ISSN 2472-1972

Sonographic Volumetric Assessment Is a More Accurate Measure Than Maximum Diameter Alone in Papillary Thyroid Cancer

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Background: Tumor size is an important prognostic factor in papillary thyroid cancer (PTC). Management guidelines, staging systems, and pathological definitions use maximum diameter (Dmax) as a surrogate marker of tumor size. However, PTC nodules are three-dimensional (3D) structures, with behavior reflective of tumor cell count, which is directly proportional to volume. We explored the relationship between sonographically determined Dmax, volume, and lymph node status (LNS) in a cohort of patients with PTC.

Methods: All patients treated for PTC between 2003 and 2015 in our institution who had sonographic 3D nodule measurements available were evaluated. We examined the relationship between diameter, volume, and LNS.

Results: A total of 159 nodules in 153 patients met the inclusion criteria. Mean nodule dimensions were $2.4 \times 1.9 \times 1.5$ cm, giving "ideal" nodule dimensions of $y \times 0.78y \times 0.62y$, where y is the Dmax. Observed volumes differed from predicted nodule volumes by an average of 26.2%. For PTC $\leq$2 cm, the coefficient of variation was 26.7%. Dmax did not correlate with the presence of lymph node metastases (Pearson coefficient 0.08), whereas volume very weakly correlated with LNS (Pearson coefficient 0.22). However, both Dmax and volume correlated very strongly with the number of nodal metastases (Pearson coefficients 0.93 and 0.89, respectively).

Conclusions: PTC nodules demonstrated significant volume heterogeneity, rendering Dmax an inaccurate marker of true tumor size. Although there was little difference between Dmax and volume in predicting nodal status or nodal disease burden, we propose that a prospective, randomized trial might demonstrate a clear clinical advantage of 3D sonographic nodule measurement over Dmax alone.

Freeform/Key Words: nodule, papillary thyroid cancer, volume

Papillary thyroid cancer (PTC), the most common thyroid malignancy, is being diagnosed with increasing frequency. Despite an overall excellent prognosis, it has the propensity to lymphatic and hematogenous dissemination with resulting morbidity and mortality. As with most malignancies, the best chance for disease control and cure is with early detection and surgical extirpation. With recent advances in the understanding of tumor biology,

Abbreviations: 3D, three-dimensional; Dmax, maximum diameter; PMC, papillary microcarcinoma; PTC, papillary thyroid cancer.

Received 31 July 2018
Accepted 8 October 2018
First Published Online 15 October 2018

attention has been focused toward determining the role and extent of surgical management of early-stage disease, with a view to balancing surgical morbidity against disease morbidity and mortality. In this context, traditional management approaches of total thyroidectomy and lymph node dissection for PTC >1 cm in maximum diameter (Dmax) have recently been challenged. Tuttle *et al.* [1] have suggested that certain low-risk PTCs <1.5 cm in Dmax may be managed with close observation alone, citing slow growth rates and a low propensity for aggressive behavior in certain PTCs with low-risk sonographic features.

In other areas of oncology, management protocols in several solid-organ malignancies have been moving toward the use of cross-sectional imaging-based volumetric assessment of malignant lesions. The Dutch-Belgian lung cancer screening trial (NELSON) based its nodule management protocol on lung nodule volume rather than diameter and nodule growth in terms of volume-doubling time. This led to much lower false-positive rates, comparable sensitivity, and significantly higher specificity when compared with standard screening protocols that use nodule diameter alone [2, 3]. In breast cancer, theoretical models have demonstrated that the propensity for metastatic spread depends on the total number of cells of a given tumor combined with the probability of each individual cell to disseminate [4, 5]. A study examining aggregate tumor volumes and diameters in multifocal breast carcinomas has shown that summing the diameters of tumor nodules significantly overestimates aggregate tumor volumes, creating the appearance that they have the same metastatic potential as unifocal tumors of similar size. This does not correlate with observed metastatic behavior [6].

Volume studies of prostate cancer specimens have shown a strong correlation between tumor volume and malignant behavior, with threshold volumes predicting the presence or absence of pelvic lymph node metastases [7] and disease-free survival [8, 9]. Theoretically, it would seem logical that cancer types that tend to a more spherical shape would have a diameter predictive of their biological behavior, whereas the Dmax of tumors that have a more ellipsoid shape, or a varied shape, would be less accurate. It is our clinical impression that the vast majority of PTCs have an ellipsoid or asymmetric shape, rendering unidimensional size measurements a less accurate marker of true tumor volume, total cell count, and hence biological behavior. This observation has been made by other researchers: ellipsoid nodules (defined as nodules that are taller than they are wide) have been shown to have specificity for malignancy of 89% to 93% with a positive predictive value of 86% [10, 11]. Choi *et al.* [12] used the volume of an ellipsoid to calculate nodule volumes in their study on interobserver variation in ultrasound measurement of thyroid nodules, as did Tuttle *et al.* [1] in their study on PTC tumor volume kinetics. The latter concluded that sonographic measurement of tumor volume facilitated earlier identification of significant nodule growth compared with measurement of diameter alone. Despite evidence in support of volume determination over Dmax alone, current guidelines and staging systems use maximum tumor diameter to stratify management approaches and prognosis [13, 14]. This study examines the accuracy of sonographically measured Dmax as a surrogate marker of tumor size and compares it with sonographic volumetric assessment and pathological lymph node status.

1. Patients and Methods

The University of Sydney Department of Endocrine Surgery database was queried for thyroidectomies performed by three surgeons (S.S., M.S., and L.D.) for PTC between 2003 and 2015. Standard practice among the three surgeons for confirmed PTC was total thyroidectomy and ipsilateral central neck dissection with or without lateral neck dissection for proven lateral compartment nodal metastases. A total of 2108 patients underwent thyroidectomy with resultant pathology confirming PTC or papillary microcarcinoma (PMC). After exclusion of incidental lesions, lesions without documented three-dimensional (3D) preoperative ultrasound measurements, or locoregionally recurrent PTCs, 153 patients with 159 nodules were included in the analysis. All ultrasound examinations were performed by third-party accredited sonographers, according to each surgeon's referral patterns, and reported by

qualified specialist radiologists. Demographic data including age and sex were recorded. Sonographic nodule volumes were calculated using the volume of an ellipsoid formula below:

$$\text{Volume} = \pi/6(\text{a}\cdot\text{b}\cdot\text{c})$$

where a, b, and c are the three measured nodule dimensions. Calculated nodule volumes were compared with nodule Dmax to assess the degree of correlation between volume and Dmax. In addition, the three measured dimensions were averaged among all nodules to obtain the average, or "ideal" PTC nodule of dimensions y, ay, by, where a and b were calculated constants obtained by dividing the mean of each of the two smaller dimensions by the mean of the maximum dimension. This allowed expression of the three "ideal" nodule dimensions relative to the maximum dimension, y. The formula for the dimensions of the "ideal" PTC nodule expressed relative to the Dmax was used to calculate "predicted" volumes for each nodule based on the Dmax alone. This formula was also used to calculate volume subgroups from Dmax subgroups for the purpose of these comparisons. Predicted and observed nodule volumes were compared to determine the accuracy of Dmax alone in assessing true tumor size (volume).

Data were gathered on lymph node status (number of nodes harvested, number of nodes containing metastatic PTC) for each patient and correlated to nodule Dmax and volume. For this analysis, multifocal PTC was excluded due to the difficulty determining which tumor had (or had not) metastasized. However, PTC with additional foci of PMC were included in the analysis. Patients underwent either no formal lymph node dissection, formal central lymph node dissection (unilateral or bilateral), or selective lateral neck dissections, depending on preoperative risk assessment of synchronous nodal disease and patient wishes.

2. Results

A total of 159 PTC nodules in 153 patients met the inclusion criteria. Among these, 146 were classified as PTC (Dmax ≥1 cm), and 13 were classified as PMC (Dmax <1 cm). The ratio of female to male patients was 3.8:1, and the mean age at diagnosis was 49.9 years. A total of 148 patients had unifocal PTC (with or without additional foci of PMC); four patients had two distinct PTCs, and one patient had three distinct PTCs. Sonographic nodule diameters ranged from 0.6 to 7.6 cm (mean, 2.4 cm), with volumes ranging from 0.05 to 99 mL (mean, 7.2 mL). Observed nodule volumes correlated to the Dmax in a roughly exponential relationship, as expected. However, there was substantial internodule volume variabilty. The relationship between nodule diameter and volume is shown in Fig. 1a–1f. The greatest variability in volume for a given diameter was observed in tumors that were 2.0 to 2.9 cm. For example, the six nodules of Dmax 2.7 cm had a range of volumes relative to the mean of 153%, with the smallest of these having a volume more in keeping with an average 1.7-cm nodule and the largest having a volume more akin to an average 3.2-cm nodule. For PTC ≤2 cm, observed volumes for a given Dmax varied by an average of 70% relative to the mean, giving a coefficient of variation of 26.7%.

A. Observed vs Predicted USS Nodule Volumes

Mean nodule dimensions were 2.4 × 1.9 × 1.5 cm, giving "ideal" nodule dimensions of $y \times 0.78y \times 0.62y$. The nodule volume as an expression of y was therefore calculated as $\text{V} \approx 0.25y^3$. "Predicted" nodule volumes were calculated using this formula. Comparing observed USS volumes (calculated using recorded USS dimensions) with predicted USS volumes (calculated using Dmax alone and "ideal" PTC dimensions) showed a mean discrepancy of 26.2% between predicted and observed volumes. Furthermore, Dmax alone was only able to predict tumor volume with an acceptable accuracy (<10% error) in 24.5% of PTC nodules and was grossly inaccurate (>50% error) in almost 10% of PTC nodules. These results are displayed in Fig. 2.

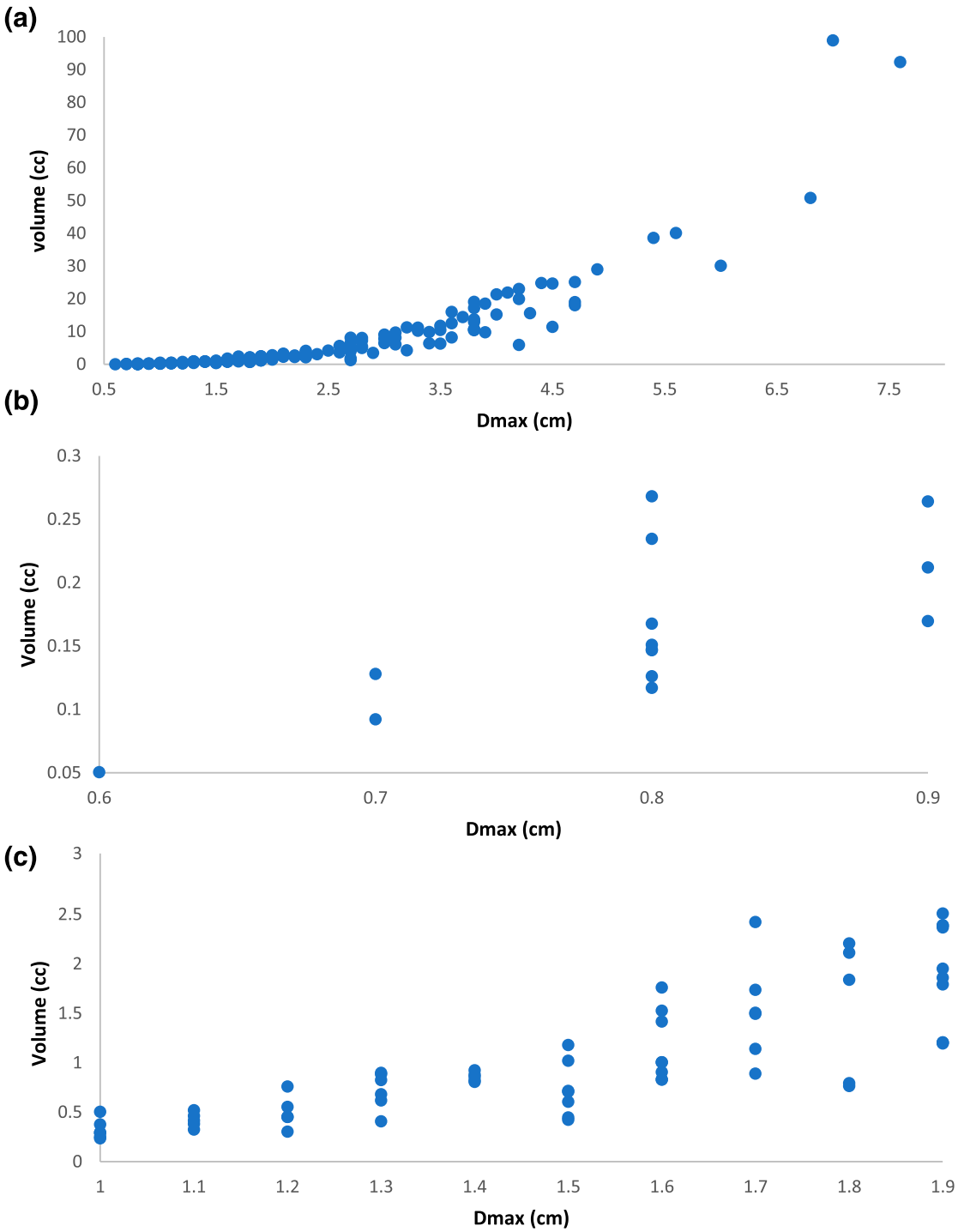

Figure 1. (a) Nodule volume (mL, *y*-axis) vs Dmax (cm, *x*-axis), all PTCs. (b) Nodule volume vs Dmax, PTC <1 cm. (c) Nodule volume vs diameter, PTC 1.0 to 1.9 cm. (d) Nodule volume vs diameter, PTC 2.0 to 2.9 cm. (e) Volume vs diameter, PTC 3.0 to 3.9 cm. (f) Volume vs Dmax, PTC ≥4 cm.

B. Nodal Status

A total of 128 patients had nodal status available. The overall rate of nodal metastases was 63%. The mean number of lymph node metastases was 3.85 (range, 0 to 26). Figures 3a and 3b demonstrate the rate of nodal metastasis by sonographic Dmax and volume subgroups. There

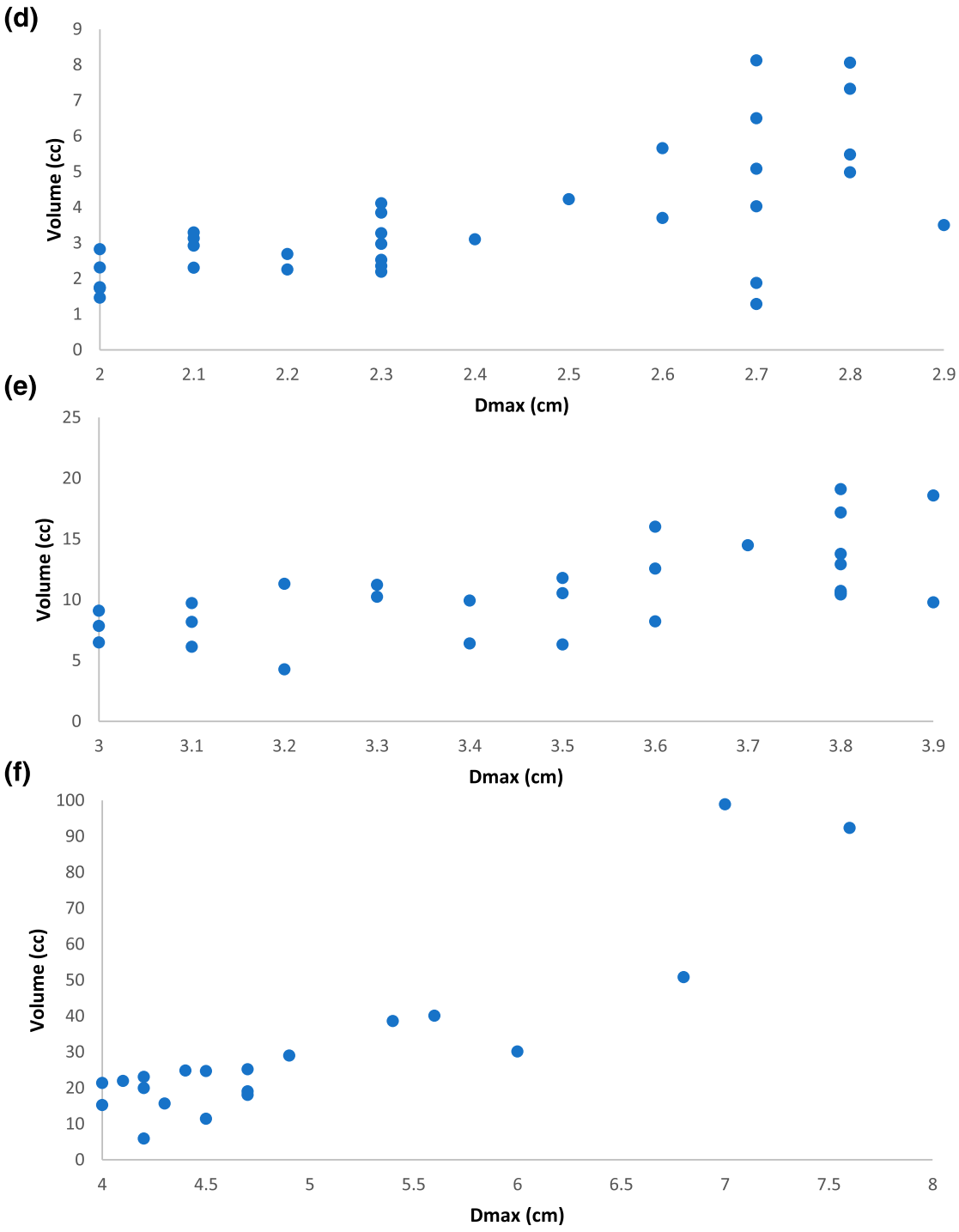

Figure 1. (Continued)

was no correlation between sonographic PTC Dmax and lymph node status (Pearson coefficient 0.08) and only a very weak correlation between sonographic volume and lymph node status (Pearson coefficient 0.22). However, there was a very strong correlation between nodal burden (number of involved lymph nodes) and both USS nodule Dmax and volume (Pearson coefficients 0.89 and 0.93, respectively). The relationships between nodule Dmax, volume, and nodal metastases are depicted in Figs. 3 and 4.

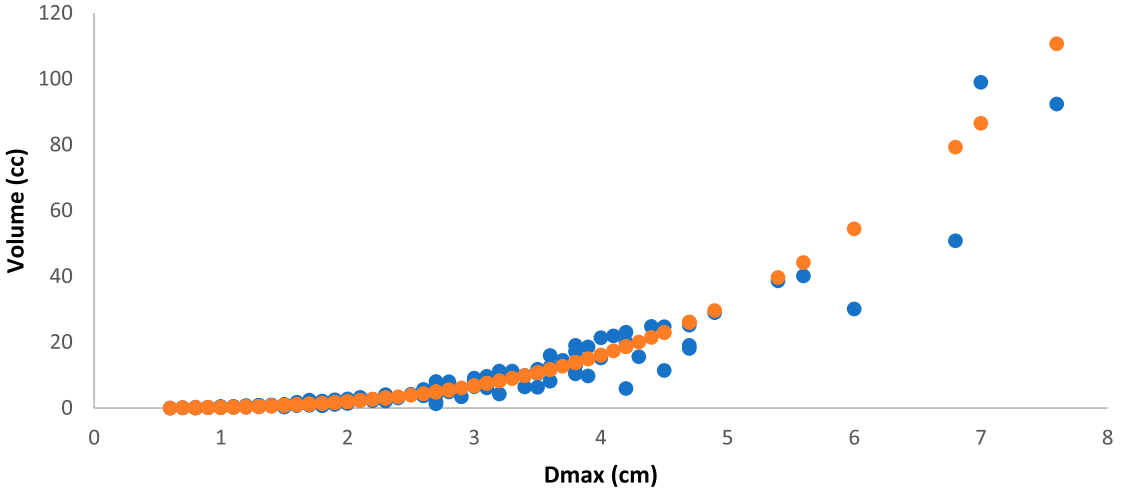

Figure 2. Observed (blue dots) and predicted (orange dots) volumes (mL, *y*-axis) vs Dmax (cm, *x*-axis).

3. Discussion

Our study suggests that in this cohort of PTC nodules, nodule dimensions varied substantially, such that a one-dimensional measurement of tumor size (Dmax) was inaccurate at reflecting predicted tumor volume more than 75% of the time. Furthermore, there was a wide spread of volumes for any given Dmax, across the spectrum of nodule sizes, confirming important shape and dimensional heterogeneity among PTC nodules. Such shape heterogeneity renders one-dimensional nodule measurements usually an inaccurate marker of true tumor size. Nodule shape as a predictor of malignancy has received attention, with studies divided as to the relative risk of spherical vs ellipsoid shape. One such study reported higher rates of malignancy among smaller thyroid nodules of a more spherical shape [15], whereas other studies have suggested ellipsoid shape (taller than wide) as more predictive of malignancy [16]. Our cohort of PTC nodules conformed roughly to an ellipsoid shape. One theory is that PTC nodules become more ellipsoid in shape as they enlarge and grow across tissue planes [17]. In our group of larger nodules (≥4 cm), 13 of 20 nodules had smaller volume than predicted, whereas 7 of 20 nodules had larger volume than predicted. This is a reflection of these larger nodules tending to be more ellipsoid in shape than the mean across all sizes. Regarding the accuracy of Dmax alone in these larger nodules, observed volumes varied by an average of 35% relative to the predicted volume. Seven of 20 nodule Dmax measurements predicted the observed volume accurately (<10% error). However, 13 of 20 (65%) Dmax values were unable to predict the volume accurately, and four of these (20%) were grossly inaccurate (>50% error). It would appear that, although a larger proportion of nodules ≥4 cm display close-to-ideal ellipsoid dimensions, there is still marked volume heterogeneity, rendering Dmax alone unreliable. It would be possible to perform these calculations, setting the smallest dimension as the constant. However, it would be difficult to reliably tell which axial measurements were being used in the true axial plane (*i.e.*, the coronal plane). Most USS reports do not clearly delineate between these two smaller measures as to which plane is being measured. Dmax (being the longitudinal measurement in the sagittal plane) does not suffer from the same ambiguity. Our cohort again confirms the high propensity of PTC to spread via lymphatics to local and regional lymph node basins, a phenomenon that appears largely independent of tumor size. Higher rates of lymph node metastases have been demonstrated among younger patients <45 years of age, suggesting that factors other than tumor cell count may be involved in PTC tumor spread [17]. It could be argued that tumor size should not be used to inform treatment decisions in patients with PTC and that other features, such as age and morphological appearance on ultrasound, are more important predictors. However, size remains a prominent feature of both management guidelines and

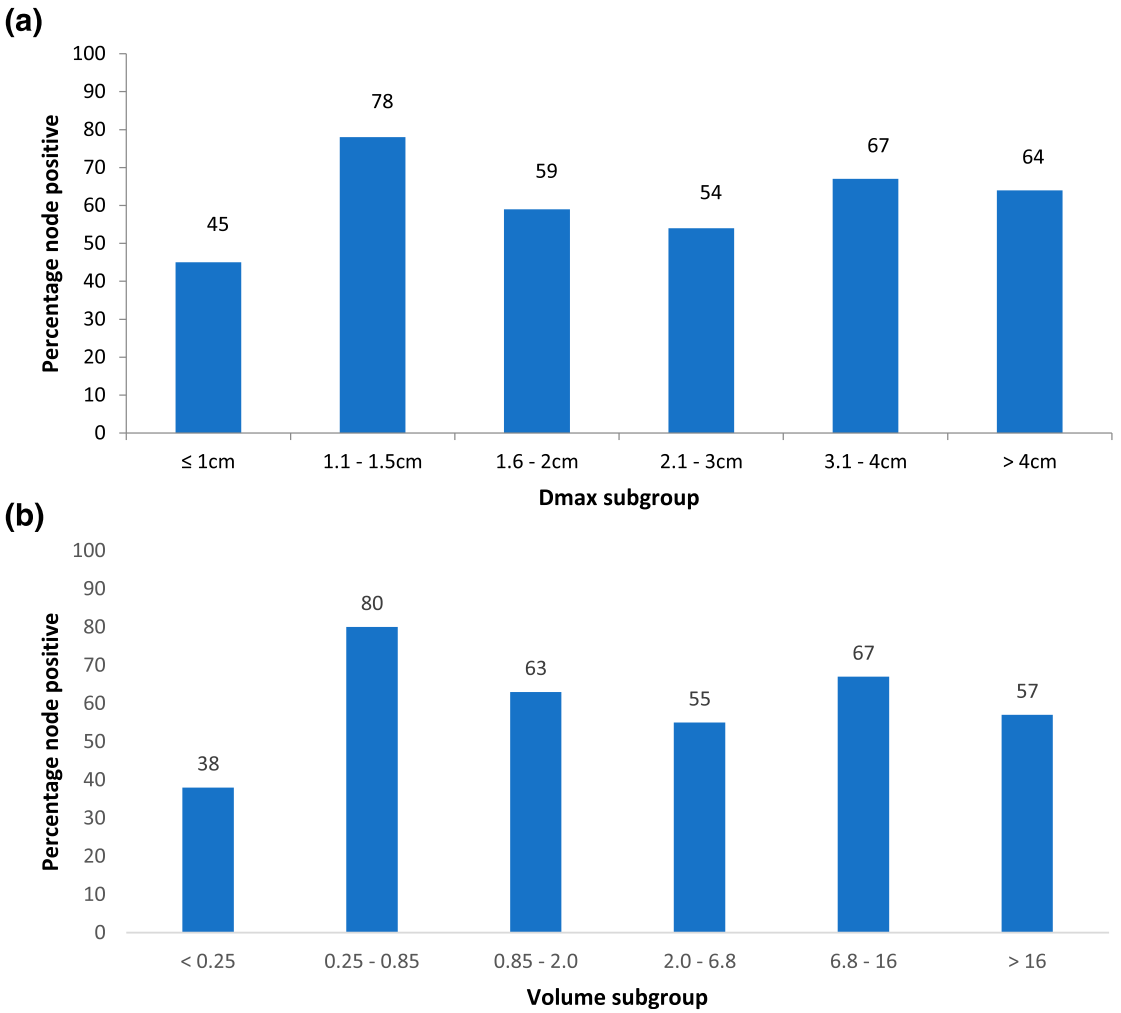

Figure 3. (a) Rate of nodal metastasis (percentage, *y*-axis) by Dmax subgroup (cm, *x*-axis). (b) Rate of nodal metastasis (percentage, *y*-axis) by sonographic volume subgroup (mL, *x*-axis).

staging systems, and size thresholds are a particularly prominent determinant in the cohort of most contention, the smaller PTCs. Furthermore, Dmax alone is used to define the ostensibly important distinction between PTC and PMC. With evidence of substantial volume variation for a given Dmax, it would seem more appropriate to develop volume thresholds to inform management in PTC. Our results confirm that both nodule Dmax and volume correlate strongly with the number of nodal metastases but not with the presence or absence of nodal metastases, although volume correlated with the latter more closely than did Dmax. The lack of a clear clinical benefit of volume measurement over Dmax may be explained by very high rates of nodal metastases across the range of PTC sizes, whereby a difference would only separate out with significance in a larger population size. Despite this, we feel strongly that a move toward standardized sonographic volumetric nodule assessment would improve the accuracy of *ex vivo* nodule size estimation and facilitate more accurate and appropriate treatment decisions.

The current study has limitations consistent with the inherent flaws of a retrospective study, including incomplete data, nonstandardized surgical treatment, and possible selection bias regarding the nodules chosen for 3D ultrasound measurement. A robust prospective study that eliminates some of these biases could be designed to aid development of volume thresholds for use in PTC guidelines and oncological staging systems moving forward. Such a study would require statistical power calculations and

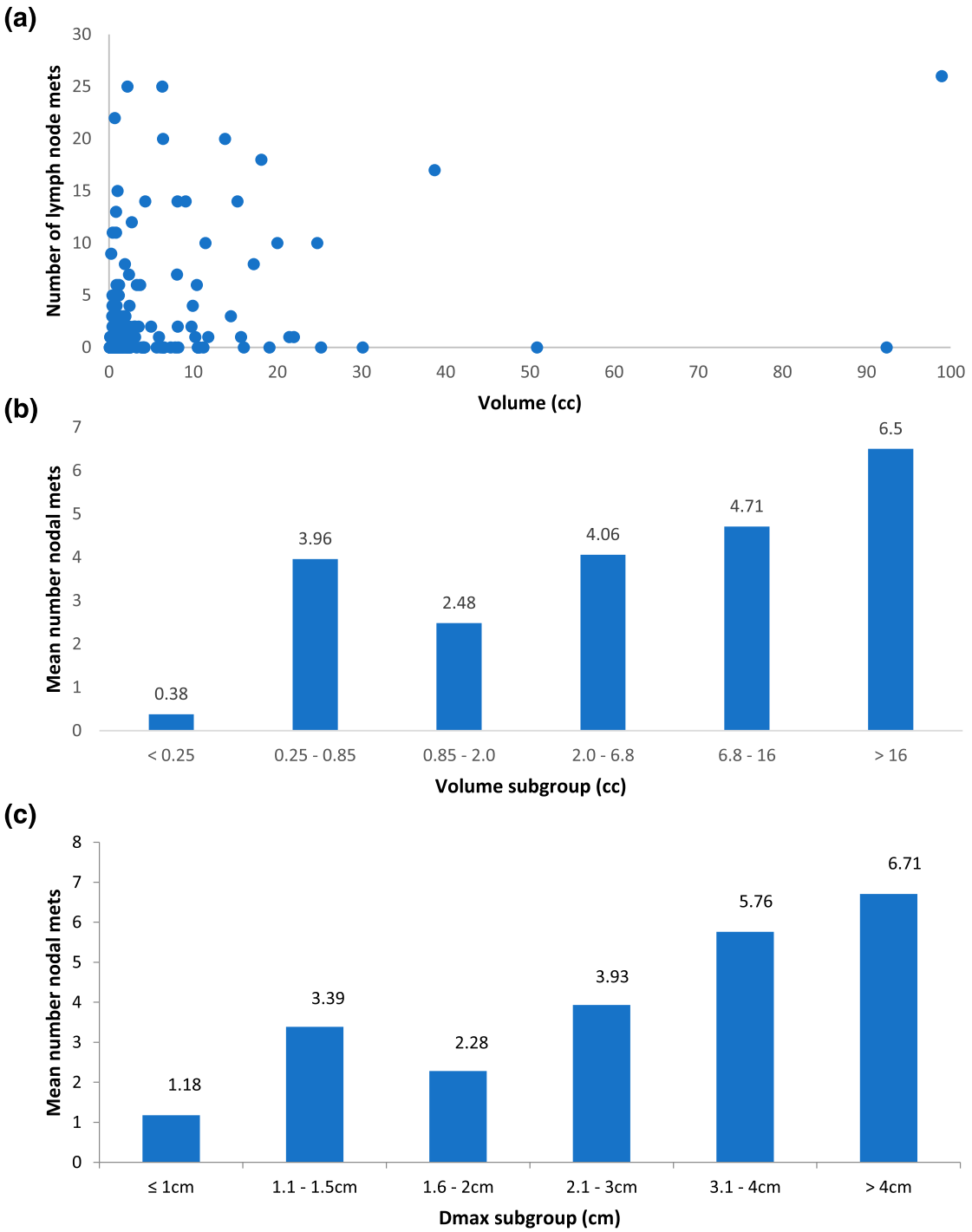

Figure 4. (a) USS nodule volume (mL, *x*-axis) vs number of lymph node metastases (*y*-axis), all PTCs. (b) Mean number of lymph node metastases by volume category. (c) Mean number of lymph node metastases by Dmax category.

would randomize patients with PTCs between 1 and 2 cm in Dmax and no clinical or sonographic lymphadenopathy to either preoperative DMax measurement alone or preoperative 3D volumetric assessment. A prospective pathological correlation with central compartment lymph node status would be performed and compared between the two trial arms.

Acknowledgments

The authors thank Professor Creswell Eastman, AO, Westmead Clinical School, University of Sydney, for his valuable contribution to this article.

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Disclosure Summary: The authors have nothing to disclose.

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