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ORIGINAL ARTICLE

Age and prognosis of papillary thyroid carcinoma: retrospective stratification into three groups

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Purpose: We investigated the prognosis according to age in papillary thyroid carcinoma (PTC) patients. **Methods:** We retrospectively evaluated 2,890 patients who underwent thyroidectomy due to PTC between May 2004 and Aug 2008. We divided patients into 3 groups: young (≤35 years old), middle (between 35 and 54 years old), and old (≥55 years old). **Results:** Median age was 47.0 years old (range, 15 to 82 years). Within a follow-up period median of 50 months, there were 148 (5.1%) locoregional recurrences, 6 (0.2%) PTC-related deaths, and 18 (0.6%) PTC-unrelated deaths. Outcomes were more favorable in the young group, with no PTC-related death despite the frequent locoregional recurrence. In the old group compared to the middle, there was a higher proportion of male, and more aggressive types as T3 or N1b, higher mean tumor number, more multiplicity, and bilaterality. The old group of ≥55 years did not show a significant difference in PTC-related deaths than other age groups in Cox analysis (OR, 0.9; P = 0.677), but a significant cutoff age in PTC-related deaths at 62.5 years was determined in ROC analysis (area under curve = 0.912). **Conclusion:** We showed that the ≤35 years group shows favorable prognosis despite the frequent locoregional recurrence and ≥62.5 years group shows a poor prognosis regardless of other factors such as male sex or tumor aggressiveness. Further multiinstitutional studies are needed to elucidate the prognosis according to patient's age.

Key Words: Age, Prognosis, Papillary thyroid carcinoma

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common malignancy arising from the thyroid, and age is an important prognostic factor. Age has been adopted in various staging systems, but each system has different age criteria, such as 45 years in tumor-node-metastasis (TNM) classification [1], 40 years in MACIS scoring systems [2], 50 years in the CIH classification [3], and 55 years in iStage system [4]. AMES systems have different age criteria for each sex, such as 41 years for males and 51 years for females [5]. Other staging systems do not include age criteria, such as EORTC (European Organization for Research and Treatment of Cancer) [6] and Clinical Class of

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University of Chicago [7].

In adolescents and young adults, lymph node metastasis, distant metastasis, and tumor multiplicity were more frequently detected than in old age patients [8-12]. Although young patients were likely to show a frequent recurrence, their cause-specific survival was reported to be excellent [11-17]. Indeed, Mazzaferri and Kloos [18] showed that recurrence rates were high in patients under 20 and over 60 years, while the carcinoma death rate increased with old age in well differentiated thyroid cancers including follicular cancers. Recent molecular analysis showed that PTC is caused by the activation of the mitogen activated protein kinase pathway. In young patients, *RET/PTC*, *AKAP9-BRAF*, and *NTRK1* recombination events are the main genetic alterations [19]. In contrast *BRAF* point mutation is predominantly involved in adult PTCs [19-21].

Identification of the prognostic indicators for age, which are biologically different, is very important in deciding an appropriate therapeutic strategy. The desire and proportion of endoscopic or robotic thyroidectomy is increasing in young patients [22], and in old or extreme ages observational strategies might be tried, since Ito et al. [23] showed no evidence of apparent disease progression in their observation group without thyroidectomy. Though the studies on extreme young and old age were reported in Korea [24,25], there are no studies across the entire age spectrum with large number of patients, to our knowledge. Therefore, in this study we investigated the difference in prognosis of PTC patients according to age.

METHODS

This was a retrospective study that included 2,890 patients who underwent thyroid operation due to PTC between May 2004 and Aug 2008. They consisted of 464 males (16.1%) and 2,426 females (83.9%), and median age was 47.0 years old (range, 15 to 82 years). None of these patients had a history of radiation exposure. Patients were divided into three groups according to age: young age group less than 35 years old, middle age between 35 and 54, and old age group between 55 and 82 years old.

The operative and follow-up profiles of all patients were analyzed. Operative assessment included patient demographics, especially age, aggressiveness, multiplicity or bilaterality of tumor and number of PTC, and central or lateral neck metastases. Patients were followed up at 3 to 6 months intervals during the first two postoperative years, and annually thereafter. Neck ultrasonography was performed with 6 or 12 months interval for regional recurrence, and positron emission tomography/computed tomography also evaluated node positive high risk patients at 2 year intervals. If patients did not return for follow-up on the year after the last follow-up, they were contacted by telephone for inclusion in this study. The median follow-up period was 50 months (range, 12 to 83 months). Follow-up events of locoregional recurrence, PTC-related death, and PTC-unrelated deaths were reviewed.

We used the t-test to compare continuous variables between each group and the chi-square test for categorical variables, and receiver operating characteristic (ROC) curve analysis to compare diagnostic performance. The Kaplan-Meier curve with a log rank test was adopted for univariate survival analysis. We used proportional hazards modeling of the relative recurrence and survival to assess the simultaneous effects of clinicopathological factors and age. Results were analyzed using PASW ver. 18.0 (IBM Co., Armonk, NY, USA). Statistical significance was defined as a P-value less than 0.05 and any odds ratio (OR) greater than 1.0 indicated worsened prognosis.

RESULTS

All patients were diagnosed with PTC. In extent of thyroidectomy, 2,453 (84.9%) total thyroidectomy and 437 (15.1%) lobectomy were performed. There were 1,705 patients (59.0%) T1, 67 patients (2.3%) T2, 1,067 patients (36.9%) T3, and 51 patients (1.8%) in T4 classification. In N classification, there were 1,202 (41.6%) N0, 565 (19.6%) N1a, 180 (6.2%) N1b, and 943 (32.6%) Nx patients. Mean number of harvested and positive nodes were 4.4 and 1.0, respectively. We regarded cases with more than T3 or N1b as aggressive PTC corresponding to TNM classification [1]. Also, 65 (2.2%) lymphovascular invasions were re-

garded as aggressive.

Within median 50 months follow-up periods, 6 (0.2%) remained thyroidal, 62 (2.1%) central, 99 (3.4%) lateral, and 27 (0.9%) central and lateral combined recurrences were occurred. Six of 7 distant metastasis proven patients were expired, and 18 (0.6%) were PTC-unrelated deaths.

Age distribution

The age distribution of the enrolled 2,890 patients is shown (Fig. 1A), and shows a normal distribution. There were 148 (5.1%) locoregional recurrences within the follow-up period. Recurrence rates of PTC were high in patients under 35 and over 65 years and surprisingly, 15.7% of recurrences were in age less than 25 years old (Fig. 1B). Six (0.2%) PTC-related death were mostly in over 65 years (Fig. 1C), 18 (0.6%) PTC-unrelated death also in exterme age.

Young, middle, and old age groups were classified on the basis of patients' distribution, and pattern of recurrence or PTC-related deaths. Our results were similar to previous studies [26,27]. Table 1 gives the clinical features predictive of recurrence and PTC-related death between three groups with multivariate analysis. There were 441 patients (15.3%) in young age group under 35 years, 1,746 (60.4%) in middle age between 35 and 54, and 703 (24.3%) in old age between 55 and 82 years old. Though the indications for total thyroidectomy in American Thyroid Association and National Comprehensive Cancer Network guidelines were generally kept, there were some exceptions in our study. With increasing age, the ratio of total thyroidectomy rather than lobectomy was increased (77.1% vs. 83.6% vs. 92.9%). Further characteristics of each age group were investigated.

Young age group less than 35 years old

There was a significant risk of central metastasis in ini-

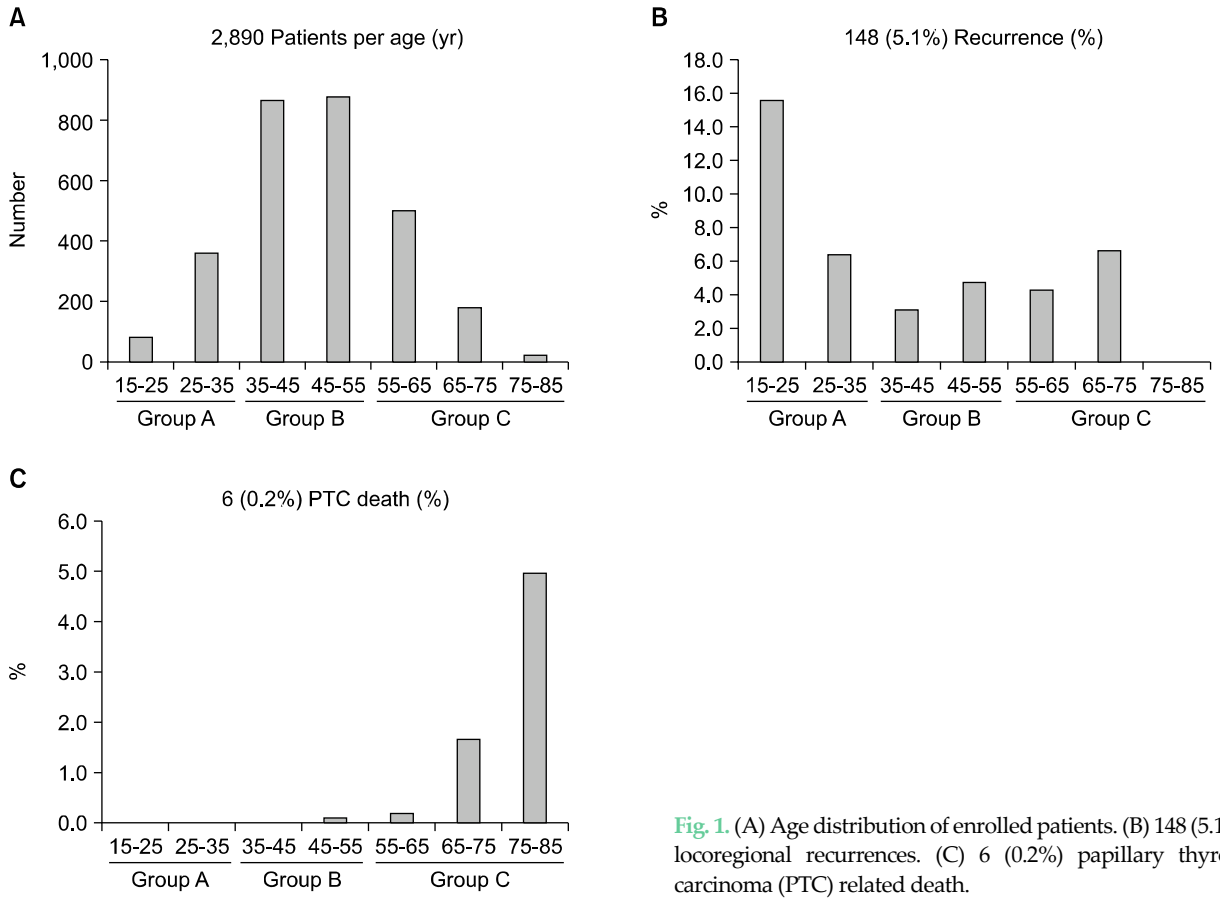

Fig. 1. (A) Age distribution of enrolled patients. (B) 148 (5.1%) locoregional recurrences. (C) 6 (0.2%) papillary thyroid carcinoma (PTC) related death.

Table 1. Clinical characteristics, recurrence, and death by age group

Characteristic	Young age group (15-34)	P-value	Middle age group (35-54)	P-value	Old age group (55-85)
Patients per group	441 (15.3)		1,746 (60.4)		703 (24.3)
Male sex	66 (15.0)	0.888	266 (15.2)	0.032	132 (18.8)
Total thyroidectomy	340 (77.1)	0.001	1,460 (83.6)	<0.001	653 (92.9)
Lobectomy	101 (22.9)	0.001	286 (16.4)	<0.001	50 (7.1)
Central neck dissection	315 (71.4)	0.110	1,178 (67.5)	0.002	429 (61.0)
Lateral neck dissection	39 (8.8)	0.600	141 (8.1)	0.243	67 (9.5)
Aggressiveness[a)]	148 (33.6)	0.212	686 (39.3)	0.002	312 (44.4)
Multiplicity	78 (17.7)	0.288	348 (19.9)	<0.001	188 (26.7)
Bilaterality	65 (14.7)	0.172	305 (17.5)	0.001	164 (23.3)
PTC number	1.2 ± 0.5	0.180	1.3 ± 0.6	0.002	1.4 ± 0.6
Central metastasis	152 (34.5)	<0.001	400 (22.9)	0.166	143 (20.3)
Lateral metastasis	30 (6.8)	0.367	99 (5.7)	0.083	53 (7.5)
Locoregional recurrence	37 (8.4)	<0.001	72 (4.1)	0.109	39 (5.5)
Distant recurrence	1 (0.2)	0.491	2 (0.1)	0.060	4 (0.3)
PTC related death	0 (0)	1.000	1 (0.1)	0.009	5 (0.7)
Other death	0 (0)	0.589	4 (0.2)	<0.001	14 (2.0)

Values are presented as number (%) or mean ± SD.
PTC, papillary thyroid carcinoma.
[a)]Tumor aggressiveness, tumor-node-metastasis stage more than T3 or N1b, and lymphovascular invasion.

Table 2. Cox analysis of variables predicting recurrence and PTC related death

Factor	Recurrence[a)]			PTC death[b)]		
	(n = 2,187)	HR	P-value	(n = 2,449)	HR	P-value
Sex						
Female	1,855	Reference		2,051	Reference	
Male	332	1.9 (1.2-3.0)	0.004	398	1.9 (1.3-2.9)	0.002
Tumor aggressiveness						
T1, T2, N0, N1a	1,381	Reference		1,479	Reference	
T3 or N1b	806	2.6 (1.8-3.8)	<0.001	970	3.5 (2.3-5.3)	<0.001
Extent of surgery						
Total thyroidectomy	1,800	Reference		2,113	Reference	
Lobectomy	387	1.7 (0.9-3.2)	0.127	336	1.2 (0.6-2.5)	0.637
Age group						
Group A (15-34)	441	1.9 (1.3-2.8)	<0.001	NA		
Group B (35-54)	1,746	Reference		1,746	Reference	
Group C (55-85)	NA			703	0.9 (0.6-1.4)	0.677

PTC, papillary thyroid carcinoma; HR, hazard ratio; NA, not available.
[a)]Between group A and B. [b)]Between group B and group C.

tial thyroidectomy in young age group versus middle or old age group (34.5% vs. 22.9% vs. 20.3%, respectively). Similarly, there was a significant increase of locoregional recurrence (8.4% vs. 4.1% vs. 5.5%). Other characteristics of sex, aggressiveness, multiplicity, bilaterality, number of PTC (1.2 ± 0.5 vs. 1.3 ± 0.6, P = 0.180) and lateral metastasis (6.8% vs. 5.7%, P = 0.367) were not different. There were no PTC-related or unrelated death. It is therefore suggested that PTC in young age group between 15 and 34 years generally shows a favorable outcome regarding PTC-related death despite the frequent locoregional recurrence (Table 1).

Age group older than 55 years old

Significant differences in various clinical characteristics

were observed in old age group. The proportion of male (18.8 vs. 15.2%, P = 0.032), and aggressiveness such as more than T3 or N1b (44.4 vs. 39.3%, P = 0.002) were higher than in middle age group. Mean number (1.4 vs. 1.3, P = 0.002), multiplicity (26.7 vs. 19.9%, P < 0.001), bilaterality (23.3 vs. 17.5%, P = 0.001) of tumors were significantly high in old age group. Central or lateral metastasis at initial surgery, locoregional, and distant recurrence were not significantly different. In contrast, there were more PTC-related deaths (0.7 vs. 0.1%, P = 0.009) and PTC-unrelated other deaths (2.0 vs. 0.2%, P < 0.001) (Table 1).

Risk factors for locoregional recurrence and PTC-related deaths

The risk factors of locoregional recurrence and PTC-related death in relation to age, sex, tumor aggressiveness, and extent of thyroidectomy at the time of operation were analyzed with Cox (Table 2) and Kaplan-Meier survival analysis (Fig. 2). Cox analysis on locoregional recurrence was done exempting the old age group to evaluate the young vs. middle age group, and excluded young age group on PTC-related death because they had no PTC-related death.

The OR of locoregional recurrence was significantly high in those with male (OR, 1.9; 95% confidence interval [CI], 1.2 to 3.0), tumor aggressiveness (OR, 2.6; 95% CI, 1.8 to 3.8), and young age group under 35 years old (OR, 1.9; 95 % CI, 1.3 to 2.8). Age, sex, and tumor aggressiveness were related to locoregional recurrences and in Kaplan-Meier analysis (Fig. 2A), though the extent of thyroidectomy was not (OR, 1.7; P = 0.127).

In analysis of PTC-related death, the mortality risk was high for males (OR, 1.9; P = 0.002) and aggressive tumors (OR, 3.5; P < 0.001). The risk of PTC-related death in the old age group was not significant (OR, 0.9; P = 0.677) in Cox analysis (Table 2), although age was significant (log rank test, P = 0.004) in Kaplan-Meier analysis (Fig. 2B). Thus, we re-analyzed another optimal cut-off age on locoregional recurrence and PTC-related death, respectively.

Optimal cut-off level of age on recurrence or death

ROC analysis was performed to determine the optimal level of age on locoregional recurrences, PTC-related, and PTC-unrelated deaths. Though other area under curve (AUC) of various continuous variables on locoregional recurrence were significant on a number of positive nodes (AUC = 0.773) and PTC size (AUC = 0.722), there were no definite cutoff levels of age on locoregional recurrence (AUC = 0.486, Fig. 3A). In contrast, significant cutoff ages were determined to 62.5 for PTC-related death (AUC = 0.912, Fig. 3B) and 56.5 years for PTC-unrelated death (AUC = 0.849, Fig. 3C).

DISCUSSION

There are many controversies regarding the proper treatment of patients in each group according to age. Identification of the prognostic indicators for age is very

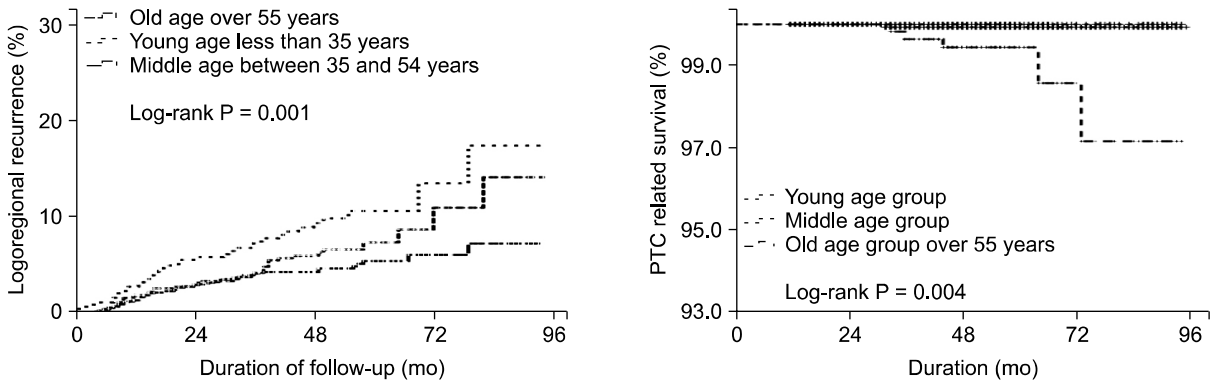

Fig. 2. Kaplan-Meier curves for locoregional recurrence (A) and papillary thyroid carcinoma (PTC) related death (B) according to young, middle, and old age group (log rank test).

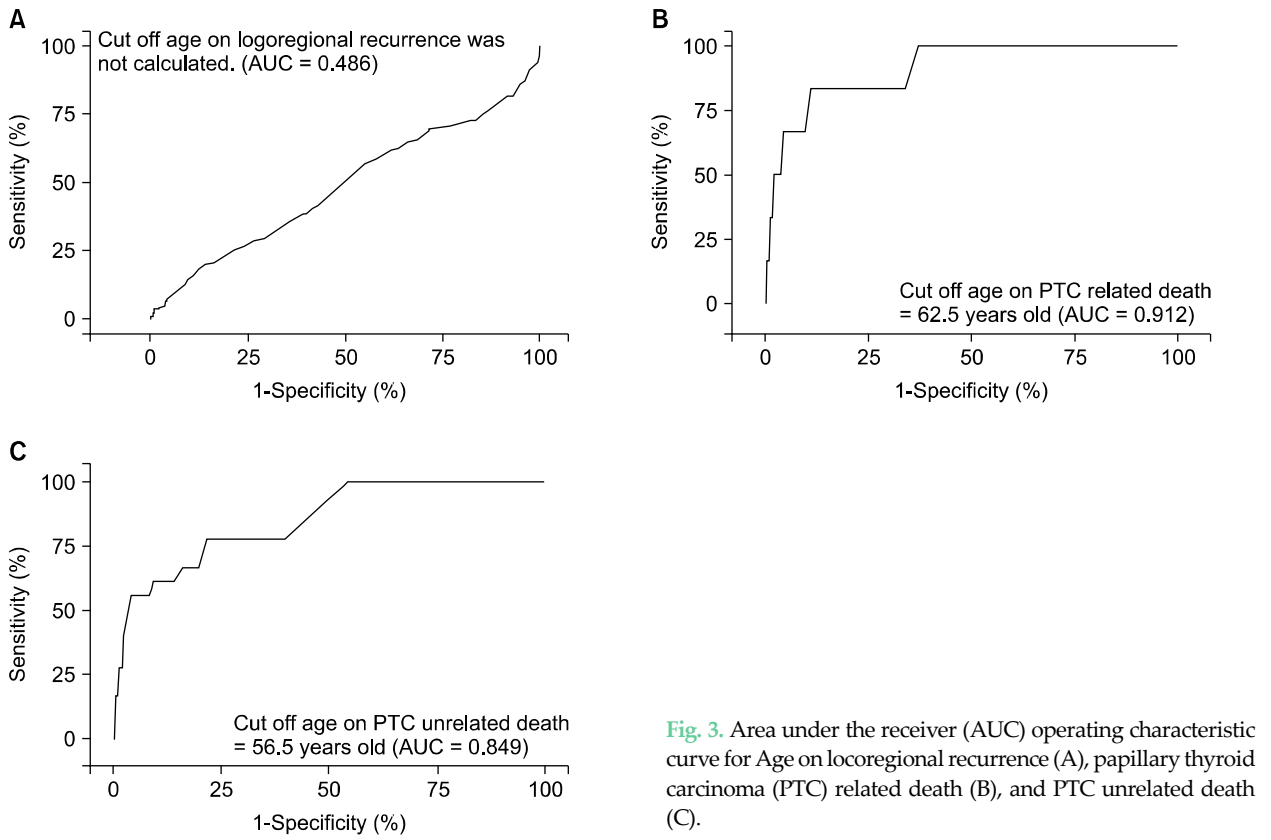

Fig. 3. Area under the receiver (AUC) operating characteristic curve for Age on locoregional recurrence (A), papillary thyroid carcinoma (PTC) related death (B), and PTC unrelated death (C).

important in deciding an appropriate therapeutic strategy. In young age groups, the desire for and proportion of endoscopic or robotic thyroidectomy is increasing [22]. The incidence of locoregional recurrence was high in patients younger than 35 years and especially less than 25 years in our study. We should be cautious in patient selection as research is still sparse on recurrence after for endoscopic or robotic thyroidectomy. Observational strategy without thyroidectomy was preferred on co-morbid old or extreme ages in our institution. Ito et al. [23] showed no evidence of apparent disease progression in observation group although patients older than 80 years old were included in. Recently we experienced some failure of watchful waiting and underwent delayed operation, especially in old age group.

Significant differences were seen in young age groups in locoregional recurrence when stratified into three age groups. It may be a reflection of the underlying differences in harvested nodes at lymph node dissection or tumor size. But in our study, more lymph node dissection was done in young age group than middle age group. Median (range) numbers of harvested nodes were 3.0 (0 to 74) vs. 2.0 (0 to 72), and tumor size was equal to 0.8 cm (0.1 to 5.0 cm). Young age group shows favorable outcomes despite the frequent locoregional recurrence. These findings were comparable to that of previous studies in a cohort study by Mazzaferri and Kloos [18] and Japanese study by Ito et al. [27].

In contrast, age factor may not be related to PTC-related death. Old age group did not show a significant difference in PTC-related deaths in Cox analysis (OR, 0.9; P = 0.677), compared to male sex (OR, 1.9) or tumor aggressiveness (OR, 3.5). It may be a reflection of high proportion of male and number of PTC, multiple or bilaterality, and aggressive tumor characteristics such as more than T3 or N1b. But from the ROC analysis, our significant age cutoff was 62.5 years (AUC = 0.912), falling between that of 55 years in iStage system [4] and 70 years in the SAG system in university of Bergen [28].

A well-established staging or classification system not

only provides clinicians and patients with useful prognostic information but also facilitates management and standardizes cancer information exchange between different medical institutions [29,30]. In other words although a retrospective single institutional study and lack of analysis on radio-active iodine therapy, our results suggest that relative performance of these age criteria remained constant.

In summary, the present study suggests that the younger than 35 years group shows favorable prognosis despite the frequent locoregional recurrence and older than 62.5 years group shows a poor prognosis regardless of other factor such as male sex or tumor aggressiveness.

CONFLICTS OF INTEREST

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

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