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Appropriateness of the revised Japanese guidelines' risk classification for the prognosis of papillary thyroid carcinoma: a retrospective analysis of 5,845 papillary thyroid carcinoma patients

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Abstract. The revised Japan Association of Endocrine Surgeons (JAES)/Japanese Society of Thyroid Surgery (JSTS) guidelines for patients with papillary thyroid carcinoma (PTC) describe four risk classes: very-low-risk, low-risk, intermediate-risk, and high-risk. Here we conducted a retrospective analysis to evaluate the appropriateness of these guidelines' risk classification of PTCs. Lymph node recurrence-free, distant recurrence-free and cause-specific survivals at 15-year of high-risk group were significantly poorer than those at 15-year of intermediate-group and these survivals of intermediate-group were poorer than of low- or very-low-risk patients. In the subset analyses based on patient age (≥55 years and <55 years), we obtained the same results in both subsets. Age significantly worsen the whole prognosis of high-risk patients and cause-specific survival of intermediate-risk patients, but not the prognosis of low- or very-low-risk patients. Therefore, the risk classification of the revised JAES/JSTS guidelines is appropriate, and therapeutic strategies should be decided based on the risk class together with the patients' age.

Key words: Papillary thyroid carcinoma, Guidelines, Prognosis, Risk classification, Age

PAPILLARY THYROID CARCINOMAS (PTCs) generally have indolent characters, but PTCs with certain clinicopathological characteristics are aggressive, resulting in a dire prognosis. Prognostic factors of PTC predicting carcinoma recurrence and death have been actively studied in Japan [1-5]. In Western countries, total or near-total thyroidectomy with ^{131}I ablation is a standard therapeutic strategy for PTC patients regardless of the biological characteristics of the tumors. Since PTCs without any aggressive features show an excellent prognosis [1], total thyroidectomy may be an overtreatment for such patients.

In Japan, in contrast, less than total or near-total thyroidectomy surgeries such as hemithyroidectomy and subtotal thyroidectomy have been widely adopted. These surgeries are adequate for PTC with an indolent character, but they are not sufficient treatment for PTCs with aggressive biological features. In order to accurately monitor postoperative changes in the patients' thyroglobulin (Tg) level (*i.e.*, the Tg doubling-time [Tg-DT] [6]) and for performing ^{131}I therapy immediately after the detection of structural recurrence to distant organs, a total thyroidectomy at initial surgery is preferable.

In the risk classification by the newest edition of the Japan Association of Endocrine Surgeons (JAES)/Japanese Society of Thyroid Surgery (JSTS) guidelines [7], PTCs are classified into four categories based on clinicopathological features. T1aN0M0 and T1bN0M0 PTCs are classified as very-low-risk and low-risk, respectively, unless significant extrathyroid extension (Ex) based on intraoperative findings is detected. A PTC is classified as high-risk if it has at least one of the following five features: (1) distant metastasis at diagnosis (M1), (2) tumor size (T) larger than 4 cm, (3) Ex-positive, (4) clinical

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Table 1 Risk classification of PTC based on the JAES/JSTS guidelines

Risk classification	Variable
Very low (L-group)**	T1aN0M0 Ex(–)
Low (L-group)**	T1bN0M0 Ex(–)
Intermediate (I-group)**	PTCs that do not belong to the very-low-, low- or high-risk categories
High (H-group)**	PTC with at least one of the following features: 1. M1 2. T > 4 cm 3. Ex(+) 4. N > 3 cm 5. Extranodal tumor extension-positive

*Ex: extrathyroid extension corresponding to T4a or T4b based on intraoperative findings. **Classification in the present study.

node metastasis (N) larger than 3 cm, and (5) extranodal tumor extension-positive. PTCs that do not belong to the very-low, low- or high-risk categories are classified as intermediate-risk (Table 1).

In the JAES/JSTS guidelines, total thyroidectomy is strongly recommended for high-risk PTC and hemithyroidectomy is regarded as appropriate for low-risk PTC if the opposite lobe is free from nodules requiring surgery. Very-low-risk PTC corresponding to low-risk papillary microcarcinoma is an indication for active surveillance [8-10], but if surgery is performed, surgical strategies are identical to those used for low-risk PTCs. For intermediate-risk patients, it is recommended that the extent of the thyroidectomy is decided on a case-by-case basis in consideration of the clinical findings, the patient's background, the patient's preference.

In the present retrospective analysis, we investigated whether the risk classification provided in the JAES/JSTS guidelines is appropriate, using a large series of PTC patients followed postoperatively for a long period. We compared the lymph node recurrence-free survival, distant recurrence-free survival, and cause-specific survival of high-risk, intermediate-risk, and low- or very-low-risk patients.

Patients and Methods

Patients

We enrolled 5,845 patients who underwent initial and locally curative surgery for PTC between January 1988 and December 2004 at Kuma Hospital. Tumor size and N factor, including the size of the nodes, were evaluated in preoperative imaging studies. Ex and extranodal tumor extension were based on intraoperative findings. All patients were diagnosed as having PTC based on a postoperative pathological examination.

We excluded patients who had other malignancies in the thyroid such as anaplastic, medullary, or follicular carcinomas and malignant lymphoma. The patients' ages ranged from 7 to 89 years (median 51 years), and there were 5,178 females and 667 males. Sixty-eight patients were classified as M1 based on preoperative imaging studies or postoperative ^{131}I scintigraphy within 1 year after surgery.

Surgical designs

Total or near total thyroidectomy was performed in 2,988 patients. The other patients underwent subtotal thyroidectomy (534 patients) and a more limited thyroidectomy (2,323 patients) such as lobectomy with isthmectomy and isthmectomy. Central node dissection was performed in 5,565 patients, and of these, 4,431 patients also underwent therapeutic or prophylactic modified radical neck dissection (MRND) also. Thirteen patients also underwent upper mediastinal dissection.

Postoperative follow-up

Eighty-two patients, accounting for 3% of the patients who underwent a total thyroidectomy, underwent ^{131}I ablation (30 mCi) after total thyroidectomy. Forty-nine of the 68 M1 patients underwent ^{131}I therapy (100 mCi) once or more; the remaining 19 did not undergo ^{131}I therapy because of old age and/or poor risk.

All of the patients were followed by blood examination and imaging studies such as ultrasound once or twice per year. Chest roentogenography, CT scan, and bone scintigraphy were also used for follow-up according to the physicians' discretion. We regarded cases as having PTC recurrence when recurred lesions were detected on imaging studies. The follow-up periods ranged from 4 to 357 months (median 177 months).

Statistical analyses

The Kaplan-Meier method with log-rank tests was adopted for the statistical analyses, which were performed using the software program StatFlex. p-values < 0.05 were accepted as significant.

Table 2 The backgrounds and surgical designs in L-, I-, and H-group patients

	L-group (n = 2,698)	I-group (n = 1,837)	H-group (n = 1,310)
Gender			
Male	183 (7%)	234 (13%)	250 (19%)
Female	2,515 (93%)	1,603 (87%)	1,060 (81%)
Age			
≥ 55 yrs	1,125 (42%)	585 (32%)	690 (53%)
< 55 yrs	1,573 (58%)	1,252 (68%)	620 (47%)
Thyroidectomy			
Total	1,061 (39%)	945 (57%)	982 (75%)
Subtotal	325 (12%)	143 (9%)	66 (5%)
Hemithyroidectomy or isthmectomy	103 (41%)	749 (34%)	262 (20%)
Lymph node dissection			
MND[1] + CND[2]	1,575 (58%)	1,658 (90%)[4]	1,198 (91%)[5]
		[609][3]	[604][3]
CND only	973 (36%)	103 (6%)	58 (4%)
		[24][3]	[5][3]
None	150 (6%)	76 (4%)	54 (5%)

[1]Modified radical neck dissection; [2]Central node dissection; [3]Number of patients who underwent therapeutic dissection; [4]Three patients underwent dissection of upper mediastinum; [5]Ten patients underwent dissection of upper mediastinum.

Results

To date, 602 and 129 patients have shown recurrence to the local lesions (regional lymph nodes and/or remnant thyroid) and distant organs (lung, bone, brain, liver, kidney *etc.*), respectively. Seventy-seven patients have shown recurrence to both local lesions and distant organs. To date, 110 patients have died of PTC.

We classified the cases of the 5,845 patients into three groups based on the JAES/JSTS guidelines (Table 1): high-risk patients (H-group) (1,310 patients), intermediate-risk patients (I-group) (1,837 patients), and low- or very-low-risk patients (L-group) (2,698 patients), and we investigated the differences in their prognoses. The background and surgical designs of the patients in each group are summarized in Table 2. The H-group included the highest percentages of male patients and patients aged ≥ 55 years among the three groups.

We investigated the local recurrence-free survival (LRFS), the distant recurrence-free survival (DRFS), and the cause-specific survival (CSS) of the patients in the three groups. For the investigation of LRFS and DRFS, we deleted the 68 patients in the H-group who had distant metastasis at surgery. Our analyses revealed that at the 15-year follow-ups, the LRFS, DRFS, and CSS rates of the H-group (74%, 90%, and 92%) were significantly poorer than those of the I-group (88%, 98% and 99%), respectively (p = 0.00000). In addition, the 15-year follow-up LRFS, DRFS, and CSS rates of the I-group were significantly poorer than those of the L-group (96%, 100%, and 100%), respectively (p = 0.00000 for LRFS and DRFS, p = 0.00015 for CSS) (Fig. 1a–c, Table 3). The M1 patients were excluded from the analyses for LRFS and DRFS.

Age is an important prognostic factor, especially for the CSS of PTC patients [2-4]. Especially for M0 patients, older age (≥55 years) was the strongest predictor of carcinoma death in a multivariate analysis [3]. In the most recent American Joint Committee on Cancer (AJCC) staging system, the age cutoff is also set at 55 years [11]. We then performed subset analyses according to the patients' ages (≥55 years and <55 years). In the subset of patients aged ≥ 55 years, the 15-year LRFS, DRFS and CSS rates of the H-group (65%, 85%, and

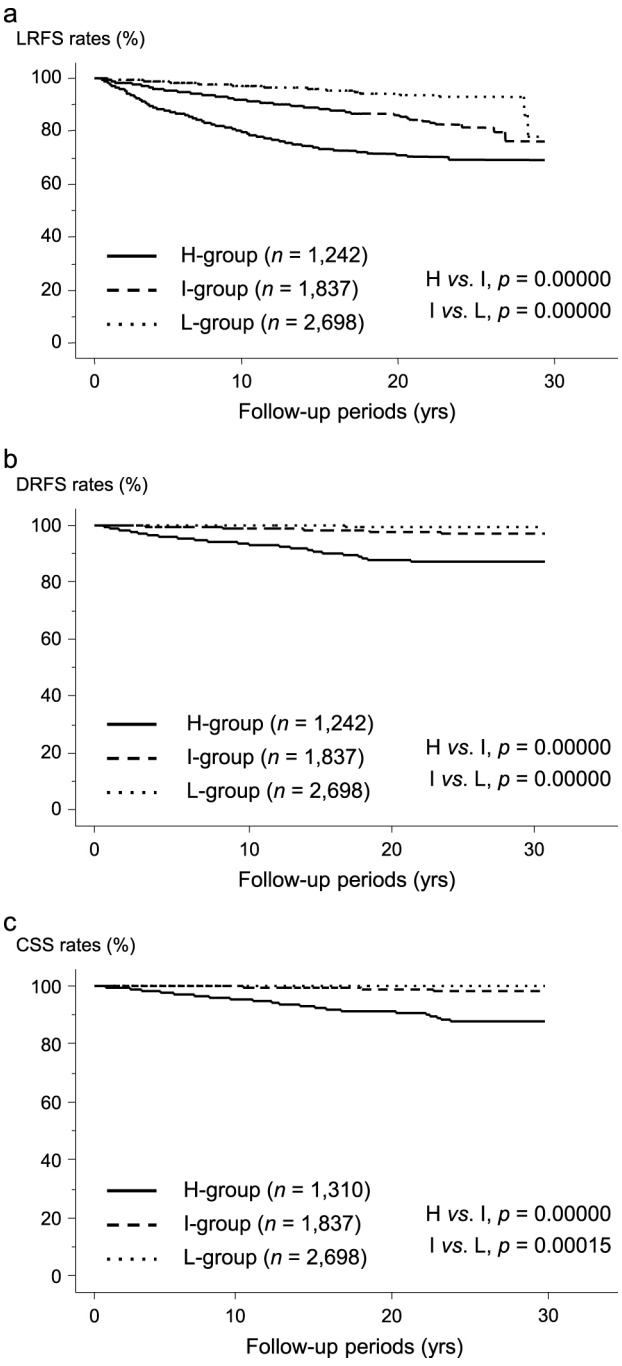

Fig. 1 The (a) LRFS, (b) DRFS, and (c) CSS of the low-, intermediate- and high-risk groups of PTC patients.

85%) were poorer than those of the I-group (87%, 97%, and 98%) ($p = 0.00000$). The 15-year prognoses of the I-group were poorer than those of the L-group (97%, 100%, and 100%), respectively ($p = 0.00000$) (Fig. 2a–c, Table 4).

Similarly, in the subset of patients <55 years old, the 15-year LRFS and DRFS rates of the H-group (79% and 95%) were significantly poorer than those of the I-group (88% and 99%), and those of the I-group were significantly poorer than those of the L-group (95% and 100%) ($p = 0.00000$). The 15-year CSS of the H-group patients (98%) was significantly poorer than that of the I-group patients (100%) ($p = 0.00004$), and the 15-year CSS of the I-group patients tended to be poorer than that of the L-group patients (100%) ($p = 0.05624$) (Fig. 3a–c, Table 5).

We next compared the LRFS, DRFS, and CSS of the patients in each risk group between those aged ≥ 55 years and those aged < 55 years (Table 6). The prognosis of the L-group patients did not significantly differ according to age. In the I-group, the DRFS tended to be poorer ($p = 0.09507$) and the CSS was significantly poorer ($p = 0.01000$) in the patients aged ≥ 55 years compared to those aged < 55 years. Among the H-group patients, those aged ≥ 55 years had significantly poorer LRFS, DRFS, and CSS ($p = 0.00000$) compared to those aged < 55 years.

Discussion

The results of our analyses demonstrated that (1) the LRFS, DRFS, and CSS of the high-risk (H-group) PTC patients were poorer than those of the intermediate-risk (I-group) patients, and those of the I-group were poorer than those of the L-group (low- or very-low-risk) patients; (2) the same results were obtained in the subset analysis based on the patients' age (cutoff 55 years); (3) old age significantly worsened all aspects of prognosis of the H-group patients and the CSS of the I-group patients.

In this patient series, the 15-year LRFS, DRFS, and CSS rates of the H-group patients were 74%, 90%, and 92%, respectively. Since H-group patients are more likely to show recurrence and die of PTC compared to the I- and L-groups, aggressive treatments—including total thyroidectomy with therapeutic or prophylactic lymph node dissection, and adjuvant ^{131}I therapy, which is reported to improve the survival of patients [12]—rather than RAI therapy should be considered after the appearance of recurrence and TSH suppression. Moreover, a careful postoperative follow-up by monitoring Tg and Tg-DT [6] is mandatory to identify the appearance of recurrence, which should be treated by ^{131}I therapy and therapy using tyrosine kinase inhibitors. It is thus appropriate that the JAES/JSTS guidelines strongly rec-

Table 3 Ten- and 15-year LRFS, DRFS, and CSS of PTC patients

	Low- or very-low-risk (L-group)	Intermediate-risk (I-group)	High-risk (H-group)	*p*-values
10-year LRFS	97%	92%	80%	0.00000 (H *vs.* I, I *vs.* L)
15-year LRFS	96%	88%	74%	
10-year DRFS	100%	99%	94%	0.00000 (H *vs.* I, I *vs.* L)
15-year DRFS	100%	98%	90%	
10-year CSS	100%	99%	95%	0.00015 (L *vs.* I)
15-year CSS	100%	99%	92%	0.00000 (H *vs.* I)

LRFS: lymph node recurrence-free survival
DRFS: distant recurrence-free survival
CSS: cause specific survival

Table 4 Ten- and 15-year LRFS, DRFS, and CSS of PTC patients aged 55 years or older (n = 2,400)

	Low- or very-low-risk (L-group)	Intermediate-risk (I-group)	High-risk (H-group)	*p*-values
10-year LRFS	98%	90%	74%	0.00000 (H *vs.* I, I *vs.* L)
15-year LRFS	97%	87%	65%	
10-year DRFS	100%	99%	90%	0.00000 (H *vs.* I, I *vs.* L)
15-year DRFS	100%	97%	85%	
10-year CSS	100%	99%	91%	0.00000 (H *vs.* I, I *vs.* L)
15-year CSS	100%	98%	85%	

Table 5 Ten- and 15-year LRFS, DRFS, and CSS of PTC patients younger than 55 years

	Low- or very-low-risk (L-group)	Intermediate-risk (I-group)	High-risk (H-group)	*p*-values
10-year LRFS	97%	94%	94%	0.00000 (H *vs.* I, I *vs.* L)
15-year LRFS	95%	88%	79%	
10-year DRFS	100%	99%	96%	0.00000 (H *vs.* I)
15-year DRFS	100%	99%	95%	0.00173 (I *vs.* L)
10-year CSS	100% (99.93%)	100% (99.82%)	99%	0.00004 (H *vs.* I)
15-year CSS	100% (99.93%)	100% (99.65%)	98%	0.05624 (I *vs.* L)

ommend total thyroidectomy for H-group patients.

In contrast, the 15-year DRFS and CSS rates of our L-group patients were both 100%, indicating that T1N0M0 patients are very unlikely to show distant recurrence and die of PTC; this finding is not discrepant with those of our previous study [1]. Therefore, RAI ablation and Tg monitoring are not necessary and hemithyroidectomy is adequate for such patients if the opposite lobe is free from nodules requiring surgery.

The prognoses of our I-group patients were much better than those of the H-group patients, but still poorer than those of the L-group patients. The JAES/JSTS guidelines recommend that the extent of thyroidectomy for intermediate-risk patients should be decided in a case-by-case fashion in consideration of clinical findings, the patient's background, and the patient's preference. Total thyroidectomy has risks and benefits. In total thyroidectomy cases, L-thyroxine administration is necessary throughout the patient's lifetime, and there is an increased incidence of significant complications such as persistent hypoparathyroidism and permanent recurrent laryngeal nerve paralysis, which requires permanent tracheostomy if bilateral paralysis occurs. In contrast, a total thyroidectomy has an advantage that the appearance

Table 6 The difference of prognosis at 15-year of PTC patients in each group between age ≥ 55 years and < 55 years

Risk classification	Variables	*p*-values between patients ≥ 55 years and < 55 years
Low- or very-low-risk (L-group)	LRFS	0.11378
	DRFS	0.63447
	CSS	0.68641
Intermediate-risk (I-group)	LRFS	0.14177
	DRFS	0.09507
	CSS	0.00100
High-risk (H-group)	LRFS	0.00000
	DRFS	0.00000
	CSS	0.00000

of recurrence can be monitored by the changes in Tg and Tg-antibody levels as indicated above [6]. The results of the present study showed that the prognoses of the I-group patients were significantly poorer than those of the L-group patients, but the difference in prognosis between the L-group and I-group was much smaller than that between the I-group and H-group. At our institution, we rather routinely perform total thyroidectomies for I-group patients, but the extent of thyroidectomy for I-group patients remains debatable and, at this stage, a case-by-case basis for making the decision regarding the extent is recommended, as indicated above.

The JAES/JSTS guidelines recommend central node dissection routinely even though it is prophylactic for PTC surgery, although it is not yet established that prophylactic central node dissection improves patients' prognosis. This is because reoperation of a central node may induce severe complications such as recurrent laryngeal nerve injury and/or permanent hypoparathyroidism [13]. In the present series of patients, prophylactic MRND was almost routinely performed, and it has been a common practice in Japanese institutions in the past. In 2006, we demonstrated that PTCs with certain risk factors such as tumor size > 3 cm, age ≥ 55, male gender, and Ex-positivity are likely to show recurrence to the lateral nodes, even though patients with these factors underwent prophylactic MRND [14]. Therefore, after 2006, our hospital has performed prophylactic MRND only for PTCs that are considered to be at high risk for node recurrence. The JAES/JSTS guidelines also describe that prophylactic MRND can be considered for high-risk patients, but is not recommended for low-risk patients. The guidelines also state that whether prophylactic MRND is performed for intermediate-risk patients should be decided in each case based on the clinicopathological features, patient's background and patient's preference. We recently demonstrated that, in a series of PTC patients with tumors ≤ 4 cm, prophylactic MRND did not improve LRFS except among the patients with Ex-positive PTCs > 3 cm [15]. The results of the present study suggest that (1) the extensive prophylactic lymph node dissection that has been performed in Japan cannot significantly prevent lymph node recurrence (with some exceptions), and (2) the indications for prophylactic MRND should be narrowed to cases with aggressive features such as large size and positive-Ex.

Age is an important prognostic factor and especially a predictor of carcinoma death [2-4]. As shown in Tables 4 and 5, the risk classification significantly reflected the patients' prognoses in the H-, I-, and L-groups in both the older and younger patients, and the classification can be applied regardless of the patients' age. As shown in Table 6, age did not affect the prognosis of the L-group patients, indicating that the therapeutic strategies, including surgical designs, for these patients can be uniform regardless of the patients' age. The I-group patients aged ≥ 55 years tended to show distant recurrence and were more likely to die of PTC than those aged < 55 years. Therefore, physicians should carefully monitor postoperative distant recurrence and its treatment in intermediate-risk patients aged ≥ 55 years. Age affected most strongly the prognosis of our H-group patients; their LRFS, DRFS, and CSS were strongly influenced by the patients' age. Our findings thus suggest that for high-risk patients, and especially for older patients, aggressive therapeutic strategies such as extensive surgery and adjuvant ^{131}I

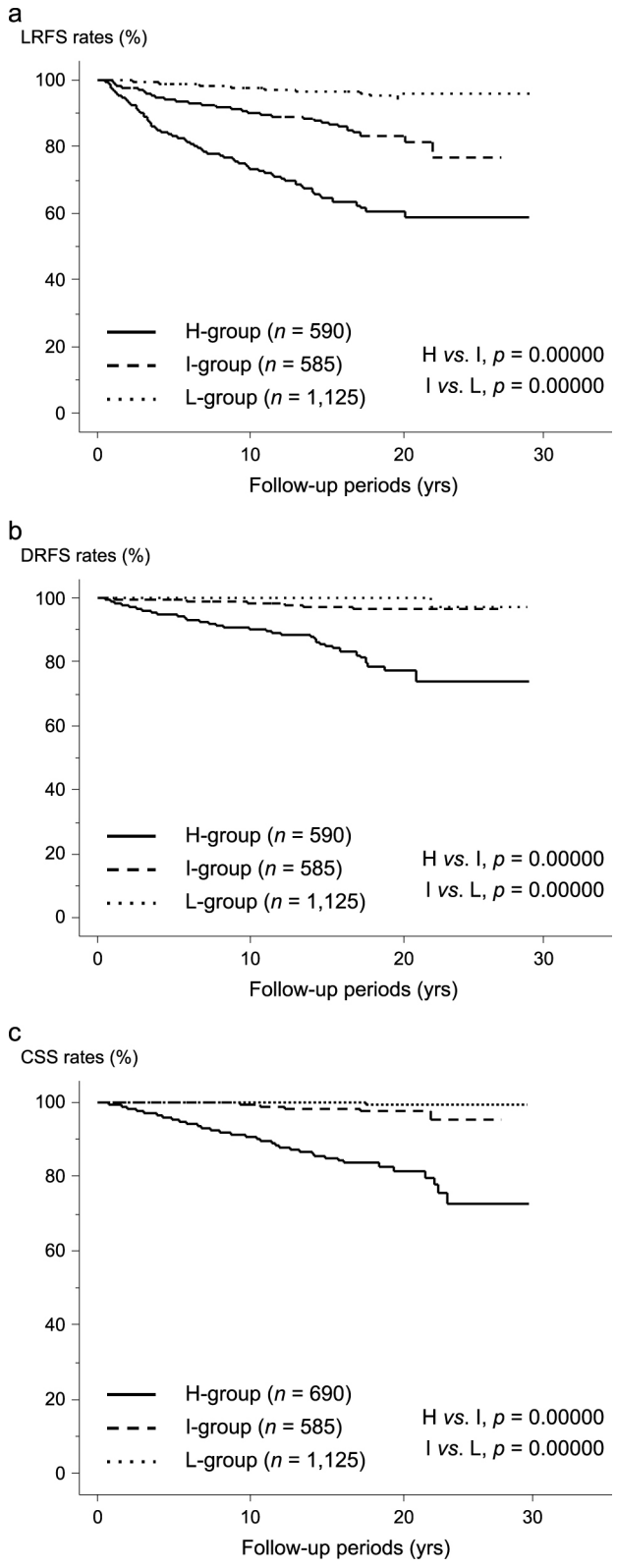

Fig. 2 The (a) LRFS, (b) DRFS, and (c) CSS of the low-, intermediate- and high-risk groups of PTC patients in the subset of patients ≥ 55 years old.

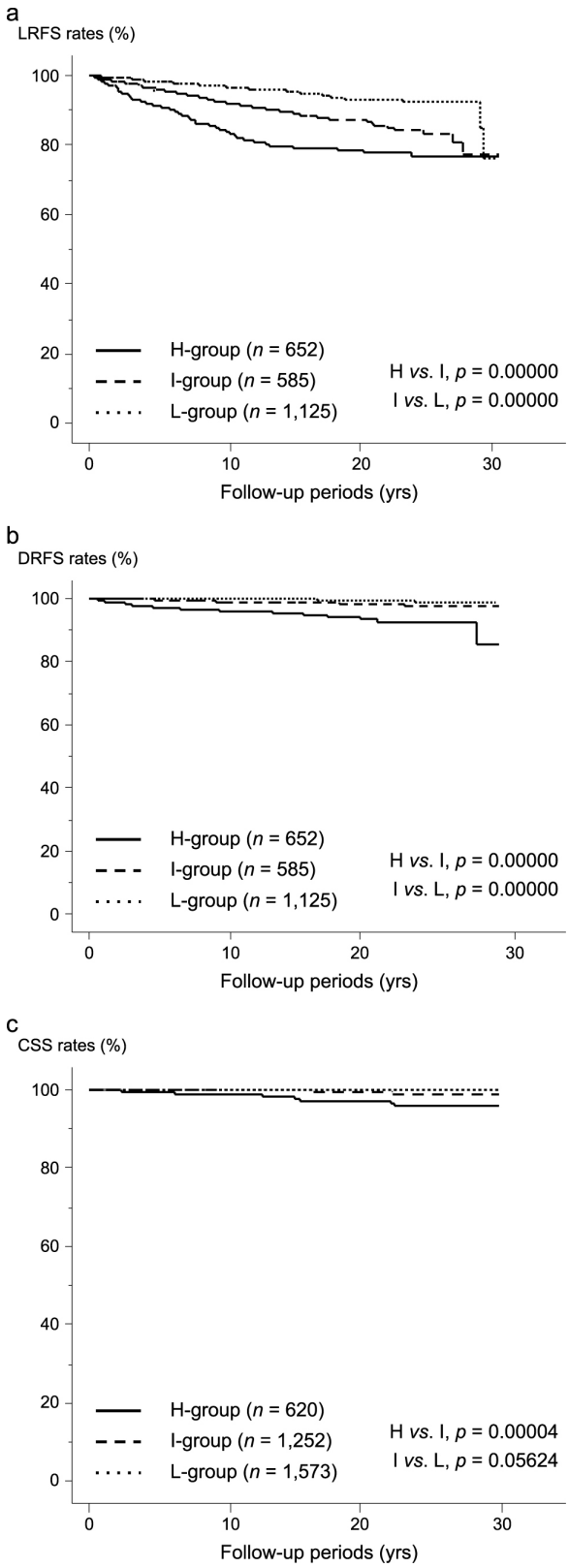

Fig. 3 (a) LRFS, (b) DRFS, and (c) CSS of the three groups of PTC patients in the subset of patients < 55 years old.

therapy followed by TSH suppression should be considered.

In summary, the results of our present analyses demonstrated that the risk classification system for PTC patients in the JAES/JSTS guidelines is appropriate, and that age significantly affected the prognosis of intermediate-risk and high-risk patients. In order to avoid overtreatment and insufficient treatment, the appropriate pre- and intraoperative evaluation of each PTC case is very important.

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