The Age Threshold of the 8th Edition AJCC Classification Is Useful for Indicating Patients with Aggressive Papillary Thyroid Cancer in Clinical Practice .

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Abstract

Background: Papillary thyroid cancer (PTC) is unique among cancers in that patient age is a consideration in staging. One of the most important modifications in the 8th Edition of the American Joint Committee on Cancer (AJCC) classification, which was introduced in 2018, was to increase the age cutoff for risk stratification in PTC from 45 to 55 years. However, whether this cutoff is useful in clinical practice remains controversial. In the present study, we assessed how well this new age threshold stratifies patients with aggressive PTC.

Methods: We retrospectively analyzed the clinicopathological features and overall survival rate of 523 patients with PTC admitted to and surgically treated at a single surgical center. We divided the patients into two groups according to age at PTC diagnosis: ≥55 years and <55 years.

Results: We found that the rates of tumor progression, lymph node metastasis (LNM) and distant metastasis were significantly higher in patients ≥55 years than in those <55 years; consequently, TNM stages were significantly higher in older than in younger patients ($p<0.05$ for all parameters). The risk of tumor progression (T3+T4) was nearly two-fold higher and the risk of LNM (N1) more than four-fold higher in older than in younger patients ($p<0.05$ for both). No patients <55 years old but 19 patients ≥55 years old (9.8% of the total group) showed distant metastasis. The rates of microcalcification, vascular and capsular invasion, extrathyroidal extension, irregular tumor shape, multifocality, bilaterality and multiplicity of foci were significantly higher in older than in younger patients ($p<0.05$ for all). The rate of disease-free survival was significantly lower in older (86.6%) than in younger (98.7%) patients ($p<0.0001$), and the rate of overall survival was significantly lower in older (90.3%) than in younger (99.4%) patients ($p<0.0001$).

Conclusions: PTC is more aggressive in patients aged ≥ 55 years than in their younger counterparts. This age therefore effectively stratifies PTC patients with a poor prognosis, indicating it is likely to be useful in clinical practice.

Background

The prevalence of papillary thyroid cancer (PTC) has been increasing steadily in many countries for several decades (1). In some countries, such as the United States, PTC has the fastest rate of increase among all malignant tumors (2). Importantly, however, most forms of well-differentiated thyroid cancer (WDTC) have a good prognosis, and the 5-year survival rate of PTC patients is generally above 97% (2–4).

The incidence of PTC has been shown to increase with age (2). Unlike other malignant tumors, patient age is regarded as an independent risk factor for PTC (5, 6). PTC also presents a much poorer prognosis in elderly people, although the reason for this finding has not been clearly defined (2, 7–9). Interestingly, PTC is unique among cancers in that patient age is part of staging (7). Some authors indicate at the necessity of improving the quality of recommendations on the diagnosis and management of thyroid

cancer (TC) (9). Several TC stratification systems use patient age as a tool for supporting decision-making regarding further therapeutic management. For example, the Mayo Clinic introduced the MACIS (metastases, age, completeness of resection, invasion and size) score for stratifying PTC and follicular thyroid cancer (FTC) (10), and the American Joint Committee on Cancer (AJCC) classification system similarly uses patient age for staging and determining the risk stratification score in WDTC (7). In these systems, age is one of the most important factors for determining further surgical and adjuvant treatment strategies for patients with PTC. In addition to age, other risk factors, including large tumor size, lymph node metastasis (LNM) and distant metastasis, have also been shown to be risk factors for a poor prognosis in WDTC (11). Singhal et al. (12) revealed that these clinical characteristics vary among pathological subtypes of PTC.

The current 8th Edition AJCC TNM classification system uses an age of 55 years as a cut-off point for risk stratification in tumor staging (13). By contrast, the previous traditional TNM staging system used an age of 45 years (13) as a cut-off for staging, and the change to 55 years prompted a debate regarding how clinically well-founded this age cutoff point is for PTC risk stratification, with some authors questioning the utility of using either threshold for risk stratification (14) and others proposing that the age threshold for staging PTC should be further increased (8). For example, a previous study showed that in PTC, overall survival decreases incrementally with age and that the optimal age threshold for PTC patients is 58.5 years (8). The same researchers (8) also proposed that in terms of the age threshold for risk stratification, PTC should not be evaluated using the same criteria as those used for FTC, and these conditions should instead be viewed as different forms of WDTC. Other authors have proposed that among older patients, there is no suitable age cutoff for decreasing surveillance (14). Hence, while many authors agree that age is one of the most important factors for risk stratification, there is disagreement regarding what the age cut-off should be or whether such a cut-off should be applied at all (15).

To address this controversy, we analyzed and compared clinical and histopathological characteristics and disease-free and overall survival rates between PTC patients aged ≥ 55 years and those aged < 55 years. This age cutoff was selected in accordance with the 8th Edition of the AJCC classification (13). We sought to assess how effectively the new age threshold of the 8th Edition of the AJCC classification stratifies patients with aggressive features of PTC.

Methods

We performed retrospective chart reviews of 523 patients admitted to and surgically treated for PTC in the First Department of General, Gastroenterological and Endocrine Surgery between 2008 and 2018. Diagnostic evaluations and surgical management were performed in accordance with the American Thyroid Association (ATA) guidelines (16). Cases of recurrent PTC were excluded from the study. All of the participants underwent ultrasound-guided fine-needle aspiration biopsy (UG-FNAB). After surgery, hematoxylin and eosin (H&E)-stained sections were evaluated by two experienced thyroid lesion pathologists to confirm the diagnosis, histopathological features and extent of the malignancy. The patients were divided into two groups according to age at PTC diagnosis: ≥55 years old (n = 217) and <

55 years old (n = 306). All patients were compared within comparable TNM stages. This division of the patients by stage subgroup for comparisons between older and younger patients was needed to eliminate comparisons of individuals with advanced disease and those with very small, indolent tumors, such as papillary thyroid microcarcinoma (PTMC).

Clinical and demographic data were collected on age, sex, UG-FNAB results, type of surgery, radioiodine therapy and survival time. Pathological characteristics data were collected on tumor size, lymph node metastasis (LNM), distant metastasis, vascular invasion, capsular invasion, microcalcification, multifocality, bilaterality and tumor extension into adjacent tissues (cancer invasion beyond the thyroid capsule).

Statistical analysis

Statistical analyses of the data were performed using Statistica 13.3 software (Tibco Software, Inc., CA, USA). Descriptive data are presented as the number of observations and the percent or as the average ± standard deviation (SD) and 95% confidence interval (95% CI). Qualitative variables were compared using Pearson chi-square, Fisher or Wald tests, and quantitative variables were analyzed using Student's t test for independent samples. Univariate logistic regression was used to analyze the association of age (as the independent variable) with tumor progression (pT3 + T4) and lymph node (pN1) or distant (pM1) metastases (as dependent variables). The Kaplan-Meier method and log-rank test were performed to compare the distributions of disease-free survival and overall survival between patients < 55 years old and those ≥ 55 years old. A p-value less than 0.05 was considered statistically significant.

Results

As reported in Table 1, the rate of diagnosis with TC before surgery was significantly higher in patients < 55 years old than in those ≥ 55 years old ($p < 0.05$). The study groups did not differ statistically in terms of sex, type of operation or number of reoperations performed.

Table 1
Demographic data, prediction of thyroid malignancy before surgery and surgical procedure in two groups of PTC patients. Data are presented as the mean ± SD or number (percent).

Variables	PTC patients aged < 55 years (n = 306)	PTC patients aged ≥ 55 years (n = 217)	p-value
Age (years)	39.65 ± 10.22	64.61 ± 7.61	< 0.0001*
Sex:	272 (89.2)	183 (84.3)	0.102
Female	33 (10.8)	34 (15.7)	0.038*
Male	189 (64.7)	121 (55.8)	0.986
Diagnosis of thyroid malignancy:	108 (35.3)	96 (44.2)	0.687
Before surgery	223 (72.9)	158 (72.8)	
After surgery	83 (27.1)	59 (27.2)	
Type of surgery:	229 (74.8)	159 (73.3)	
Total	77 (25.2)	58 (26.7)	
Partial			
Reoperation:			
No			
Yes			
*- statistically significant			

With regard for tumor staging, we found that the rates of tumor progression, LNM and distant metastasis were significantly higher, and consequentially that TNM stages were significantly higher, in patients ≥ 55 years old than those < 55 years old ($p < 0.05$ for all parameters) (Table 2).

Table 2
Thyroid tumor pathology in PTC patients. Data are presented as the number of observations (percent).

Variable	PTC patients aged < 55 years (n = 306)	PTC patients aged ≥ 55 years (n = 217)	p-value
pTNM stage:	265 (86.6)	168 (77.4)	0.0007*
I	41 (13.4)	31 (14.3)	0.003*
II	0 (0.0)	10 (4.6)	< 0.0001*
III	0 (0.0)	8 (3.7)	< 0.0001*
IV	118 (39.3)	89 (41.1)	
Tumor stage (pT):	150 (50.0)	86 (39,6)	
pT1a	30 (10.0)	29 (13.4)	
pT1b	1 (0.3)	6 (2.8)	
pT2	0 (0.0)	3 (1.4)	
pT3	1 (0.3)	4 (1,8)	
pT4a	250 (81.7)	100 (46.1)	
pT4b	49 (16.0)	96 (44.2)	
Lymph node metastasis (pN):	3 (1.0)	3 (1.4)	
pN0	4 (1.3)	18 (8.3)	
pN1a	276 (90.2)	174 (80.2)	
pN1b	0 (0.0)	19 (8.8)	
pNx	30 (9.8)	24 (11.0)	
Distant metastasis (pM):			
pM0			
pM1			
pMx			
*- statistically significant			

Based on these results, we conducted a univariate logistic regression analysis using an age of > 55 years as a risk factor for cancer progression, defined as advancement to a high TNM stage (T3 + T4). As shown in Table 3, the risk of tumor progression (T3 + T4) was nearly two-fold higher and the risk of LNM (N1)

more than four-fold higher in older patients than in younger patients ($p < 0.05$ for both). No patients < 55 years old showed distant metastasis, but 19 patients ≥ 55 years old (9.8% of the total group) showed distant metastasis.

Table 3
Univariate logistic regression analysis of age as risk factor for cancer progression in terms of T, N and M stage. Descriptive data are presented as the number (percent), and the results were calculated by chi-square Wald test.

Covariate "Age"	***pT*:**		***OR***	***± 95% CI***	***p-value***
	pT1 + pT2 (n = 446)	***pT3 + pT4 (n = 77)***			
< 55 years	272 (61.0)	34 (44.0)	1.98	1.21–3.22	0.006*
≥ 55 years	174 (39.0)	43 (56.0)			
Covariate "Age"	*pN*:*		*OR*	*± 95% CI*	*p-value*
	pN0 (n = 351)	*pN1 (n = 150)*			
< 55 years	250 (71.0)	52 (35.0)	4.66	3.09–7.02	< 0.0001*
≥ 55 years	101 (29.0)	98 (65.0)			
Covariate "Age"	*pM*:*		*OR*	*± 95% CI*	*p-value*
	pM0 (n = 450)	*pM1 (n = 19)*			
< 55 years	276 (61.0)	0 (0.0)	-	-	< 0.0001*
≥ 55 years	174 (39.0)	19 (100.0)			
*- statistically significant					

Clinical and histopathological features differed significantly between the older and younger patient groups (Table 4). Compared to patients aged < 55 years, patients aged ≥ 55 years demonstrated significantly higher rates of microcalcification, vascular and capsular invasion, extrathyroidal extension, irregular tumor shape, multifocality, bilaterality and multiplicity of foci ($p < 0.05$ for all) but no difference in hypoechogenicity. The rate of clear tumor margins was significantly lower in older than in younger patients ($p = 0.009$).

Table 4
Clinical and histopathological features of PTC patients. Data are presented as the number of observations (percent).

Variables	PTC patients aged < 55 years (n = 306)	PTC patients aged ≥ 55 years (n = 217)	p-value
Microcalcification:	116 (37.9)	183 (84.3)	< 0.0001*
Yes	190 (62.1)	34 (15.7)	0.140
No	65 (21.2)	35 (16.1)	0.007*
Echogenicity:	241 (78.8)	182 (83.9)	< 0.0001*
Hyperechoic	142 (46.6)	127 (58.5)	< 0.0001*
Hypoechoic	163 (53.4)	90 (41.5)	< 0.0001*
Vascularity:	66 (21.6)	119 (54.8)	0.025*
High	240 (78.4)	98 (45.2)	0.009*
Low	66 (21.6)	119 (54.8)	0.036*
Extrathyroidal extension:	240 (78.4)	98 (45.2)	0.002*
Yes	66 (21.6)	119 (54.8)	0.0005*
No	240 (78.4)	98 (45.2)	
Capsular invasion:	161 (52.8)	93 (42.9)	
Yes	144 (47.2)	124 (57.1)	
No	160 (52.5)	89 (41.0)	
Vascular invasion	145 (47.5)	128 (59.0)	
Yes	232 (76.1)	147 (67.7)	
No	73 (23.9)	70 (32.3)	
Tumor shape	290 (95.1)	190 (87.6)	
Regular	15 (4.9)	27 (12.4)	
Irregular	258 (84.6)	165 (76.0)	
Clear margins	43 (14.1)	35 (16.2)	
Yes	4 (1.3)	17 (7.8)	
No	0 (0.0)	0 (0.0)	

*- statistically significant

Variables	PTC patients aged < 55 years (n = 306)	PTC patients aged ≥ 55 years (n = 217)	p-value
Diagnosed as multifocal:			
No			
yes			
Diagnosed as bilateral:			
No			
Yes			
Number of foci:			
1			
2			
3			
4			
*- statistically significant			

We created models of disease-free and overall survival using age as the predictive variable. The probabilities of disease-free survival in PTC patients < 55 and ≥ 55 years old during the observation period (2008–2018) are shown in Fig. 1. The rate of disease-free survival was significantly lower in older patients (86.6%) than in younger patients (98.7%) ($p < 0.0001$). Our analysis of the ratios of patients who survived over time (indicating overall survival at each time point) in each group from 2008–2018 showed that at the final time point, overall survival was significantly lower in older patients (90.3%) than in younger patients (99.4%) ($p < 0.0001$) (Fig. 2).

Discussion

Our findings support our hypothesis, based on the 8th edition of the AJCC classification, that in classical PTC, patients aged ≥ 55 years have comparatively worse prognoses than those < 55 years. We reveal that the incidence of aggressive pathological features was higher and the incidence of histopathological characteristics associated with an aggressive course much higher in PTC patients in the older group than in those in the younger group. These findings might explain why this age cut-off is effective. This may explain our observation that among patients with the same pTNM stage, prognoses were much worse in patients aged ≥ 55 years than in those aged < 55 years. In our study, we also found that the incidence of pathological features characteristic of aggressive cases of PTC increased with patient age, with individuals with aggressive characteristics of PTC being slightly older than those without such characteristics. To extend the life spans of older patients with PTC, it is crucial to assess all risk factors

for aggressive entities of PTC and as well as postsurgical prognosis; while some demographic factors, including sex, are not correlated with aggressive features of PTC, we found that older age is correlated with a more aggressive course.

With regard for the anatomical region of metastasis, we found that younger patients primarily showed neck LNM, while older patients primarily showed distant metastasis. A potential partial explanation for this observation lies in the histopathological characteristics of PTC in these groups of patients. Compared to younger PTC patients, in older PTC patients, we observed a higher number of aggressive features, indicating the potential for more aggressive tumor spread (to distant regions and not only to regional lymph nodes). Consistent with these results, we additionally found that the prevalence of LNM was higher in older than in younger PTC patients.

Our survival analysis further suggested that prognoses are worse in older patients than their younger counterparts, potentially because the incidence of aggressive PTC features is higher in the older group. We noted that forms of PTC without capsular infiltration were much more frequently observed in younger than in older patients, while infiltrative subtypes were more common in older than in younger patients; these findings might explain the better prognoses observed in the younger patients. Similarly, some authors have reported that patients with encapsulated PTC have an excellent prognosis, while those with infiltrative tumors have a comparatively worse prognosis (17, 18). Importantly, some genetic differences between encapsulated and infiltrative neoplasms have been identified (18). Nikiforov et al. (17) determined that most patients with encapsulated PTC underwent only lobectomy, and patients treated in this way had a very low risk of adverse outcomes over long-term follow-up. Based on these and similar findings, in 2016, cases of encapsulated PTC were formally classified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (17, 19). Conversely, some authors found that not only was there no difference in postsurgical outcomes between PTC patients treated with lobectomy vs. thyroidectomy, but also that radioactive iodine (RAI) therapy provided no survival benefit (4, 20–22). The survival analysis performed in our study suggests that clinicians should consider both patient age and the results of histopathological examinations when treating PTC patients. This approach may save some patients, especially younger individuals with comorbidities, from undergoing unnecessary aggressive therapies. Even the 2015 ATA Management Guidelines for Patients with Differentiated Thyroid Cancer recommends hemithyroidectomy without RAI therapy in low-risk patients (16), and some authors have, based on these guidelines, begun to identify which groups of patients may be at risk of overtreatment with RAI ablation after surgery for low-risk PTC (23).

The situation is completely different in PTMC patients. Ito et al. (24), for example, revealed that there are significant age-specific differences in cancer biology among indolent, clinically silent PTMC and advanced PTC – in particular, the incidences of larger tumors, LNM and disease progression were estimated to be lower in older patients and higher in younger patients. Similar observations were presented by Kim et al. (6), who showed that extrathyroidal extension and LNM were significantly less frequent in older patients with PTMC than in patients with larger PTC. They suggested, based on this finding, that older patients with clinically silent PTMC should be considered for active observation rather

than surgical treatment (6). In our study, we identified some clinical and histopathological characteristics of PTC that, when absent, may permit clinicians to avoid aggressive therapy in older patients. Additionally, we confirmed that among PTC patients, LNM, capsular and vascular invasion, extrathyroid extension, microcalcification and distant metastasis are more common in older than in younger patients, and are risk factors for a poor prognosis. We observed these features mainly in patients ≥ 55 years old. According to some authors, the use of LNM in risk stratification remains controversial (25), while many other studies have presented LNM as a significant risk factor for poor outcomes in PTC (13, 26). In contrast, other authors have reported inconsistent conclusions concerning the impact of LNM on PTC (25). Analyses have also shown that in FTC but not PTC, an older age at diagnosis is a significant risk factor for disease-specific mortality (27). Zhang et al. (28) compared younger, middle-aged and older patients with PTC and found that bilateral LNM was more likely to occur in the older patients (45–65 years old) than in the younger groups. They additionally concluded that the tumors in the older group were more likely than those in the middle and younger groups to show capsular and extrathyroidal invasion. Kim et al. (6) proposed that tumor size and LNM are independent predictors of recurrence in older patients with PTC. De Castro et al. (29) added that tumor size, local extent (T stage) and nodal status (N stage) are also important prognostic factors in patients ≥ 45 years old. In our study, we observed that some risk factors, such as LNM, capsular invasion and distant metastasis, were more common in older patients than in younger patients.

In our study, we found that an age of 55 years is a clearly useful cut-off threshold for stratifying PTC patients, with patients younger and older than this age having better and poorer prognoses, respectively, consistent with a recent study (14). Those authors used Cox proportional hazards analysis to assess the association between specific risk factors and the prognosis of WDTC and showed, consistent with our findings, that an age of 55 years is an effective cut-off threshold for risk stratification in PTC patients. This age threshold effectively stratifies patients with aggressive tumors, and our data indicate there is no need to increase this threshold. We confirmed the results reported by Gillanders et al. (30), which supported increasing the age threshold from 45 to 55 years. Because the evidence supporting the use of an age of 45 years as a cut-off for stratification had become controversial, we performed our study and show that an age of 55 years seems very reasonable, contrary to some authors who proposed that no age cut-off is appropriate for significant risk stratification (31, 32). Our data indicate that an age cutoff of 55 years could help clinicians perform risk stratification. For example, patients aged ≥ 55 years are more likely than their younger counterparts to present PTC with clinicopathological features pathognomonic for aggressive entities, while < 55 years old very often have indolent, clinically silent PTC. The aggressive clinicopathological features observed in older PTC are likely responsible for their comparatively poorer survival and prognosis. Access to these data may help clinicians deciding whether to perform more radical treatment. Equally important is that clinicians may be able to prevent unnecessary surgery and aggressive postsurgical RAI therapy in older patients with PTC without invasive features on histopathological examination.

Conclusions

Overall, our results support the notion that the individual risk stratification and treatment of older patients with PTC is reasonable. PTC is more aggressive in patients aged ≥ 55 years than in their younger counterparts. This age therefore effectively stratifies PTC patients with a poor prognosis, indicating it is likely to be useful in clinical practice.

Our study has some limitations. First, it is limited by its retrospective design, which prevented adjustment for some confounding factors. Second, this was a single-center analysis; to better understand this issue, multicenter analysis will be necessary. Third, due to the indolence of PTC and PTMC, our study was conducted over a relatively short follow-up period; a longer follow-up period is needed to completely assess the impact of PTC characteristics on prognosis and mortality.

Abbreviations

PTC
Papillary Thyroid Cancer
AJCC
American Joint Committee on Cancer
LNM
Lymph Node Metastasis
TNM
Tumor Node Metastasis
WDTC
Well-Differentiated Thyroid Cancer
FTC
Follicular Thyroid Cancer
H&E
Hematoxylin and Eosin
PTMC
Papillary Thyroid Microcarcinoma
ATA
American Thyroid Association
UG-FNAB
Ultrasound-Guided Fine-Needle Aspiration Biopsy
SD
Standard Deviation
CI
Confidence Interval
NIFTP
Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features
RAI
Radioactive Iodine

Declarations

Ethics approval and consent to participate

Our study protocol was approved by the Bioethics Committee of Wroclaw Medical University, Poland (KB-783/UMW). We obtained oral consent instead of written consent from the participants because the data were analyzed retrospectively and anonymously on the basis of medical records. The authors did not have access to patient-identifying information or direct access to the study participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KK made following contributions: conceptualization, data obtaining, formal analysis, investigation, methodology, project administration, resources, writing of the original draft, review and editing.

DD made following contributions: formal analysis, investigation, methodology, project administration, validation, result's interpretation and original draft writing.

ŁN made following contributions: data obtaining, formal analysis, investigation, methodology, resources and editing.

BW made following contributions: data obtaining, formal analysis, resources and supervision.

JR made following contributions: formal analysis, methodology, project administration, resources, supervision and editing.

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Figures

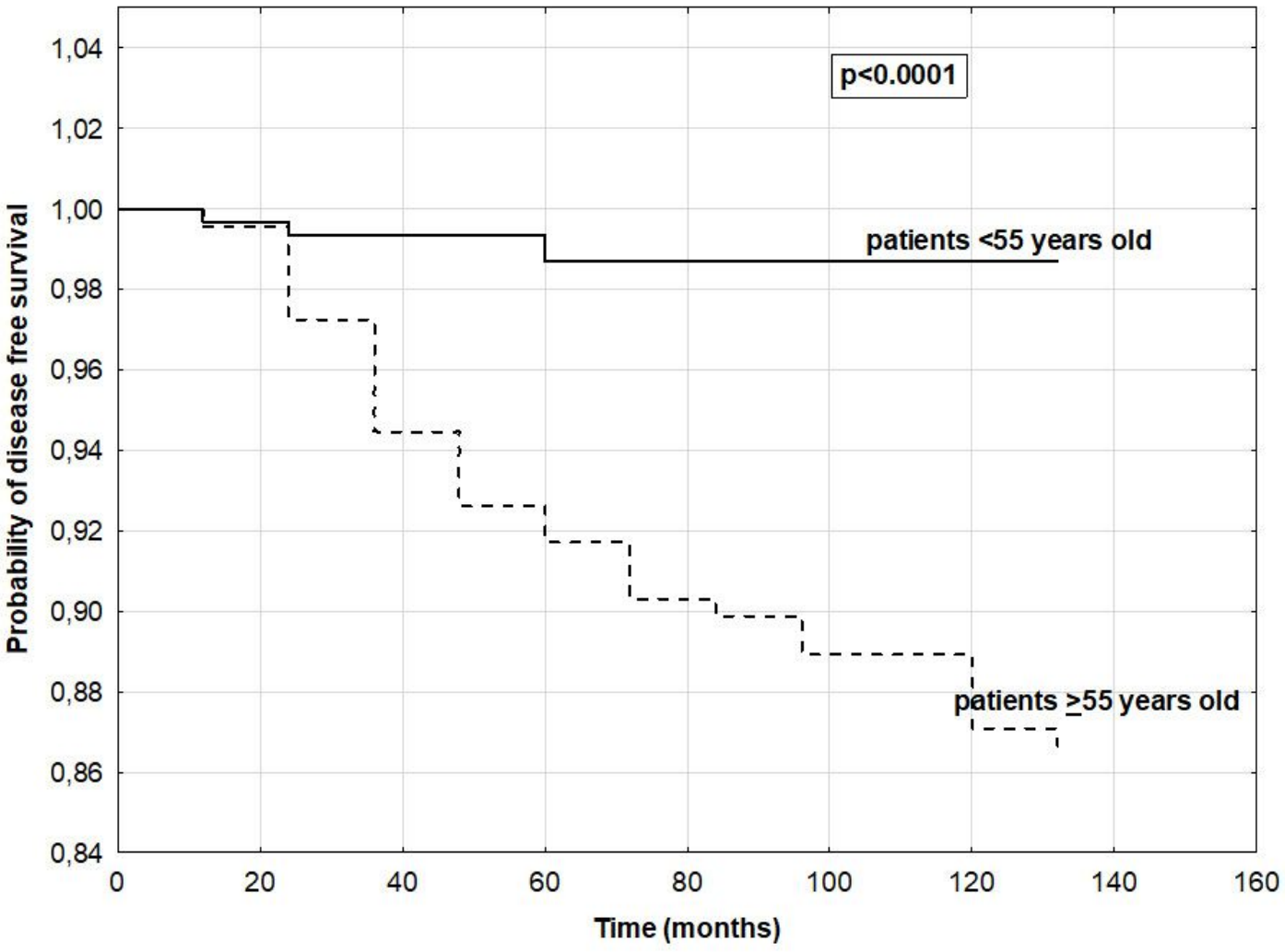

Figure 1

Relationship between time and TC recurrence (disease-free survival) in the two age groups.

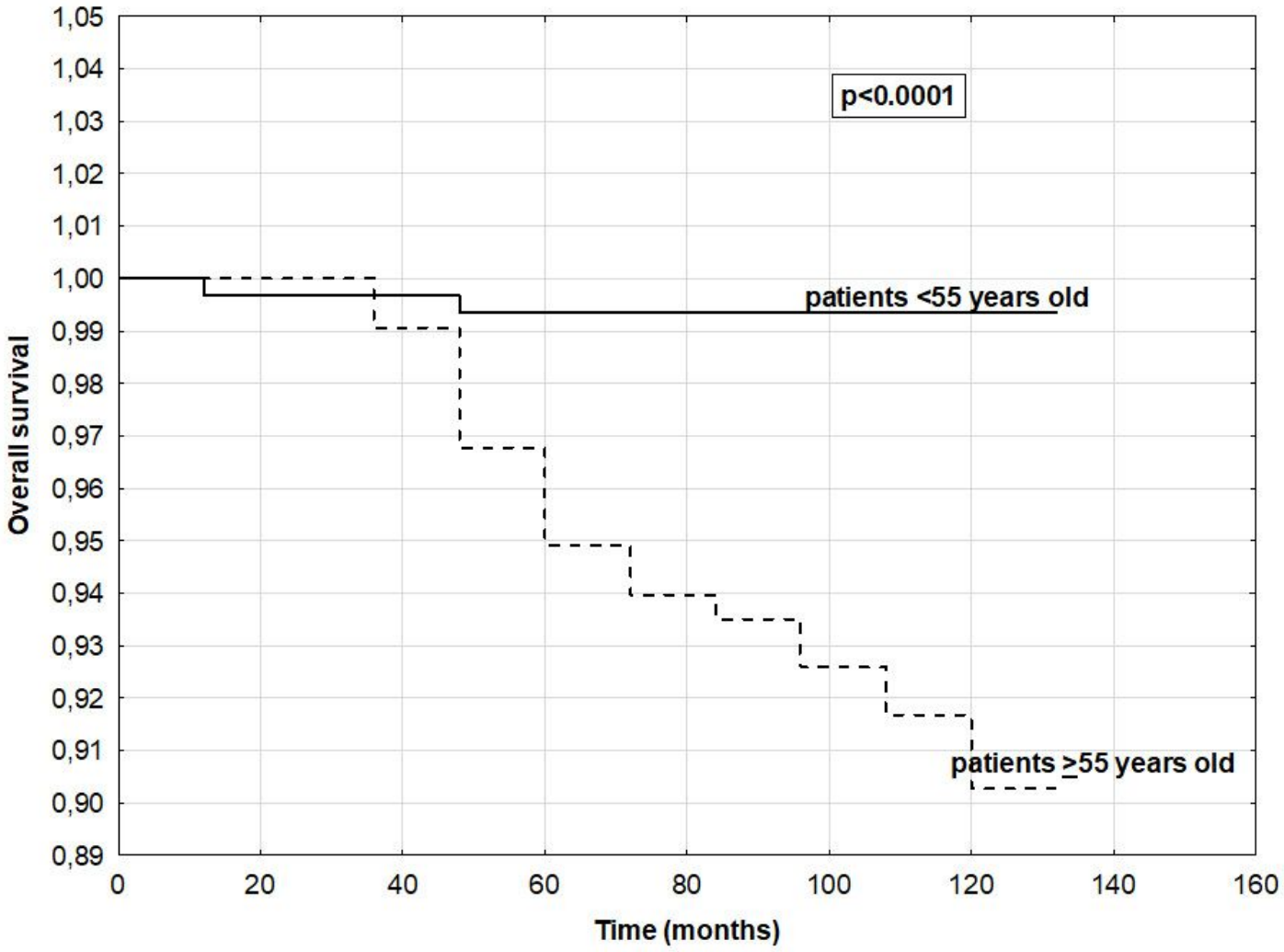

Figure 2

Relationship between overall survival and time in the two age groups.

Supplementary Files

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- supplement10.pdf
- supplement11.doc