Prognostic significance of vascular invasion and cell-proliferation activity in widely invasive follicular carcinoma of the thyroid

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Abstract. Widely invasive follicular thyroid carcinoma (wi-FTC) is regarded as having an aggressive character and a dire prognosis, but it has not been known whether all wi-FTCs have a dire prognosis. Herein we retrospectively analyzed the cases of 133 patients with wi-FTCs to determine the prognostic significance of vascular invasion and cell-proliferation activity based on the Ki-67 labeling index (LI). Of the 119 patients without distant metastasis (M0), 11 (9.2%) showed recurrence during the postoperative follow-up. In a univariate analysis, the recurrence-free survival (RFS) rates of the M0 patients with vascular invasion and those with a Ki-67 LI ≥5% were significantly poorer (p = 0.0013 and p = 0.0268, respectively) than those of the patients without vascular invasion or with a Ki-67 LI <5%. Other clinicopathological factors such as patient age, gender, tumor size, and oxyphilic tumor were not significantly related to the patients’ RFS. In a multivariate analysis, positive vascular invasion independently affected the RFS (p = 0.0133), but Ki-67 >5% did not (p = 0.1348). To date, only five patients have died of their thyroid carcinoma; four cases were M1. In conclusion, although M0 wi-FTC generally has a favorable prognosis, cases with positive vascular invasion or a high Ki-67 LI are likely to recur, and careful postoperative follow-up is necessary.

Key words: Widely invasive follicular carcinoma, Prognostic factor, Ki-67 labeling index

Patients and Methods

FOLLICULAR THYROID CARCINOMA (FTC) is the second most common carcinoma arising from thyroid follicular cells. In the past, FTC was classified into two categories, i.e., minimally and widely invasive FTCs. In the newest World Health Organization (WHO) classification, FTC was re-classified into three categories: minimally invasive FTC (mi-FTC, with minimal capsular invasion only), encapsulated angioinvasive FTC (ea-FTC, vascular invasion with no or minimal capsular invasion), and widely invasive FTC (wi-FTC, extensive capsular invasion regardless of vascular invasion) [1]. In 2007, we reported that widely invasive FTCs showed a more dire prognosis than minimally invasive FTCs [2]. In 2013, we demonstrated that M1 and large tumor size significantly affected the prognoses of patients with wi-FTC [3]. However, in those studies, we did not investigate whether vascular invasion affects the patients’ prognoses. We also demonstrated that the cell-proliferation activity evaluated by determining the Ki-67 labeling index (LI) can predict a poor prognosis of both mi-FTC and papillary thyroid carcinoma (PTC) [4, 5]. However, it has not been known whether the Ki-67 LI reflects the prognosis of wi-FTC patients. We conducted the present study to determine whether vascular invasion and cell-proliferation activity based on the Ki-67 LI have prognostic significance in wi-FTC.

Patients

We extracted the cases of the 162 patients who underwent their initial surgery at Kuma Hospital (Kobe, Japan) between 1998 and 2016. In our prior study, we enrolled patients who underwent their initial surgery between 1988 and 2007 [3]; however, the pathological specimens produced between 1988 and 1997 had been routinely decalcified and the immunostaining of Ki-67 was thus not possible. In addition, the number of tissue
sections was much lower than that of the sections produced after 1997, and it would thus be inappropriate to evaluate the degree of vascular invasion for these specimens. We omitted the cases operated on between 1988 and 1997. All patients had been diagnosed with wi-FTC by attending pathologists. For the present study, one expert pathologist (M.H.) reviewed all of the hematoxylin- and eosin (H&E)-stained sections of all of the patients. The definition of extensive invasion has not yet been unified, but the pathologist’s diagnostic criterion for wi-FTC is FTC showing macroscopic (grossly apparent) capsular invasion in the surgical specimen.

The tumors of 13 of the patients were diagnosed as poorly differentiated carcinoma (PDC) based on the newest WHO classification [1] and analyzed separately. We excluded the cases of six patients who were diagnosed with other diseases (four papillary thyroid carcinomas, one follicular adenoma, and one mi-FTC). Ten patients were excluded from the analyses due to short postoperative follow-up periods (<12 months). We thus enrolled a final total of the cases of 133 patients with wi-FTC: 28 males and 105 females, age at initial surgery 14–88 years, median 49 yrs. Fifty-three of these patients underwent a total thyroidectomy as an initial surgery. Of the remaining 80 patients who underwent a hemithyroidectomy, subtotal thyroidectomy, or isthmectomy, 53 underwent a completion total thyroidectomy as a second surgery. The remaining 27 did not undergo a completion total thyroidectomy for various reasons such as poor performance status, patient’s refusal, and surgeon’s discretion.

Seventy-eight patients were administered radioactive iodine (RAI) for scintigraphy, adjuvant therapy, or therapy for distant metastasis. Our series included 14 M1 patients; the distant metastases of eight of these patients were detected by preoperative imaging studies, and those of the remaining six were detected by postoperative RAI administration or other imaging studies such as computer tomography (CT) and positron emission tomography (PET)-CT. We followed patients mainly in our outpatient clinic, by blood examinations (thyroid stimulating hormone, free thyroxine or free triiodothyronine, thyroglobulin and, although not always, anti-thyroglobulin antibody) and imaging studies such as ultrasound once or twice per year. For the M1 cases and the cases considered high-risk by physicians, CT examinations (mainly of the chest) were also performed at the physician’s discretion. For patients who were referred to other hospitals, we sent questionnaires annually to evaluate their conditions. The follow-up periods ranged from 15 to 247 months (median 76 months).

**Evaluation of vascular invasion**

Vascular invasion was defined as the presence of tumor cell nests covered with endothelium in a blood vessel within or beyond the capsule. We cut surgical specimens at intervals of 3–4 mm. The number of vascular invasion sites was counted in all preparations for each case by the pathologist (M.H.).

**Immunohistochemistry for Ki-67**

Ki-67 immunohistochemical staining was performed using primary antibodies against Ki-67 (MIB-1, 1:200 dilution, Dako, Glostrup, Denmark). The Ki-67 labeling index was estimated by counting ≥500 carcinoma cells in the hot spot. The Ki-67 LI values were available for 111 of the 133 patients. We performed Ki-67 immunostaining in the section in which the density of carcinoma cells was highest. The remaining cases had no Ki-67 LI data because of the lack of tissue sections and decalcification preventing immunostaining.

**Postoperative follow-up**

We followed patients mainly in our outpatient clinic, by blood examinations (thyroid stimulating hormone, free thyroxine or free triiodothyronine, thyroglobulin and, although not always, anti-thyroglobulin antibody) and imaging studies such as ultrasound once or twice per year. For the M1 cases and the cases considered high-risk by physicians, CT examinations (mainly of the chest) were also performed at the physician’s discretion. For patients who were referred to other hospitals, we sent questionnaires annually to evaluate their conditions. The follow-up periods ranged from 15 to 247 months (median 76 months).

**Definition of carcinoma recurrence**

In this study, we regarded each case as showing recurrence only when recurred lesions were detected by an imaging modality. Elevation of thyroglobulin and/or thyroglobulin-antibody was not counted as a carcinoma recurrence.

**Statistical analyses**

The χ²-test was adopted to compare variables. The Kaplan-Meier method and log rank test were used to analyze the time-dependent variables. For the multivariate analysis, the Cox-regression model was adopted. We omitted the M1 cases from the analysis of the RFS. A p-value <0.05 was considered significant. Stat View 5.0 software (SAS, Cary, NC, USA) was used for the analyses.

**Results**

We first compared various clinicopathological features of the groups of patients with PDC and wi-FTC. As summarized in Table 1, in the PDC group (n = 13), the tumor size was significantly larger (p = 0.0284), vascular invasion was significantly more frequent (p < 0.0001), and the Ki-67 LI was significantly higher (p = 0.0001) compared to the wi-FTC group (n = 133). The recurrence-free survival (RFS) rate and the cause-specific survival (CSS) rate were both significantly lower (p < 0.0001 and p = 0.0147, respectively) in PDC than in wi-FTC (Fig. 1a, b). The 5-year and 10-year RFS rates of the wi-FTC...
patients were 94.3% and 87.3% whereas those of the patients with PDC were 60% and 40%, respectively. The 5-year and 10-year CSS rates of the wi-FTC group were 99.2% and 95.5% and those of the PDC group were 84.6% and 75.2%, respectively.

Table 2 shows the relationships between the M factor and clinicopathological features. Only the number of vascular invasion foci was significantly related to M1 ($p = 0.0265$). Metastatic lesions in 13 of the 14 patients were initially RAI-avid. Three patients were administered a tyrosine kinase inhibitor for their distant metastasis. The metastatic lesion was stable for one patient and progressed in one patient. The remaining patient was lost to follow-up.

We then investigated the prognostic significance of various clinicopathological features for the RFS in the wi-FTC group. To date, 11 of the 119 M0 patients (9.2%) showed recurrence; the sites of recurrence were lung ($n = 4$ patients), bone ($n = 6$), cervical lymph nodes ($n = 2$), adrenal gland ($n = 2$), and thyroid bed ($n = 1$). Three patients showed recurrence to two or more organs. Ten of the 11 M0 patients with recurrence were administered RAI; the metastatic lesions of six of the patients were RAI-avid.

The cases that were positive for vascular invasion showed a significantly poorer ($p = 0.0013$) RFS rate than those with no vascular invasion (Fig. 2a). In our series, however, the number of vascular invasion foci (1–3 vs. ≥4) was not related to the patients’ RFS ($p = 0.8163$). The RFS rate of the patients with a high Ki-67 LI (≥5%) was significantly poorer ($p = 0.0268$) than that of the patients with a low Ki-67 LI (Fig. 2b). Other factors such as older age (cut-off at 55 years, $p = 0.9823$), male gender ($p = 0.9828$), and oxyphilic tumor ($p = 0.5452$) were not significantly related to the RFS rate. Large tumor size (>4 cm) did not show prognostic significance ($p = 0.1934$), which is discrepant with our finding in the previous study [3].

We then performed a multivariate analysis to examine the RFS rate for the M0 patients that included vascular

### Table 1

| Variable                        | Widely invasive FTC ($n = 133$) | PDC ($n = 13$) | Total | $p$-value |
|---------------------------------|---------------------------------|----------------|-------|-----------|
| Age: ≥55 yrs                    | 70 (52.6%)                      | 7 (53.8%)      | 77    | 0.9333    |
| <55 yrs                         | 63 (47.4%)                      | 6 (46.2%)      | 69    |           |
| Sex                             |                                 |                |       |           |
| Male                            | 28 (21.0%)                      | 5 (38.5%)      | 70    | 0.1700    |
| Female                          | 105 (79.0%)                     | 8 (61.5%)      | 76    |           |
| Tumor size:                     |                                 |                |       |           |
| >4 cm                           | 60 (45.1%)                      | 10 (76.9%)     | 70    | 0.0284    |
| ≤4 cm                           | 73 (54.9%)                      | 3 (23.1%)      | 76    |           |
| Distant metastasis at presentation: |                                 |                |       |           |
| Yes                             | 14 (10.5%)                      | 3 (23.1%)      | 17    | 0.1781    |
| No                              | 119 (89.5%)                     | 10 (76.9%)     | 129   |           |
| *No. of vascular invasion foci: |                                 |                |       |           |
| 0                               | 100 (75.2%)                     | 0 (0.0%)       | 100   | <0.0001   |
| 1–3                             | 22 (16.5%)                      | 0 (0.0%)       | 22    |           |
| 4–9                             | 3 (0.2%)                        | 3 (23.1%)      | 6     |           |
| ≥10                             | 8 (6.1%)                        | 10 (76.9%)     | 18    |           |
| Ki-67 LI:                       |                                 |                |       |           |
| <5%                             | 73 (65.8%)                      | 1 (12.5%)      | 74    |           |
| ≥5%, <10%                       | 15 (13.5%)                      | 0 (0.0%)       | 15    | 0.0001    |
| ≥10%                            | 23 (20.7%)                      | 7 (87.5%)      | 30    |           |
| (unknown, 22)                   | (unknown, 5)                    |                |       |           |
| Oxyphilic:                      |                                 |                |       | <0.0001   |
| Yes                             | 11 (8.3%)                       | 0 (0.0%)       | 11    |           |
| No                              | 122 (91.7%)                     | 13 (100%)      | 135   |           |

* In all preparations. FTC, follicular thyroid carcinoma; LI, labeling index; PDC, poorly differentiated carcinoma.
invasion and the Ki-67 LI (Table 4). Positive vascular invasion independently affected the RFS ($p = 0.0133$), but the Ki-67 LI $\geq 5\%$ did not ($p = 0.1348$). In our series, 58 patients showed negative vascular invasion and a low Ki-67 LI ($<5\%$), and only one patient (1.7\%) showed recurrence to the bone (77 months after surgery). This patient underwent RAI therapy and is still alive 152 months post-surgery.

To date, only five of the patients in this series of wi-FTC patients died of thyroid carcinoma. Of these, four had distant metastases at surgery (bone in three patients and lung in one patient), indicating that four of the 14 M1 patients (28.6\%) died of thyroid carcinoma. The remaining patient was M0, but at 101 months after surgery, distant recurrences to the lung, bone, and adrenal gland were observed. This patient died of thyroid carcinoma 150 months after the surgery. The metastases of all five of the patients who died of thyroid carcinoma were initially RAI-avid. The 5-year and 10-year CSS rates of the M1 patients were 92.9\% and 63.3\% whereas those of the M0 patients were 100\% and 100\%, respectively (Fig. 3).

**Discussion**

We investigated the prognosis and prognostic factors of patients with wi-FTC. Our original series included 13 patients with PDC, whose prognoses were much poorer than those of the wi-FTC patients. It is therefore important to carefully diagnose whether an individual case is PDC or wi-FTC based on a postoperative pathological examination by experienced thyroid pathologists. Our present findings demonstrated that in the patients with wi-FTC, (1) vascular invasion significantly and independently predicted carcinoma recurrence, and (2) a high Ki-67 LI was also related to carcinoma recurrence.
although it was not revealed to be an independent prognostic factor.

In our hospital, we diagnose FTC with grossly apparent capsular invasion in surgical specimens as wi-FTC as described above in the Patients section. Wi-FTC is regarded as having aggressive behavior and showing a dire prognosis. However, in our present series, the prognosis of the M0 wi-FTC patients was not so poor unless vascular invasion was detected on a pathological examination; the patients’ 5- and 10-year RFS rates were 98.5% and 91.2%, respectively. Those positive for vascular invasion showed much poorer prognoses; the patients’ 5- and 10-year RFS rates were 80.4% and 74.2%, respectively. In our series, the incidence of patients with vascular invasion was low at only 24.8% for the entire series, 21.9% for the M0 patients, and 50.0% for the M1 patients. This incidence of vascular invasion among M0 patients (21.9%) is much lower than that in a study of M0 patients in Italy (51.8%) [6]. The reasons for this discrepancy are unknown, but endemic factors may be involved.

Our patients with a low (<5%) Ki-67 LI also showed comparably favorable prognoses with 5-year and 10-year RFS rates at 98.4% and 95.0%, respectively. In contrast, the RFS of the wi-FTC patients who had a high Ki-67 LI was poor; the 5-year and 10-year RFS rates for the patients with a high Ki-67 LI were 86.3% and 67.5%, respectively. In contrast to vascular invasion, a high Ki-67 LI was not regarded as an independent predictor of carcinoma recurrence, but high cell-proliferation activity affected the RFS of the patients to some extent.

In our earlier study, the prognosis of the wi-FTC patients was poorer than the result observed herein, with 5-year and 10-year RFS rates at 82% and 67% and CSS rates at 98% and 89%, respectively [3]. The earlier study enrolled 79 patients with wi-FTC who underwent surgery between 1987 and 2007. In the earlier series, six of the 79 patients were diagnosed with wi-FTC based on significant vascular invasion regardless of whether capsular invasion was present/absent, which is subject to the diagnostic criteria used during that era. In addition, the prognosis of the M1 patients was poorer than revealed in the present study. These differing findings indicate that the series in the earlier study included a greater proportion of aggressive cases compared to that in the present study.

The analyses in our earlier study indicated that tumor size >4 cm significantly reflected the wi-FTC patients’ prognoses [3]. In the present study, large tumor size did not show prognostic significance. In our series, the inci-

### Table 2 Relationships between the M factor and clinicopathological features in widely invasive FTC

| Variable                      | M1 (n = 14) | M0 (n = 119) | Total | p-value |
|-------------------------------|-------------|--------------|-------|---------|
| Age: ≥55 yrs                  | 9 (64.3%)   | 61 (51.2%)   | 70    | 0.3559  |
| <55 yrs                       | 5 (35.7%)   | 58 (48.8%)   | 63    |         |
| Sex                           |             |              |       |         |
| Male                          | 4 (28.6%)   | 24 (20.1%)   | 28    | 0.4922  |
| Female                        | 10 (71.4%)  | 95 (79.9%)   | 73    |         |
| Tumor size:                   |             |              |       |         |
| >4 cm                         | 3 (21.4%)   | 57 (47.9%)   | 60    | 0.0597  |
| ≤4 cm                         | 11 (78.6%)  | 62 (52.1%)   | 73    |         |
| No. of vascular invasion foci |             |              |       |         |
| 0                             | 7 (50.0%)   | 93 (78.1%)   | 100   |         |
| 1–3                           | 4 (28.6%)   | 18 (15.1%)   | 22    | 0.0265  |
| 4–9                           | 0           | 3 (2.5%)     | 3     |         |
| ≥10                           | 3 (21.4%)   | 5 (4.2%)     | 8     |         |
| Ki-67 LI:                     |             |              |       |         |
| <5%                           | 5 (41.7%)   | 68 (68.7%)   | 73    |         |
| ≥5%, <10%                     | 2 (16.6%)   | 13 (13.1%)   | 15    | 0.1264  |
| ≥10%                          | 5 (41.7%)   | 18 (18.2%)   | 23    |         |
| (unknown, 2)                  | (unknown, 2)|             |       |         |
| Oxyphilic:                    |             |              |       |         |
| Yes                           | 0           | 11 (9.2%)    | 11    | 0.2349  |
| No                            | 14 (100%)   | 108 (90.8%)  | 122   |         |

* In all preparations. FTC, follicular thyroid carcinoma; LI, labeling index.
dence of tumors >4 cm in the group of M1 patients tended to be even lower ($p = 0.0597$) than that in the M0 patients (Table 2). Currently, our hospital actively performs surgery for nodules suspected of being a follicular tumor >4 cm, and such nodules (including wi-FTC) could be curatively treated before disease progression. Alternatively, as indicated above, the biological

### Table 3

Five- and 10-year RFS rates of the patients based on clinicopathological features other than vascular invasion and Ki-67 LI

| Variable          | 5-year RFS rate | 10-year RFS rate | $p$-value |
|-------------------|-----------------|------------------|-----------|
| Age ≥55 yrs (n = 61) | 94.0%           | 87.3%            | 0.9823    |
| <55 yrs (n = 58)  | 94.7%           | 87.2%            |           |
| Sex               |                 |                  |           |
| Male (n = 24)     | 95.0%           | 83.1%            | 0.9828    |
| Female (n = 95)   | 94.2%           | 87.9%            |           |
| Tumor size        |                 |                  |           |
| >4 cm (n = 57)    | 93.9%           | 81.8%            | 0.1934    |
| ≤4 cm (n = 62)    | 94.7%           | 91.7%            |           |
| Oxyphilic         |                 |                  |           |
| Yes (n = 11)      | 100%            | 100%             | 0.5452    |
| No (n = 108)      | 93.7%           | 85.1%            |           |

RFS, recurrence-free survival; LI, labeling index.

### Table 4

Multivariate analysis of vascular invasion and the Ki-67 LI for the RFS of widely invasive FTC

| Variable          | $p$-value | HR     | 95%CI         |
|-------------------|-----------|--------|---------------|
| Ki-67 ≥5%         | 0.1348    | 2.899  | 0.718–11.765  |
| Vascular invasion (+) | 0.0133   | 5.848  | 1.443–23.810  |

FTC, follicular thyroid carcinoma; LI, labeling index; RFS, relapse-free survival.

**Fig. 2** a: The RFS of the vascular invasion-positive and -negative patients with wi-FTC. b: The RFS of the wi-FTC patients with Ki-67 LIs ≥5% or <5%.
characteristics can be expected to differ between the patients in our present and past series. These differences may explain the discrepant results regarding the prognostic significance of large tumor size.

Age is regarded as one of the most important prognostic factors of differentiated thyroid carcinoma (FTC and papillary thyroid carcinoma). Indeed, in their analysis of 121 patients with mi- or wi-FTC, Sugino et al. observed that old age was a significant risk factor for postoperative distant metastases [7]. Our present analyses did not indicate any prognostic significance of old age in the patients with wi-FTC, which is consistent with our earlier study [3]. Another of our investigations demonstrated that although old age has prognostic value for mi-FTC, it does not for wi-FTC [8]. The American Joint Cancer Committee tumor-node-metastasis classification set the age cutoff at 55 years for differentiated thyroid cancer [9], but our present findings show the possibility that setting an age cutoff may not be appropriate, at least for wi-FTC.

In our series, 78 patients were administered various doses of RAI for ablation, adjuvant therapy, or therapy for metastasis. Distant metastases at diagnosis in 13 of the 14 patients and recurred lesions in six of the 10 patients who were administered RAI were RAI-avid. However, all five of the patients who died of thyroid carcinoma had RAI-avid metastatic/recurred lesions. Therefore, our results did not confirm that RAI treatment prolonged the survival of patients. Further studies are necessary to examine this issue.

In our series, 78 patients were administered various doses of RAI for ablation, adjuvant therapy, or therapy for metastasis. Distant metastases at diagnosis in 13 of the 14 patients and recurred lesions in six of the 10 patients who were administered RAI were RAI-avid. However, all five of the patients who died of thyroid carcinoma had RAI-avid metastatic/recurred lesions. Therefore, our results did not confirm that RAI treatment prolonged the survival of patients. Further studies are necessary to examine this issue.

Reports from several countries have described a poorer prognosis of oxyphilic carcinoma compared to non-oxyphilic carcinoma [8-11], although some studies showed opposite findings [12, 13]. In Japan, all previous studies regarding FTC [2, 3, 14] and the present study showed that the prognosis of oxyphilic cell carcinoma did not significantly differ from that of non-oxyphilic cell carcinoma. The reason for this discrepancy remains unknown, but we speculate that some endemic factors might be involved.

In the Japanese guidelines issued by the Japan Association of Endocrine Surgeons, it is stated that since wi-FTC has an aggressive character, if the first surgery is a hemithyroidectomy, a completion total thyroidectomy is recommended along with RAI therapy [15]. Our present findings indicate that a total thyroidectomy is mandatory for wi-FTC cases with vascular invasion and/or a Ki-67 LI ≥5% even though these cases are classified as M0. However, in our present series, the prognosis of M0 wi-FTC without these features was very favorable. Further studies are needed to elucidate the appropriate extent of thyroidectomy for such patients.

As indicated in the Introduction, in the newest WHO classification, FTC is classified into three categories, which are mi-FTC (capsular invasion only), ea-FTC (vascular invasion with no or minimal capsular invasion), and wi-FTC (extensive capsular invasion regardless of vascular invasion) [1]. In 2013, we investigated the prognostic factors of mi-FTC (based on the latest WHO classification), and our findings demonstrated that extensive vascular invasion (≥4 foci) was an independent prognostic factor for the DFS and CSS of M0 patients [16]. Therefore, it is likely that the prognosis of ea-FTC is poorer than mi-FTC based on the present WHO classification. However, in this study, the prognosis of wi-FTC without vascular invasion was rather favorable, and further studies are needed comparing the prognosis of ea-FTC with wi-FTC without vascular invasion. In addition, in contrast to ea-FTC, we showed that the number of invasive foci did not affect the prognosis of wi-FTC patients with vascular invasion. As shown in Table 2, the number of M0 cases with vascular invasion was small in
our series; 18 with invasive foci ≤3 and eight with invasive foci >4. Therefore, the prognostic significance of the number of invasive foci in wi-FTC is to be investigated and elucidated by enrolling much larger numbers of patients in, for example, a multicenter study.

This study has some limitations. It was a retrospective analysis. Although the number of enrolled patients was larger than that in our earlier study, it was still small at 133. In addition, event numbers of carcinoma recurrence and death are small at 11 and 5, respectively, and the number of variables for multivariate analysis is limited. Although vascular invasion was evaluated in all cases, the Ki-67 labeling index could not be calculated in 22 patients, which may make the analysis inaccurate. We made an effort to trace patients who were transferred to other hospitals by sending a questionnaire, but a considerable number of patients were lost to follow-up.

In conclusion, although the prognosis of wi-FTC without distant metastasis at surgery was not very dire, positive vascular invasion significantly and independently predicted carcinoma recurrence. High cell-proliferation activity also affected the RFS of the patients to some extent, although it did not independently predict carcinoma recurrence. Close and careful examination after a total thyroidectomy is mandatory, especially for patients with these pathological characteristics.

Conflict of Interest

The authors have nothing to declare.

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