph nodes removed from the lateral neck of these patients was 37.1 (range, 15–68). On the average 7.3 (range, 0–20) of these removed lymph nodes from the lateral neck had metastases.

For 18 patients (16.2% of entire cohort), more extensive central neck compartment surgery was planned based on CT findings. Of these patients, 10 (55.6%) had macrometastatic disease in the lymph nodes removed from the central compartment. Seven of the eight unnecessarily performed CNDs consisted of a limited CND because mildly suspicious nodal disease was seen on CT. This is

TABLE 1 Preoperative baseline characteristics

	Total group (*n* = 111) *n* (%)	Management change (*n* = 25) *n* (%)	No management change (*n* = 86) *n* (%)	*p* Value
Mean age at surgery (years)	48.0 ± 14.6	44.4 ± 15.2	49.0 ± 14.4	0.168
Female sex	89 (80.2)	23 (92.0)	66 (76.7)	0.152
Family history of DTC	98 (88.3)	21 (84.0)	77 (89.5)	0.484
Radiation exposure in history	4 (3.6)	1 (4.0)	3 (3.5)	0.999
Diagnosis				0.835
Incidental	32 (28.8)	6 (24.0)	26 (30.2)	
Asymptomatic	58 (52.3)	14 (56.0)	44 (51.2)	
Symptomatic	5 (4.5)	1 (4.0)	4 (4.7)	
FNA result				0.376
Bethesda 5	28 (25.2)	8 (32.0)	20 (23.3)	
Bethesda 6	83 (74.8)	17 (68.0)	66 (76.7)	
Ultrasound tumor stage				0.301
T1a	16 (14.4)	2 (8.0)	14 (16.3)	
T1b	55 (49.5)	11 (44.0)	44 (51.2)	
T2	40 (36.0)	12 (48.0)	28 (32.6)	

DTC differentiated thyroid cancer, *FNA* fine-needle aspiration

TABLE 2 Analysis of changes in surgical plan after computed tomography (CT)

	Change in surgical plan *n* (%)	Percentage of entire cohort (*n* = 111)
Total	25	22.5
True-positive	16 (64.0)	
False-positive	9 (36.0)	
Lateral neck dissection	7	6.3
True-positive	6 (85.7)	
False-positive	1 (14.3)	
Central neck dissection	18	16.2
True-positive	10 (55.6)	
False-positive	8 (44.4)	

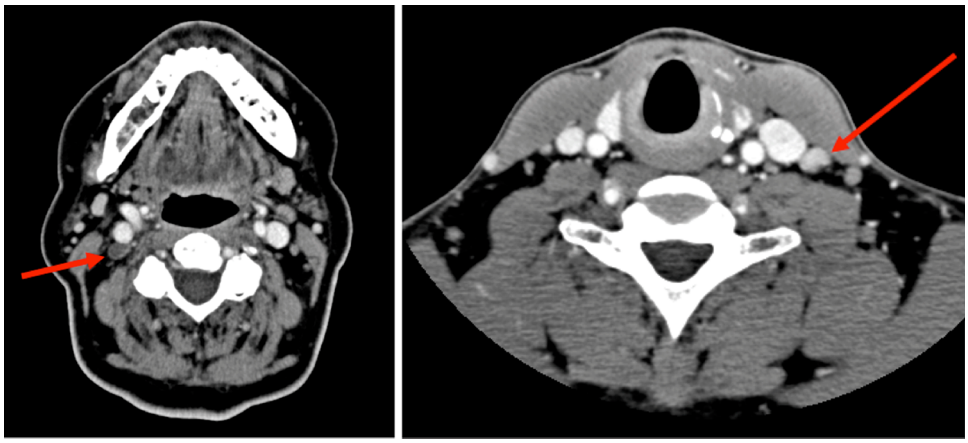

FIG. 1 Computed tomography (CT) scan of two patients with an altered surgical plan due to preoperative lymph node findings on CT not noted in the initial assessment

reflected in the difference in the average number of lymph nodes resected from the central compartment. On the average, 3.5 lymph nodes were removed from the patients who underwent an unjustified limited CND compared with the removal of 7.9 lymph nodes in the CNDs that did harbor macrometastatic disease.

The operative reports showed that in 12 (66.7%) of the 18 patients for whom CND was planned based on new CT findings, suspicious-looking lymph nodes in the central neck also were seen at the intraoperative assessment by the surgeon. However, in 5 (41.7%) of the 12 cases, these suspicious lymph nodes were negative for metastases based on histopathologic examination. Of the six cases with a planned CND based on CT findings but without abnormalities seen intraoperatively by the surgeon, three had non-microscoscopic lymph node metastases.

In the group that had a change in surgical plan based on CT findings 12 patients (48%) underwent RAI compared with 26 patients (30.2%) in the group without a change in surgical plan after CT imaging ($p = 0.017$). Of the 25 patients who underwent a neck dissection based on new CT findings, 1 patient needed long-term replacement therapy for hypoparathyroidism that developed after surgery for thyroid malignancy with lateral lymph node metastasis. No other direct complications (hematoma or bilateral laryngeal nerve paralysis) or persistent complications (spinal accessory nerve palsy or unilateral laryngeal nerve paralysis seen on laryngoscopy) 6 months after surgery were reported.

DISCUSSION

This study showed that a standard preoperative neck CT performed for patients with clinically low-risk DTC, defined as non-invasive tumors smaller than 4 cm without suspicious lymph nodes shown on US, changed the surgical management planned for 22.5% of the patients. Of 25 patients, 16 benefited from the CT-directed change in management due to the removal of clinically significant lymph node disease not seen on US. For 6.3% of the entire cohort, LNDs (levels 1–5) were performed based on the additional information from CT, with a true-positive rate of 85.7%.

Whereas previous reports compared the diagnostic performance of both US and CT for patients with DTC, the current study investigated the clinical consequence of CT for surgical planning for patients with clinically low-risk DTC.[14,17] Studies exploring the effect on surgical decision making are consistent with our data. In line with our results, Lesnik et al.[14] found that adding CT to the workup

of patients with newly diagnosed papillary thyroid cancer changed the surgical plan for 25% due to macroscopic lymph node disease in the central and/or lateral neck compartments.

To help the surgeon plan the extent of the thyroid operation, poorly visualized areas on US can be readily visualized through CT. This includes retropharyngeal and mediastinal lymph node localization as well as tracheal, esophageal, laryngeal, or vascular invasion.[18,19]

Another important advantage of CT is its wide availability, even in low-volume settings where most thyroid cancers are currently treated. Many studies have shown that US assessment is operator-dependent and support the idea that CT may be used in practice settings without available high-volume interpreters.[20–22]

Nevertheless, potential disadvantages of performing standard preoperative CT exist and need to be taken into account, such as costs and radiation exposure.[14,23] One argument against CT focuses on the iodide contrast use for thyroid cancer patients needing RAI. Recent studies show that preoperative administration of contrast for CT purposes does not cause long-term iodine retention and should not lead to hesitancy in using this method.[24–26]

A large body of evidence has shown that macroscopic lymph node metastasis has significant prognostic significance.[27–31] A structurally incomplete response to initial therapy results in significantly worse outcomes, so a complete resection of cancerous tissue from the thyroid and from cervical macroscopic lymph nodes is essential.[32,33]

In discussing the addition of CT imaging to the standard preoperative workup, it also is important to consider the consequences of unnecessarily performed neck dissections or RAI based on the additional CT findings. No patient in our study cohort who underwent an unjustified CND or LND based on CT findings had any intra- or postoperative complications in up to 6 months. Only one of the nine patients who underwent an unnecessary CND or LND, in this case a CND, had RAI. The reason for adding RAI for this pT1aN0 patient was based on the patient's advanced age (> 60 years) and thyroid histology (20% of tumor existed of tall cells), not on the preoperative CT findings. To determine whether the surgical intervention based on the addition of preoperative CT does in fact lead to lower clinically relevant recurrence rates, long-term follow up data are needed.

This study also aimed to identify specific patient or clinical tumor characteristics that might predict the helpfulness of CT.[15] As shown in Table 1, we found no statistically significant characteristics linked to a change in management and thus we were unable to narrow the indication for a preoperative CT for patients with clinically low-risk DTC. As an example, for 2 of the 16 T1a tumors, the CT led to a neck dissection that harbored macrometastatic nodal disease.

Different factors need to be considered in determining the cost-effectiveness of adding CT to the standard workup of clinically low-risk DTC. Our results show that for every patient who benefited from the CT findings, 6.9 patients with clinically low-risk DTC underwent a CT scan, and 8.1% of the patients had unnecessary and potentially harmful lymph node dissections. The incremented costs of a standard CT scan should be weighed against future costs saved by the prevention of treatments for clinically relevant recurrences and their impacts on quality of life. A previous study calculated that the cost for surveillance of low-risk disease to detect a recurrence is more than six times the cost for detection of recurrence in an intermediate- or high-risk patient.[34]

The strength of this study was the standardization of all thyroid cancer patients receiving preoperative CT in a prospective cohort evaluated and treated by the same surgeons and radiologists. This ensured homogeneity in surgical planning and treatment.

A limitation to this study was the heterogeneity in performance of the US in the workup of the patients. Many US procedures (48.7%) were performed outside the academic center. This could have caused inconsistency in the comprehensiveness of the US imaging, supported by the finding that 24% of the ultrasounds lacked description of cervical lymph nodes and had to be excluded from the analysis. This may ultimately be a good reflection of this study's external validity because it may be a realistic reflection of current clinical practice.

CONCLUSIONS

In a prospective cohort of clinically low-risk DTC patients, a standard preoperative CT changed the surgical management for a substantial number of the patients, leading to more extensive operations involving central and/or lateral neck dissections for clinically significant nodal disease. This highlights the fact that in certain practice settings with variable-quality US imaging available, adding a preoperative staging CT scan may be favorable for detecting clinically significant metastatic nodal disease. Further long-term clinical correlation with postsurgical recurrence and cost-effectiveness assessment will be helpful for informing CT use in future preoperative thyroid cancer guidelines.

DISCLOSURE The authors declare that they have no conflict of interest.

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