INTRODUCTION

Cancer staging plays a pivotal role in the battle against cancer. First and foremost, staging provides cancer patients and their physicians with critical information and guidelines for understanding the prognosis, the likelihood of survival, the relevant timelines, and the best treatment approach. Developing and improving the cancer staging systems is a never-ending...
was 20,226. Two-hundred ninety-nine patients who received were participated in this study. Initially, pool of the subjects at Seoul Metropolitan Government - Seoul National University Hospital. Boramae Medical Center and Seoul National University Hospital. Informed consent was waived from IRB.

Definitions of clinicopathological parameters

Patients’ ages were defined as the age at the time of diagnosis for primary breast cancer. The TNM staging was described according to the 7th edition of the AJCC.

Definition and classification of T and Tv

The T and Tv data were obtained from the final postoperative pathologic reports in the medical records. T was defined as the maximum tumor dimension and was recorded to the nearest millimeter. Tv was calculated by the equation of \( (4\pi \times r_1 \times r_2 \times r_3)/3 \), under the assumption that these measurements are the semi-axes of a prolate spheroid. The values of \( r_1 \), \( r_2 \), and \( r_3 \) were defined as the half of the largest, intermediate, and shortest dimension of the tumor, respectively. All of \( r_1 \), \( r_2 \), and \( r_3 \) were recorded to the nearest millimeter. The T category of the primary tumor was determined by pathologic measurement as T1 (tumor ≤ 20 mm in its greatest dimension), T2 (tumor > 20 mm but ≤ 50 mm in its greatest dimension), and T3 (tumor > 50 mm in its greatest dimension) according to the 8th edition of the AJCC Cancer Staging Manual. In this study, the Tv category of the primary tumor was determined by 2 cutoff values: the mean of Tv values for T = 2.0 cm (n = 874, mean = 2.056 cm³) and the mean of Tv values for T = 5.0 cm (n = 81, mean = 20.733 cm³). Accordingly, Tv was classified into 3 categories; Tv1 (Tv ≤ 2.056 cm³), Tv2 (Tv > 2.056 cm³ but ≤ 20.733 cm³), and Tv3 (Tv > 20.733 cm³).

Statistical analyses

Data were presented as frequency and percentage for categorical variables. The Kaplan-Meier method was used for the estimation of survival rates and log-rank tests were used to determine the significance of differences between 2 or more survival curves. The \( \chi^2 \) values of log-rank test were used to compare the statistical powers of clinicopathological parameters. The Cox proportional hazards model was used for the estimation of survival rates and log-rank tests were used to determine the significance of differences between 2 or more survival curves. The \( \chi^2 \) values of log-rank test were used to compare the statistical powers of clinicopathological parameters.
for univariate and multivariate analysis. The hazard ratio (HR) was calculated according to a cutoff value of a 95% confidence interval (CI). We used the Pearson correlation coefficient to evaluate bivariate correlation between T and Tv and positive nodes. We carried out receiver operating characteristic (ROC) curve analysis to illustrate the performance of T and Tv regarding overall survival rates, and calculated the value of the area under the curve (AUC). Time duration of overall survival were defined as the time from operation to death from any cause. All statistical analyses were carried out using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). All tests were 2-sided and we regarded the results of statistical analyses as significant when the P-value was less than 0.05.

RESULTS

Clinicopathological characteristics
The total number of subjects was 8,996. Female patients were 8,969 (99.7%) and male patients were 23 (0.3%). The mean age was 51.1 ± 10.7 years (range, 19–93 years). Operation dates were between September 25, 1995 and December 31, 2015. The mean follow-up period was 72.1±42.8 months (range, 0–253 months). The total number of deaths during this period was 626 (7.0%). The mean size of T and Tv were 2.3 ± 1.5 cm (range, 0.1–17.0 cm) and 6.0 ± 20.9 cm 3 (range, 0.001–1,005.3 cm 3), respectively. The clinicopathological characteristics of the study subjects are summarized in Table 1. The subject numbers of T1, T2, and T3 tumors were 4,803 (53.4%), 3,777 (42.0%), and 416 (4.6%), respectively, and those of the Tv1, Tv2, and Tv3 tumors were 4,496 (50.0%), 4,044 (45.0%), and 456 (5.1%), respectively. The proportions of stages I, II, and III by T were 40.9%, 43.2%, and 9.7%, respectively, and the proportions of stages I, II, and III by Tv were 37.8%, 45.9%, and 10.0%, respectively. Of the 4,803 T1 tumors, 4,204 (87.5%) were Tv1 tumors, and 599 (12.5%) were Tv2 tumors. Of the 3,777 T2 tumors, 3,369 (89.2%) were Tv2 tumors, and 292 (7.7%), and 116 (3.1%) were Tv1 and Tv3 tumors, respectively. Of the 416 T3 tumors, 340 (81.7%) were Tv3 tumors, and 76 (18.3%) were Tv2 tumors (Table 2).

Survival analysis
The survival curves according to both T and Tv were well separated (all P < 0.001). All of the \( \chi^2 \) values by log-rank test for Tv were larger than those of T, respectively (Fig. 1A, B). The survival curves according to both conventional stage by T and new stage by Tv were also well separated (all P < 0.001). The \( \chi^2 \) values between stages I and II, and between stages I and III by Tv were larger than those of conventional stages by T, respectively (Fig. 1C, D). Fig. 2A depicts the survival curves according to the combination of T and Tv. The T1 & Tv1 group showed the best survival rate and the T3 & Tv3 group showed the worst survival rate. Grossly, the survival curves could be classified into 3 groups according to Tv rather than T; the first group with T1 & Tv1 and T2 & Tv1, the second groups with T1 & Tv2, T2 & Tv2, and T3 & Tv2, and the third group with T2 & Tv3 and T3 & Tv3. Although the survival rate of the T2 & Tv1 group seemed to be higher than that of the T1 & Tv2, there was no statistically significantly difference between them (Fig. 2B). In T1 and T2 tumors, the Tv1 group showed superior survival to that of the Tv2 group (log-rank test; P < 0.001, P = 0.001 respectively) (Fig. 3A, B). Although the T1 group showed a higher survival rate than that of the T2 group in Tv2 tumors (log-rank test; P < 0.001) (Fig. 3C), there was no difference between them in terms of the Tv1 tumors (Fig. 3D). The \( \chi^2 \) value between Tv1 and Tv2 in T2 tumors (\( \chi^2=12.0 \)) (Fig. 1B) was larger than the \( \chi^2 \) value between T1 and T2 in Tv2 tumors (\( \chi^2=10.2 \)) (Fig. 1D).

Table 1. Baseline characteristics of the study subjects (n = 8,996)

| Characteristic | Number (%) |
|---------------|------------|
| Sex           |            |
| Female        | 8,969 (99.7) |
| Male          | 23 (0.3)    |
| Age (yr)      | 51.08 ± 10.7 |
| ≤50           | 4,686 (52.1) |
| >50           | 4,303 (47.8) |
| T             |            |
| T1            | 4,803 (53.4) |
| T2            | 3,777 (42)  |
| T3            | 416 (4.6)   |
| Tv            |            |
| Tv1           | 4,496 (50)  |
| Tv2           | 4,044 (45)  |
| Tv3           | 456 (5.1)   |
| N             |            |
| N0            | 5,758 (64.0) |
| N1            | 1,883 (20.9) |
| N2            | 528 (5.9)   |
| N3            | 263 (2.9)   |
| M             |            |
| M0            | 8,996 (100) |
| M1            | 0 (0)       |
| Stage (by T)  |            |
| I             | 3,681 (40.9) |
| II            | 3,883 (43.2) |
| III           | 870 (9.7)   |
| Stage (by Tv) |            |
| I             | 3,401 (37.8) |
| II            | 4,127 (45.9) |
| III           | 904 (10.0)  |

Values are presented as number (%) or mean ± standard deviation.
Tv, tumor volume.
Table 2. Subjects distribution according to T and Tv categories

| Category | No. (%) | T1 | T2 | T3 | Total |
|----------|---------|----|----|----|-------|
|          | No.     | 4,204 | 599 | 0  | 4,803 |
|          | % in T  | 87.5 | 12.5 | 0  | 100  |
|          | % in Tv | 93.5 | 14.8 | 0  | 53.4 |
| T1       | No.     | 292  | 3,369 | 116 | 3,777 |
|          | % in T  | 7.7  | 89.2 | 3.1 | 100  |
|          | % in Tv | 6.5  | 83.3 | 25.4 | 42.0 |
| T2       | No.     | 0    | 76   | 340 | 416  |
|          | % in T  | 0    | 18.3 | 81.7 | 100  |
|          | % in Tv | 0    | 1.9  | 74.6 | 4.6  |
| T3       | No.     | 0    | 1    | 456 | 456  |
|          | % in T  | 0    | 100  | 100 | 100  |
|          | % in Tv | 100  | 100  | 100 | 100  |
| Total    | No.     | 4,496 | 4,044 | 456 | 8,996 |
|          | % in T  | 50.0 | 45.0 | 5.1 | 100  |
|          | % in Tv | 100  | 100  | 100 | 100  |

Tv, tumor volume.

Fig. 1. Overall survival curves according to T category (A), Tv category (B), Stage by T (C), and Stage by Tv (D). Tv, tumor volume.

Fig. 2. Overall survival curves according to the combination of T and Tv category (A), and the survival curves for the T2 & Tv1 group and the T1 & Tv2 group (B). Tv, tumor volume. *No statistical significance between the 2 survival curves.
Cox regression analysis
Univariate analysis demonstrated that both the T and Tv categories were significant prognostic factors (both P < 0.001) (Table 3). The HRs of the Tv categories were larger than those of the T categories, respectively; the HRs of T2 and T3, with reference to T1 were 3.083 and 6.723, and the HRs of Tv2 and Tv3 with reference to Tv1 were 3.344 and 7.239, respectively. Tv stage groups also showed larger HRs when compared to those of T stage groups; the HRs of stage II (by T) and stage III (by T) with reference to stage I (by T) were 2.640 and 7.759, and the HRs of stage II (by Tv) and stage III (by Tv) with reference to stage I (by Tv) were 3.319 and 8.995, respectively. The HRs of the N categories are also described in Table 3. Multivariate analysis showed that Tv was still an independent prognostic factor as well as T after adjusted with N category.

ROC curve analysis
ROC curve analysis of overall survival rates showed that the AUCs of Tv and T were 0.712 (95% CI, 0.691–0.732; P < 0.001) and 0.699 (95% CI, 0.679–0.719; P < 0.001), respectively (Supplementary Fig. 1).

Correlation analysis
Positive correlations were observed between the number of positive nodes and conventional 1-dimensional tumor size (coefficient = 0.325; P < 0.001) (Supplementary Fig. 2A) and between the number of positive nodes and 3-dimensional Tv (coefficient = 0.321; P < 0.001) (Supplementary Fig. 2B).

**DISCUSSION**

The AJCC TNM staging system has become the global standard for gathering, communicating, and exchanging cancer information worldwide and is widely used by clinicians, the surveillance community, registrars, researchers, the medical industry, patient advocates, and cancer patients [1]. This system classifies cancers by the size and extent of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence or absence of distant metastases (M), supplemented in recent years by evidence-based prognostic and predictive factors. Conventionally, maximum 1-dimensional tumor size has been used as the only criterion for T classification in breast cancer since the 1st edition of AJCC TNM staging system. We hypothesized that 3-dimensional Tv might be a more appropriate method for determining primary tumor burden than 1-dimensional T, and as a result, Tv would be a superior prognosticator than conventional 1-dimensional T classification in several aspects.

Both conventional 1-dimensional T classification and 3-dimensional Tv classification were efficient prognostic factors in breast cancer. However, the results of the Kaplan-Meier estimator and the log-rank test (Fig. 1) used in this study showed that Tv is a more powerful prognosticator than

![Image](https://via.placeholder.com/150)

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**Fig. 3.** Overall survival curves for T1 and T2 in T1 tumors (A) and T2 tumors (B), and the survival curves for T1 and T2 in Tv1 tumors (C) and Tv2 tumors (D). Tv, tumor volume.
### Table 3. Univariate and multivariate analyses for T and Tv classification

| Category | Univariate analysis | P-value | Multivariate analysis by T<sup>a</sup> | P-value | Multivariate analysis by Tv<sup>b</sup> | P-value |
|----------|---------------------|---------|----------------------------------------|---------|----------------------------------------|---------|
| T        | Reference           | <0.001  | Reference                               | <0.001  | -                                      | -       |
| T1       |                     |         |                                        |         |                                        |         |
| T2       | 3.083 (2.556–3.718) | <0.001  | 2.415 (1.986–2.936)                     | <0.001  | -                                      | -       |
| T3       | 6.723 (5.132–8.806) | <0.001  | 3.529 (2.619–4.755)                     | <0.001  | -                                      | -       |
| Tv       | <0.001              |         |                                        |         |                                        | <0.001  |
| Tv1      | Reference           | -       |                                        |         |                                        |         |
| Tv2      | 3.344 (2.743–4.076) | <0.001  | -                                      | -       | 2.589 (2.108–3.178)                     | <0.001  |
| Tv3      | 7.239 (5.528–9.749) | <0.001  | -                                      | -       | 3.828 (2.849–5.145)                     | <0.001  |
| N        | <0.001              |         |                                        |         |                                        | <0.001  |
| N0       | Reference           |         |                                        |         |                                        |         |
| N1       | 1.866 (1.537–2.264) | <0.001  | 1.552 (1.276–1.889)                     | <0.001  | 1.519 (1.248–1.850)                     | <0.001  |
| N2       | 3.846 (3.043–4.862) | <0.001  | 2.723 (2.138–3.469)                     | <0.001  | 2.714 (2.132–3.456)                     | <0.001  |
| N3       | 7.551 (5.929–9.617) | <0.001  | 4.734 (3.646–6.147)                     | <0.001  | 4.633 (3.571–6.011)                     | <0.001  |
| Stage (by T) | <0.001 |         |                                        |         |                                        |         |
| I        | Reference           | -       |                                        | -       |                                        | -       |
| II       | 2.640 (2.111–3.301) | <0.001  | -                                      | -       |                                        | -       |
| III      | 7.759 (6.107–9.857) | <0.001  | -                                      | -       |                                        | -       |
| Stage (by Tv) | <0.001 |         |                                        |         |                                        |         |
| I        | Reference           | -       |                                        | -       |                                        | -       |
| II       | 3.139 (2.461–4.002) | <0.001  | -                                      | -       |                                        | -       |
| III      | 8.995 (6.949–11.643)| <0.001  | -                                      | -       |                                        | -       |

Values are presented as hazard ratio (95% confidence interval).
Tv, tumor volume.

<sup>a</sup>T category was adjusted with N category, and vice versa. <sup>b</sup>Tv category was adjusted with N category, and vice versa.
conventional T. Although all of the P-values were less than 0.001 in the T1, T2, and T3 groups and in the Tv1, Tv2, and Tv3 groups, the χ² values of the Tv categories were larger than those of the T categories. Similar findings were observed in stage by T and stage by T. Although previous studies have reported the prognostic roles of Tv in various solid cancers, a considerably smaller number of studies have been performed on breast cancer. All of these papers calculated the Tv of primary breast cancer by using images generated by mammography’s, PET-CT’s, and breast MRI’s. This study is the first paper to report the prognostic influence of Tv on breast tumors as calculated microscopically in 3-dimensions. Atkinson et al. [20] reported the relationship between primary Tv at detection, the number of positive nodes, and the probability of the time until the first distant metastasis occurred and was examined in a group of 2,663 women with breast cancer. The time until metastasis was shown to decrease and the probability of metastasis increase as Tv and the number of nodes increased was shown. Tv was calculated from mammography’s; tumor length and width were recorded for each patient and Tv was calculated under the assumption that these measurements were the axes of a prolate spheroid. Several papers reported the impact of metabolic Tv measured by PET-CT on the prognosis of breast cancer. Kim et al. reported that the metabolic Tv of primary tumors was associated with shorter disease free survival periods and shorter overall survival periods by performing univariate analysis on the PET-CT data of 53 operable primary breast cancer patients. Son et al. [26] reported that univariate and multivariate analyses indicated that nonsurvivors had a higher mean metabolic Tv according to PET-CT’s than survivors who had distant metastasis at the time of initial diagnosis. Several papers reported the prognostic impact of Tv determined by breast MRI’s on patients who received neoadjuvant chemotherapy [21,22,24,25,27]. Partridge et al. [21] reported the impact of breast Tv determined by MRI measurements for the prediction of response to neoadjuvant chemotherapy and recurrence-free survival using 62 breast cancer patients undergoing neoadjuvant chemotherapy and concluded that MRI-determined Tv was more predictive of recurrence free survival than T1, suggesting that volumetric changes measured using MRI may provide a more sensitive assessment of treatment efficacy. Akazawa et al. [22] reported the prognostic effect of reduction in total Tv measured with 3D-MRI for locally-advanced breast cancer patients, treated with primary chemotherapy, using data from 51 patients with locally advanced breast cancer treated with four cycles of docetaxel before surgery. The results revealed that the patients whose total Tv decreased by 75% or more after neoadjuvant chemotherapy showed significantly better prognoses than others, while tumor size measured with calipers, ultrasonography, and 2-dimensional MRI showed no significant relationship to patient prognosis.

In this study, we hypothesized that the T2 & Tv1 groups would show a lower survival rate than that of the T1 & Tv2 group according to conventional T classification. Although, the survival curves showed a tendency for a better prognosis of T2 & Tv1 than of T1 & Tv2, there was no statistical significance (Fig. 2). The number of subjects in the 2 groups might not have been sufficient to show statistical significance (n = 289 for T2 & Tv1, n = 594 for T1 & Tv2). Although our study did not show superior survival rates in T2 & Tv1 as compared to T1 & Tv2, the survival rates of T2 & Tv1 were, at least, not inferior to those of T1 & Tv2. There was also no statistical significance regarding overall survival between T3 & Tv2 and T2 & Tv3. And the number of subjects in each group were 75 and 115, respectively.

We hope that further study with an increased number of subjects will prove our hypothesis.

Subgroup analysis of T1, T2, Tv1, and Tv2 revealed that Tv classification had a greater prognostic prediction value for breast cancer than T classification. The Tv1 group showed superior survival rates than Tv2 for T1 and T2 tumors. On the contrary, there was no statistical significance between the T1 and T2 groups for Tv1 tumors. Su et al. [9] analyzed 274 patients with stage I non-small cell lung cancer who had received preoperative chest computed tomography scans with complete resection and Tv was semiautomatically measured from chest computed tomography scans by using an imaging software program. They reported that patients with tumor diameters ≤ 2 cm and 2–3 cm were stratified into 2 groups with significantly different DFS and OS on the basis of Tv. But Tv was not a significant factor in the patient group with tumor diameters > 3 cm. Our study also showed that Tv was a significant prognostic factor in T1 and T2, but lost its significance with T3 tumors (data not shown). Insufficient numbers of subjects was likely responsible for the outcome of this study, so further study is needed to prove the hypothesis.

Univariate analysis demonstrated that the HR’s of Tv categories were larger than those of T categories. The HR’s of staging by Tv categories were also larger than those of stages by T categories. These findings could be indirect evidences for the usefulness of Tv classification over conventional T classification. Tv was a significant independent prognostic factor as well as T and N according to the results of the multivariate analysis. Su et al. [9] reported that although Tv and the greatest tumor diameter were significant factors per univariate analysis, only Tv was an independent prognostic factor per multivariate analysis in stage I non-small cell lung cancer. Jorns et al. [10] reported that Tv was a significant independent prognostic factor for cancer specific survival in T1 clear cell renal cell carcinoma. They estimated the Tv using three tumor dimensions recorded in pathology reports and the equation for the volume of an ellipsoid: \( \frac{\pi}{6} (\text{length } \times \text{ width } \times \text{ height}) \). Jiang et al. [11] and Liu et al. [12] reported that the T2NM staging system may be
more reliable than the conventional TNM staging system for prognostic assessment using TNM stages I–III gastric cancer patients who underwent curative gastrectomy.

Although ROC curve analysis of overall survival rates showed a slightly higher AUC value for TV compared to T1, the difference was too small to be clinically significant (AUC = 0.712 for TV; AUC = 0.699 for T). Su et al. [9] reported similar results in stage I, non-small cell lung cancer. The ROC curves for predicting overall survival showed that the AUC of TV and the greatest tumor diameter were 0.645 (95% CI, 0.569–0.721; P = 0.001) and 0.641 (95% CI, 0.565–0.718; P = 0.001), respectively. Correlation analysis showed almost the same Pearson correlation coefficient values between tumor size and TV of positive node numbers. We could not observe the differences between the T and TV categories for prognostication power in the subgroup analyses according to N categories (data not shown).

Although this study demonstrated the practical usefulness of TV classification compared to conventional T classification, it had several limitations. First, the number of subjects was not sufficient to achieve the statistically significant results, particularly in the subgroup analyses. The most important finding was that the T2 & TV1 groups showed a tendency towards superior survival prediction compared to the T1 & TV2 groups, but there was no statistical difference. Second, although we tried to select the best cutoff points for the TV categories, they were still arbitrary. More effort may be needed to find the best cut off values which could better reveal the superiority of TV classification over conventional T classification. Third, we could not analyze breast cancer specific survival due to the unavailability of information. Last, this study showed the potential clinical usefulness of TV compared to T classification, but the clinical benefit of TV over conventional T classification in terms of prognostication was not big enough to urge its immediate clinical application. Further validation studies are needed to accumulate more evidence to support the results of this study.

In conclusion, TV classification works well for predicting the prognosis of breast cancer patients. According to the results, it is a better predictor than conventional T classification in several aspects. Further studies are needed to validate the practical usefulness of TV classification in clinical settings.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY MATERIALS

Supplementary Figures can be found via https://www.astr.or.kr/src/sm/astr-95-183-s001.pdf.

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Supplementary Fig. 1. Receiver operating characteristic curves for T and Tv regarding overall survival. AUC, area under the curve; Tv, tumor volume.

Supplementary Fig. 2. Two-dimensional scatter plots and Pearson correlation analyses to depict correlations between the number of positive nodes and tumor size (A) and between the number of positive nodes and tumor volume (B).