Visceral Pleural Invasion Classification in Non–Small-Cell Lung Cancer in the 7th Edition of the Tumor, Node, Metastasis Classification for Lung Cancer: Validation Analysis Based on a Large-Scale Nationwide Database

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Objective: In the 7th tumor, node, metastasis (TNM) classification, visceral pleural invasion (VPI) is defined as invasion beyond the elastic layer, including invasion to the visceral pleural surface, and T1 tumors with VPI are upgraded to T2a. To validate this, we analyzed the survival of non–small-cell lung cancer patients from a nationwide database and evaluated the prognostic impact of VPI.

Methods: The clinicopathological characteristics and prognosis of 4995 patients who were included in the registry study of the Japanese Joint Committee of Lung Cancer Registry were retrospectively analyzed with a special interest in the prognostic impact of VPI. These patients underwent surgery in 2004 and were pathologically staged as T1a-3N0. VPI was defined as including PL1 and PL2 according to the 7th TNM Classification, but the Japanese Joint Committee of Lung Cancer Registry did not collect data regarding staining or how extensively VPI was evaluated in each participating institution.

Results: The survival differences were statistically significant between PL0 and PL1, PL1 and PL2, as well as PL2 and T3. There were no significant survival differences between T1a with VPI and T1b without VPI, or between T1a with VPI and T2a without VPI. There were no significant survival differences between T1b with VPI and T2a without VPI, or between T1b with VPI and T2b without VPI. There were no significant survival differences between T2a with VPI and T2b without VPI, or between T2b with VPI and T2b without VPI. T3 showed significantly worse prognosis than T2a with VPI and T2b with VPI.

Conclusions: In addition to the current TNM classification recommendations, in which T1 tumors with VPI are upgraded to T2a, T2a tumors with VPI should be classified as T2b.

Key Words: TNM classification, NSCLC, visceral pleural invasion

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Visceral pleural invasion (VPI) of lung cancer has been known to be a poor prognostic factor.[1–10] In the 7th edition of the tumor, node, metastasis (TNM) classification for lung cancer, pleural invasion status is classified as follows: PL0, tumor within the subpleural lung parenchyma or superficial invasion into the pleural connective tissue beneath the elastic layer; PL1, tumor invasion beyond the elastic layer; PL2, tumor invasion to the pleural surface; and PL3, tumor invasion into any part of the parietal pleura.[11,12] Although the current TNM classification does not describe a survival difference between PL1 and PL2[11,12], VPI is defined to include PL1 and PL2. Tumors of 3 cm or less (T1a and T1b) with VPI (PL1 and PL2) are upgraded to T2a, whereas tumors greater than 3 and 7 cm or less (T2a and T2b) with VPI remain unchanged as T2.[13] These recommendations—to upgrade the T-classification according to VPI status—were based on the results of five retrospective studies[1–3,8,14] and not on the large-scale data accumulated by the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Project.[11]

In 2009, 253 Japanese institutions submitted information to the Japanese Joint Committee of Lung Cancer Registry (JJCLCR) regarding the outcome and clinicopathologic profiles of patients who had undergone surgical resection for primary lung cancer in the year 2004.[15] We retrospectively analyzed the survival of almost 5000 patients with pulmonary non–small-cell lung cancer (NSCLC) without node involvement from this registration to evaluate the impact of VPI on survival, and we

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propose incorporating VPI into T-status classification in the forthcoming TNM classification of the Union for International Cancer Control (UICC) staging system.

PATIENTS AND METHODS

Patient Cohort

As described previously, the JJCLCR performed a nationwide retrospective registry study in 2010 on the outcome and clinicopathologic profiles of resected primary lung neoplasms in Japan.[15] Only primary lung cancers that had been resected in 2004 at certified teaching hospitals in Japan, with a follow-up period of at least 5 years, were considered eligible for the registration. The committee received the registered data of 11,663 patients from 253 teaching hospitals. The registry questionnaire included the following items: (1) demographic background, (a) date of registry, (b) sex, (c) birth month and year, and (d) date of diagnosis; (2) preoperative status, (a) Eastern Cooperative Oncology Group performance status, (b) preoperative comorbidity, (c) smoking status, and (d) status of serum tumor markers (CEA, SCC or CYFRA, SLX and NSE, or Pro-GRP); (3) clinical T factors, (a) tumor size, (b) extent of invasion to the main bronchus, (c) pleural invasion, (d) intrapulmonary metastasis, (e) status of pleural effusion, (f) extent of atelectasis, and (g) status of invaded organ; (4) clinical N factor (status of removal of and metastasis to each lymph node); (5) clinical M factor (metastasized organ); (6) type of surgery, (a) induction therapy, (b) extent of lung resection, (c) place of tumor origin, (d) extent of lymph node removal, (e) gross curative status, (f) status of residual tumor, (g) lavage cytology findings, and (h) combined resection; (7) postoperative morbidity; (8) tumor histology; (9) adjuvant therapy; (10) pathological T factors, (a) tumor size, (b) extent of bronchial involvement, (c) pleural invasion, (d) intrapulmonary metastasis, (e) status of pleural effusion, (f) pleural dissemination, (g) status of atelectasis, and (h) status of invaded organ; (11) pathological N factor (status of removal of and metastasis to each lymph node); and (12) pathological M factor (metastasized organ). The extent of resection (exploratory, R0, R1, or R2) was also registered. Although the Japan Lung Cancer Society also recommends using not only hematoxylin and eosin (HE) staining but also elastic staining such as Victoria-blue van Gieson staining in VPI evaluation, the JJCLCR did not collect data regarding staining or how extensively VPI was evaluated in each participating institution. Diseases were staged based on the 7th edition of the UICC TNM classification.[11,12] Histopathologic classifications were described according to World Health Organization criteria.[16] Recurrent or multiple lung cancers were not included in the registration.

Of the 11,663 patients, 4995 patients (42.8%) underwent pulmonary resection (lobectomy or greater) and systematic mediastinal lymph node dissection for pathologically T1aN0, T1bN0, T2aN0, T2bN0, or T3N0 NSCLC. All these patients had curative resection, which was defined as complete removal of the ipsilateral hilar and mediastinal lymph nodes together with the complete resection of the primary tumor. Patients who had induction chemotherapy, radiotherapy, or both, and patients with evidence of residual tumor at the surgical margin, malignant effusion, interlobar invasion, or distant metastasis, verified intraoperatively or by means of postoperative pathologic examination were excluded from this study.

Statistical Analysis

Pleural invasion status was classified according to the 7th edition of the UICC TNM classification[11–13]: PL0, tumor within the subpleural lung parenchyma or superficial invasion into the pleural connective tissue beneath the elastic layer; PL1, tumor invasion beyond the elastic layer; PL2, tumor invasion to the pleural surface; and PL3, tumor invasion into any part of the parietal pleura. In the following descriptions, T-classification is determined excluding VPI status, but PL3 tumors are classified as T3.

First, we analyzed the overall survival of PL0, PL1 and PL2 or T3 patient groups. Second, defining VPI to include PL1 and PL2, we analyzed the overall survival of the pT1a patient groups with or without VPI, pT1b with or without VPI, pT2a with or without VPI, and pT2b with or without VPI or T3. The follow-up period was defined as the time from the date of surgery to the most recent follow-up examination. The survival period was defined as the number of months from the day of surgery to the day of death from any cause. Survival curves were estimated using the Kaplan-Meier method. Differences in survival were tested using the log-rank test. A p value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using software packages (SAS version 9.1.3 [SAS Institute, Inc., Cary, NC], SPSS version 19 [IBM Corp., New York, NY]).

This study was approved by the institutional review board of Osaka University Medical Hospital, where the office of JJCLCR is located, on August 13, 2009 (approval no. 09124).

RESULTS

Patient Characteristics and Visceral Pleural Invasion

Table 1 shows the patient characteristics. There were 2981 men and 2014 women, aged 15 to 90 years (median, 67 years). The extent of pulmonary resection was pneumonectomy (n = 65), bilobectomy (n = 122), and lobectomy (n = 4808). The histological types were adenocarcinoma (n = 3638), squamous cell carcinoma (n = 1028), adenosquamous carcinoma (n = 84), large-cell carcinoma (n = 149), and other histological types (n = 96).

Survival Differences

The overall 5-year survival rates for PL0 (n = 3606), PL1 (n = 727), PL2 (n = 219), and T3 (n = 443) patients were 87%, 77%, 69%, and 54%, respectively. There were significant survival differences between PL0 and PL1 ($p < 0.001$), between PL1 and PL2 ($p = 0.023$), and between PL2 and T3 ($p < 0.001$) patients (Fig. 1).

The survival curves stratified by T and VPI status are shown in Figure 2*A*. Figure 2*B* shows the survival impact of VPI on T1a tumors. Although T1a tumors with VPI had a

TABLE 1. Patient Characteristics

	No. of Patients (%)				
	VPI Factor of T1/T2 Cases				
Characteristics	**PL0**	**PL1**	**PL2**	**T3**	**Total**
Age, yr					
Median (range)	67 (15–89)	68 (31–90)	68 (30–85)	69 (34–83)	67 (15–90)
Sex					
Men	2034 (56)	466 (64)	142 (64)	339 (77)	2981 (60)
Women	1572 (44)	261 (36)	77 (36)	104 (23)	2014 (40)
Surgery					
Lobectomy	3477 (96)	706 (97)	215 (98)	410 (93)	4808 (96)
Bilobectomy	95 (3)	12 (2)	3 (1)	12 (3)	122 (2)
Pneumonectomy	34 (1)	9 (1)	1 (1)	21 (5)	65 (1)
Histology					
Adenocarcinoma	2743 (76)	505 (70)	168 (77)	222 (50)	3638 (73)
Squamous cell carcinoma	660 (18)	168 (23)	37 (17)	163 (37)	1028 (21)
Adenosquamous carcinoma	55 (2)	14 (2)	2 (1)	13 (3)	84 (2)
Large-cell carcinoma	81 (2)	32 (4)	7 (3)	29 (7)	149 (3)
Others	67 (2)	8 (1)	5 (2)	16 (4)	96 (2)
Tumor diameter, cm					
<2	1558 (43)	199 (27)	40 (18)	29 (7)	1826 (37)
2.1–3	1125 (31)	215 (30)	72 (33)	71 (16)	1483 (30)
3.1–5	805 (22)	252 (35)	81 (37)	130 (29)	1268 (25)
5.1–7	118 (3)	61 (8)	26 (12)	72 (16)	277 (6)
≥7.1–	–	–	–	141 (32)	141 (3)
Total	3606	727	219	443	4995

VPI status was defined according to the 7th edition of the tumor, node, metastasis classification for lung and pleural tumors.
VPI, visceral pleural invasion

significantly poorer prognosis than T1a tumors without VPI ($p < 0.001$), there were no significant survival differences between T1a tumors with VPI and T1b tumors without VPI ($p = 0.083$) or T2a tumors without VPI ($p = 0.221$).

Figure 2*C* shows the survival impact of VPI on T1b tumors. Although T1b tumors with VPI had a significantly poorer prognosis than T1b tumors without VPI ($p = 0.001$), there were no significant survival differences between T1b

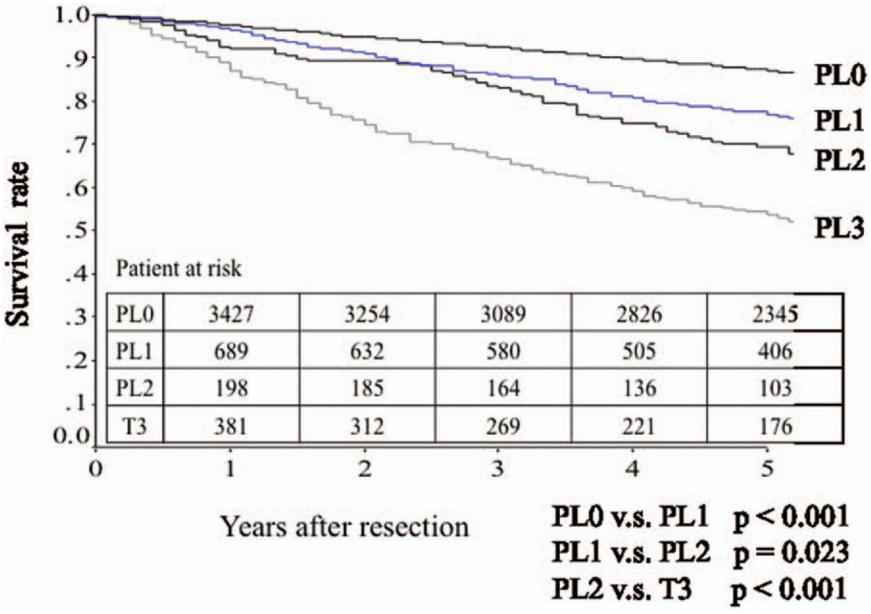

FIGURE 1. Overall survival curves of PL0, PL1, PL2, and T3 patients.

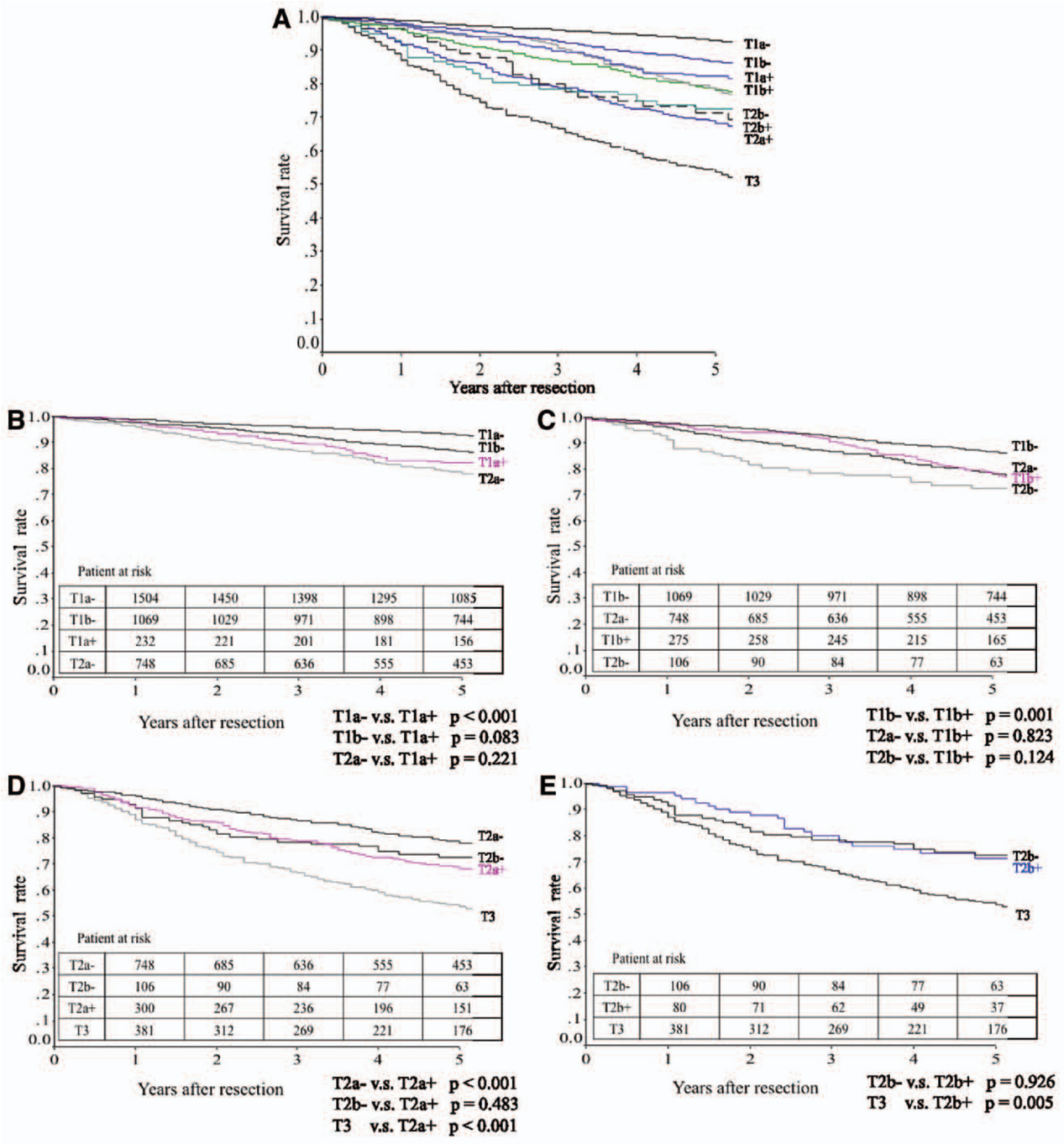

FIGURE 2. (*A*) Survival curves stratified by T stage and VPI status. (*B*) Survival curves of T1a/VPI–, T1b/VPI–, T2a/VPI–, and T1a/VPI+. (*C*) Survival curves of T1b/VPI–, T2a/VPI–, T2b/VPI–, and T1b/VPI+. (*D*) Survival curves of T2a/VPI–, T2b/VPI–, T2b/VPI–, and T2a/VPI+.(*E*) Survival curves of T2b/VPI–, T3, and T2b/VPI+.

tumors with VPI and T2a tumors without VPI ($p = 0.823$) or T2b tumors without VPI ($p = 0.124$).

Figure 2*D* shows the survival impact of VPI on T2a tumors. T2a tumors with VPI had a significantly poorer prognosis than T2a tumors without VPI ($p < 0.001$). There were no significant survival differences between T2a tumors with VPI and T2b tumors without VPI ($p = 0.483$). T2a tumors with VPI had a significantly better prognosis than T3 tumors ($p < 0.001$).

Figure 2*E* shows the survival impact of VPI on T2b tumors. There were no significant survival differences between T2b tumors with VPI and T2b tumors without VPI ($p = 0.926$). T2b tumors with VPI had a significantly better prognosis than T3 tumors ($p = 0.005$).

DISCUSSION

VPI is known to be a poor prognostic factor of NSCLC patients and is defined as a factor to upgrade T1a/T1b tumors to T2a in the 7th Edition of the TNM Classification for Lung and Pleural Tumours.[11,12,14] Travis et al.[13,17,18] recommend the use of elastic stains when invasion beyond the elastic layer is not clear on evaluation of HE sections. Although the Japan Lung Cancer Society also recommends using not only HE staining, but also elastic staining such as Victoria-blue van Gieson staining in VPI evaluation, the JJCLCR did not collect data regarding staining or how extensively VPI was evaluated in each participating institution. This is a major limitation of the present study.

In the present study, PL1 patients had a significantly poorer prognosis than PL0 patients, consistent with many previous reports.[1–10] PL2 patients had a significantly poorer prognosis than PL1 patients. The survival difference between PL1 and PL2 patients remains controversial. Kawase et al.[10] analyzed a cohort of more than 2700 patients, using the current VPI definition and elastic staining in all cases for VPI diagnosis, and reported no survival differences between PL1 and PL2 patients. Moreover, several other researchers have reported similar results.[2,6,9] In contrast, Sakakura et al.[4] reported significant differences in survival between PL1 and PL2 patients, but they did not describe whether or not they used elastic stains in diagnosing VPI status. In the data of the JJCLCR registry, it is not clear in what portion of the accumulated cases elastic staining was employed, and there remains some uncertainty regarding the determination of pleura invasion. Some PL0 patients might have been miscategorized as PL1 without the use of elastic staining, which may have led to the significant survival difference observed between PL1 and PL2 patients. To conclude whether or not a difference between PL1 and PL2 survival is valid, it is necessary to study more patients with VPI diagnoses made with the help of elastic staining.

To analyze the prognostic impact of VPI on T-status classification in the current cohort, we defined VPI to include PL1 and PL2 patients, as defined by the 7th edition of the TNM Classification for Lung and Pleural Tumours. T1a with VPI had a significantly poorer prognosis than T1a without VPI, but there were no significant survival differences between T1a with VPI and T1b without VPI, or between T1a with VPI and T2a without VPI. To summarize, T1a with VPI had prognosis similar to that of T1b/T2a without VPI, which suggests it is credible to upgrade T1a with VPI to T2a.

T1b with VPI had a significantly poorer prognosis than T1b without VPI, but there were no significant survival differences between T1b with VPI and T2a without VPI or between T1b with VPI and T2b without VPI. To summarize, T1b with VPI had a similar prognosis to T2a/T2b without VPI, which suggests it is reasonable to upgrade T1b with VPI to T2a, as described in the 7th edition of the TNM Classification for lung cancer.[11,12]

The most significant information of the present study is the outcome of T2a with VPI. T2a with VPI had a significantly poorer prognosis than T2a without VPI. There were no significant survival differences between T2a with VPI and T2b without VPI. T2a with VPI had a significantly better prognosis than T3. To summarize, T2a with VPI had a similar prognosis to T2b without VPI, which suggests T2a with VPI should be upgraded to T2b.

TABLE 2. T-Classification Comparison

Tumor Diameter, cm	VPI Ctatus	7th Edition T-Classification	Our Proposal
<2	−	T1a	T1a
<2	+	T2a	T2a (or T1b)
2.1–3	−	T1b	T1b
2.1–3	+	T2a	T2a
3.1–5	−	T2a	T2a
3.1–5	+	T2a	T2b
5.1–7	−	T2b	T2b
5.1–7	+	T2b	T2b

VPI– = PL0, VPI+ = PL1 or PL2.
VPI, visceral pleural invasion.

In the current cohort, there were no significant survival differences between T2b with VPI and T2b without VPI. T2b with VPI had a significantly better prognosis than T3. To summarize, T2b with VPI had a prognosis similar to that of T2b without VPI, which suggests there is no need to upgrade T2b with VPI. These suggestions are summarized in Table 2, and they include some differences from the conclusions of previous publications.[2,8,10]

A major limitation of the current study is that we do not know how thoroughly VPI was evaluated including elastic staining, in each participating institution. The differences observed may have been attributable to misdiagnoses of VPI status due to the lack of elastic staining use. However, the recommendation of the 7th edition of the TNM classification, that is, to upgrade T-classification according to VPI status, was determined on the basis of the results of some retrospective studies of small cohorts, in contrast to the large number cohort accumulated by the IASLC Lung Cancer Project. Moreover, the IASLC Lung Cancer Project also lacks detailed information on VPI status evaluation methodology. Therefore, we consider that a worldwide large-scale study that is limited to patients whose VPI status is diagnosed using elastic staining is necessary to determine the true impact on survival of pleural invasion and VPI.

In conclusion, in addition to the current TNM Classification recommendations—to upgrade tumors of 3 cm or less with VPI to T2a—tumors greater than 3 cm and 5 cm or less with VPI should be upgraded to T2b. However, more detailed further research is necessary for the next edition of the TNM classification for lung and pleural tumours, using a large-scale database with VPI status diagnosed using elastic staining.

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