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Original Article

Long-term outcomes of older patients with papillary thyroid carcinoma – should there be another age cut-off beyond 45 years old?

Running head: Age >60 years further increases death risk

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SYNOPSIS

Advanced age (>60 years) was an independent predictor of cancer-specific survival in patients with papillary thyroid carcinoma aged ≥ 45 years. Therefore, having another age cut-off beyond 45 years old appears justifiable for stratifying risk of cancer-related death. This has important implications for current stratification systems.

ABSTRACT

Background:

Although an age cut-off of 45 years has often been adopted to stratify cancer risk in papillary thyroid carcinoma (PTC), both cancer-specific survival (CSS) and disease-specific survival (DFS) continue to worsen beyond this cut-off. We aimed to see if advanced age (i.e. >60 years) at diagnosis was an independent predictor of CSS and DFS in older (≥45 years) patients.

Methods:

Four-hundred and seven PTC patients with a minimal follow-up of 7 years were analyzed. Standard protocol was followed. CSS and DFS were estimated using Kaplan-Meier and compared with log-rank test. Variables which were significant by log-rank test were entered into the Cox regression analysis.

Results:

After a median follow-up of 15.1 years, 51 (12.5%) died of PTC while 80 (20.5%) developed at least one recurrence. For CSS, age >60 years (HR=3.027, 95%CI=1.369–6.690,p=0.006), tumor size >4cm (HR=2.043, 95%CI=1.141–4.255,p=0.049), central nodal metastases (HR=2.726, 95%CI=1.198–6.200,p=0.017), lateral nodal metastases (HR=5.247, 95%CI=2.987–9.216,p<0.001) and distant metastases (HR=4.297, 95%CI=1.726–2.506),p=0.002) were independent predictors. For DFS, only tumor size >4cm (HR=1.733, 95%CI= 1.030 – 3.058,p=0.049), central nodal metastases (HR=2.362, 95%CI=1.010–5.523,p=0.047) and lateral nodal metastases (HR=4.383, 95%CI=2.388–8.042,p<0.001) were independent predictors.

Conclusions:

Advanced age was an independent predictor of CSS and there was a continuing increase in cancer-related death risk beyond age >60 years. However, advanced age was not an independent predictor of DFS. Therefore, having another age cut-off appears justifiable for stratifying risk of cancer-related death but less so for disease recurrence. Tumor size, central and lateral nodal metastases independently predicted CSS and DFS.

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma and its incidence has doubled in the past two decades [1]. Although it is generally associated with an excellent outcome, its prognosis depends on the presence of certain clinicopathologic characteristics [2]. Age at diagnosis has long been recognized as one of the most important prognostic factors in PTC [2,3]. Given that patients aged <45 years have significantly better prognosis than those aged ≥45 years, many risk stratification systems including the more popular 7th UICC *TNM* (Tumor, Node and Metastasis) staging system utilizes an age cut-off of 45 years to stratify risk [3]. Although this might be convenient, this strategy assumes that all patients aged >45 years would have a fairly uniform tumor risk regardless of whether he or she is significantly older or closer to the age cut-off. However, it is becoming increasingly clear that both the risk of cancer-related death and disease recurrence progressively increase even after the age of 45 years [4-9] In fact, some groups have proposed that perhaps another age cut-off of 60 years should be considered when stratifying tumor risk and individual treatment in older (≥45 years) patients [4-6]. However, to our knowledge, these studies did not account for other significant prognostic factors in their analysis. Furthermore, most of their patients had microcarcinoma and so less-than half of patients underwent total or near-total thyroidectomy and received radioactive iodine (RAI) afterwards. Given these issues, our study aimed to see if advanced age at diagnosis (i.e. >60 years) remained an independent predictor of cancer-specific (CSS) and disease-free survivals (DFS) in older patients. This was carried out by analyzing a large patient cohort that had suffered clinically-significant PTC requiring total or near-total thyroidectomy and RAI ablation afterwards and had been followed up for a median of 15 years.

PATIENTS AND METHODS

From 1970 - 2006, 988 consecutive patients with histologically-proven PTC underwent total or near-total thyroidectomy in our institution. Of these, 33 (3.3%) patients with incomplete follow-up data were excluded while 107 (10.8%) with microcarcinoma (<1cm) and 441 (44.6%) aged <45 years were also excluded. Therefore, 407 (41.2%) were eligible for analysis with a minimal follow-up of 7 years. To ensure an accurate and updated follow-up status of all patients, a careful manual search of all patients' status in the territory-wide Clinical Management System (CMS) was performed. The CMS is a computerized database linking up all public hospitals and provides inpatient medical records corresponding to over 90% of inpatient bed days in the territory. The latest date of follow-up or the date of death and the cause of death were recorded from the CMS. All causes of death were further confirmed by careful examination of the medical record, autopsy report and / or death certificate. All relevant clinical, pathological and perioperative data were collected prospectively after 1994 and follow-up data were regularly updated in a computerized database.

Management of PTC

Details of surgical treatment, RAI ablation criteria, postoperative care and follow-up protocol had been described previously [2] Preoperative lymphatic mapping by neck ultrasound (USG) was not routinely done until in the latter study period. Total or near-total thyroidectomy was preferred for all patients with a preoperative diagnosis of PTC. Simultaneous therapeutic central (level VI) +/- lateral (levels II-V) selective neck dissection was performed for clinically-proven cervical nodal metastasis. Prophylactic level VI neck dissection was not routinely performed. Two months after initial surgery, a standard ablative RAI dose of 3 giga-Becquerels (GBq) or 80 millicuries (mCi) was given after LT4 withdrawal or with

recombinant TSH. TSH-suppressive LT4 treatment was commenced immediately afterwards. This was followed by the post-therapy scan 4-7 days later. The subsequent therapy for distant metastases usually comprised 5.5 GBq (or 150 mCi) RAI and was administered periodically every 6-month until no more uptake on scan or disease progressed despite treatment. The decision for RAI ablation was based on the presence of ≥1 risk factors such as tumor size > 1.5cm, lymph node metastasis, age >45 years old, extrathyroidal extension, possible postoperative neck residual disease and distant metastasis. External beam radiotherapy (EBRT) to the neck was given to patients with extensive extrathyroidal tumor extension, incomplete resection, and/or extracapsular nodal metastasis. In some cases of incomplete resection, EBRT was given before RAI.

Follow-up protocol

All postoperative patients were followed up within 4 weeks in our specialized clinic. A follow-up visit was conducted at 3 to 6 monthly in the first 5 years and annually thereafter. Clinical examination and thyroglobulin (Tg) were done at each visit. Disease recurrence was generally made by a combination of basal Tg trend, USG, CT/ MRI or FDG-PET scan and confirmed by fine needle aspiration cytology (FNAC) or histology if possible while locoregional recurrence (LRR) was defined as an identifiable neck lesion on USG which was confirmed on FNAC and/or histology [10]. The exact location of LRR and distant recurrence were recorded. To simplify the analysis for DFS and disease recurrence, those presenting with distant metastases were excluded from analysis.

Statistical analysis

CSS and DFS were estimated using the Kaplan-Meier method and compared with log-rank test. Variables which were significant in the univariate analysis (by log-rank test) were entered into the multivariate analysis using Cox-regression analysis. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

The cohort comprised mostly women (73.2%) and ethnic Chinese (92.4%). The mean age was 60.0 ± 10.9 years while the mean tumor size was 2.3 ± 0.9cm. There were 103 (25.3%) patients who presented with palpable cervical lymph node metastases while 16 (3.9%) presented with distant metastases. After a median follow-up of 15.1 (7.3 – 47.5) years, 51 (12.5%) patients died of PTC while another 38 (9.3%) patients died of non-thyroidal malignancy and 68 (16.7%) died of a medical or natural cause. The 5-year, 10-year and 15-year CSS were 97.0%, 93.6% and 92.0%, respectively. At the time of analysis, 18 (4.4%) patients were still alive with detectable local and distant disease while 11 (2.7%) patients were reverted to disease-free after treatment. After excluding the 16 patients who presented with distant metastases, there were 80 (20.5%) patients who suffered at least one recurrence during the study period. At the time of first recurrence, 61 (76.3%) had LRR only while 13 (16.3%) had distant recurrence only and 6 (7.5%) had both LRR and distant recurrence. The 5-year, 10-year and 15-year DFS were 87.2%, 80.9% and 78.8%, respectively while the 5-year and 10-year locoregional DFS were 89.2% and 83.8%, respectively. Therefore, just over 10% developed LRR within 5 years from initial therapy.

Table 1 shows clinicopathological factors and treatment predictive of CSS. Age >60 years ($p<0.001$), tumor size > 4cm ($p=0.003$), presence of tumor multifocality ($p=0.046$), extrathyroidal extension ($p<0.001$), central and lateral nodal metastases ($p<0.001$), distant metastases ($p<0.001$), incomplete resection ($p<0.001$) and EBRT ($p<0.001$) were significantly associated with a worse CSS. Figure 1a shows the CSS curves between those aged 45 – 60 years (n=224) and those aged > 60 years (n=183). EBRT was a poor prognostic factor because patients who received EBRT generally had more aggressive tumor features and/or less complete resection (see supplementary table 1). Similar findings were found in patients who received RAI (see supplementary table 2).

Table 2 shows the multivariate analysis of risk factors for CSS. After adjusting for other significant factors, age >60 years (HR=3.027, 95%CI=1.369 – 6.690, p=0.006), tumor size >4cm (HR=2.043, 95%CI=1.141 – 4.255, p=0.049), central nodal metastases (or N1a) (HR=2.726, 95%CI=1.198 – 6.200, p=0.017), lateral nodal metastases (or N1b) (HR=5.247, 95%CI=2.987 – 9.216, p<0.001) and distant metastases on presentation (HR=4.297, 95%CI=1.726 – 2.506), p=0.002) turned out as independent predictors for CSS. These 4 factors remained significant regardless of whether age, tumor size or both were entered as continuous or categorical variables. When age at diagnosis was further categorized into 45-60 years, 61-70 years and >70 years, the overall model did not change and there was a progressive increase in the risk of cancer-related death with each older age category (relative to age of 45-60 years, HR (95%CI) for 61-70years and >70years were 2.340 (1.268 – 5.855) and 3.908 (1.624 – 9.205), respectively).

Table 3 shows clinicopathological factors and treatment predictive of DFS. Age >60 years (p=0.015), male sex (p<0.001), study period before 1990 (p=0.027), no preoperative USG (p=0.006), tumor size >4cm (p<0.001), presence of extrathyroidal extension (p<0.001), central and lateral nodal metastases (p<0.001), incomplete resection (p=0.002), RAI (p=0.011) and EBRT (p=0.004) were significantly associated with a worse DFS. Figure 1b shows the DFS curves between those aged 45 – 60 years (n=222) and those aged >60 years (n=169). Those 16 patients presenting with distant metastases were excluded. Similar to CSS, RAI and EBRT were poor prognostic factors for DFS because patients who received either or both of these treatments generally had more aggressive tumor features and less complete resection.

Table 4 the multivariate analysis of risk factors for DFS. After adjusting for other significant factors, only tumor size >4cm (HR=1.733, 95%CI= 1.030 – 3.058, p=0.049), central nodal metastases (HR=2.362, 95%CI=1.010 – 5.523, p=0.047) and lateral nodal metastases (HR=4.383, 95%CI=2.388 – 8.042, p<0.001) turned out as independent predictors of DFS.

When tumor size was entered as a continuous variable, the overall result did not change. Age at diagnosis did not turn out an independent predictor of DFS regardless of whether it was entered as a categorical or continuous variable.

DISCUSSION

Our data confirmed that advanced age (or age >60years) was an independent predictor of CSS in older patients with PTC regardless of whether it was entered as a continuous or categorical variable. This finding is consistent to what others have reported [4-9] and supports the argument that perhaps another age cut-off beyond 45 years old might be justifiable. Our data also showed that there was a progressive increase in risk of cancer-related death as age increased beyond the arbitrary cut-off of 60 year old. This has important implications on current risk stratification systems [2]. After adjusting for other significant prognostic factors, the risk of cancer-related death for those aged >70 years appeared significantly higher than those aged between 60 – 70 years and between 45 – 60 years. In fact, after adjusting for other significant factors, relative to those aged 45-60 years, the risk of cancer-related death for those aged >60-70 years and >70 years were almost 2.5 and 4 times higher, respectively. Based on these findings, one may argue that perhaps, two or more cut-offs after 45 years might be even more appropriate in further improving current risk stratification. Although this might be true, we believe having two separate age cut-offs after 45 years increases the complexity of the current stratification system (namely, the *TNM* staging system) and reduces its practicality and usability [2].

However, interestingly, unlike other recent studies [11,12], our data did not show that advanced age significantly increased recurrence when other significant factors had been adjusted for. Although there was a significantly lower 10-year DFS in those aged >60 years than those aged 45-60 years (74.6% vs. 84.3%, *p*=0.015), age>60 years did not turn out as an independent predictor for DFS. Therefore, from our analysis, another age cut-off might only be appropriate for predicting risk of cancer-related death but less so for disease recurrence in older patients. However, it is worth noting that given the relatively high overall LRR rate and a great proportion of LRR occurring shortly after initial surgery (around 10% of LRR within

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5 years), we strongly suspect that some of these LRRs might have been persistent and residual diseases rather than true recurrences. One possible explanation for this is because preoperative USG was not routinely performed during the early study period and so some of these LRRs might have been non-palpable nodal metastases which later became clinically evident years after initial surgery. This would also explain why no preoperative USG turned out a significant factor of poor DFS and why the rate of DFS significantly improved in the latter study period especially after year 2001 when compared to the earlier periods. Given these confounding factors, it was difficult to interpret the significance of advanced age on DFS. Nevertheless, this emphasizes the importance of having proper preoperative lymph node mapping by USG and perhaps, performing adequate extent of selective neck dissection especially in the presence of clinically nodal metastases. Perhaps, this is the precise reason why the dynamic or delayed risk stratification system based on response to therapy might be a better tool for predicting recurrences and DFS than using the traditional clinicopathologic features [13,14].

Although the overall impact of nodal metastases on cancer survival still remains under debate, it is clear that its impact is significantly greater in older patients. This is supported by several recent studies [11,12,15,16]. Similar to others, our data found that the presence of lateral nodal metastases (or N1b) was an independent predictor of worse CSS and DFS. In fact, older patients with N1b conferred over 5 times higher risk of cancer-related death than older patients without nodal metastases (or N0/Nx). Interestingly, the presence of central nodal metastases (or N1a) also conferred over 2.7 times higher risk of death than N0/Nx, although a significant higher risk of death was reported recently [11]. However, it is worth noting that since preoperative USG and prophylactic neck dissection were not routinely practiced during most of the study period, these results implied that perhaps only clinically-evident or palpable nodal metastases had any significant impact on cancer survival.

Similar to nodal metastases, tumor size was also found to be an independent predictor for CSS and DFS in older patients with PTC. This finding has also similarly reported by several other groups and concurs to the current 7th edition *TNM* staging which regards both size or local extent (i.e. *T* staging) and nodal status (*N* staging) as important components of stage groupings in patients aged ≥45 years [3].

Given the poorer CSS in patients aged >60 years, we would advocate a more careful and detailed preoperative staging assessment as well as a more aggressive surgical and therapeutic approach than their younger counterparts.

Despite these findings, we acknowledged certain shortcomings. Firstly, since the number of patients was moderate, non-significant findings in the multivariate analysis might be due to inadequate power. Secondly, since this study was conducted over a long-time period, changes in clinical management were inevitable and might have had a confounding effect on the survival analyses. Also since using pre- and post-operative USG in detecting nodal metastases and prophylactic central neck dissection have now become routine in our practice, the present findings only represent our earlier experience. Therefore, larger prospective studies with longer follow-up period are required to confirm our findings.

Conclusion

Advanced age at diagnosis (>60 years) was an independent predictor of CSS in older patients and there was a continuing increase in risk of cancer-related death for those aged >60 years. However, advanced age at diagnosis was not an independent predictor of DFS or disease recurrence. Therefore, another age cut-off might be justifiable for stratifying risk of cancer-related death and less so for disease recurrence in older patients with PTC. Tumor size, central and lateral nodal metastases independently predicted CSS and DFS in older patients.

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Table 1. Clinicopathological factors and treatments predictive of cancer-specific survival

	Number of patients (n=407)	Number of cancer-related deaths (n=51)	Cancer-specific survival (%)			p-value*
			5-year	10-year	15-year	
Age at diagnosis						**<0.001**
- 45 – 60 years	224 (55.0)	11 (21.6)	99.1	97.5	97.5	
- >60 years	183 (45.0)	40 (78.4)	94.5	89.0	86.2	
Sex						0.712
- Male	109 (26.8)	14 (27.5)	98.2	93.0	91.7	
- Female	298 (73.2)	37 (72.5)	96.6	93.9	92.2	
Study period						0.788
- ≤ 1990	110 (27.0)	30 (58.8)	97.2	92.7	91.7	
- 1991 – 2000	125 (30.7)	13 (25.5)	96.0	93.6	91.2	
- ≥ 2001	172 (42.3)	8 (15.7)	97.7	96.5	96.5	
Preoperative ultrasound						0.106
- Not done	154 (37.8)	33 (64.7)	97.4	93.8	91.4	
- Done	253 (62.2)	18 (35.3)	96.8	93.6	93.6	
Tumor size						**0.003**
- ≤ 4cm	346 (85.0)	34 (66.7)	97.9	95.5	93.8	

-> 4cm	61 (15.0)	17 (33.3)	91.5	84.4	82.6	
Tumor multifocality						**0.046**
- Absent	276 (67.8)	29 (56.9)	97.0	94.5	93.2	
- Present	131 (32.2)	22 (43.1)	96.9	92.4	88.2	
Extrathyroidal extension						**<0.001**
- Absent	243 (59.7)	15 (29.4)	99.6	97.5	95.8	
- Present	164 (40.3)	36 (70.6)	93.7	88.2	86.5	
Nodal status#						**<0.001**
- None (N0/Nx)	247 (60.7)	18 (35.3)	98.7	98.3	96.0	
- N1a	45 (11.1)	2 (3.9)	100.0	97.2	97.2	
- N1b	115 (28.3)	31 (60.8)	91.9	81.8	80.6	
Distant metastases on presentation						**<0.001**
- Absent	391 (96.1)	42 (82.4)	97.1	94.6	92.9	
- Present	16 (3.9)	9 (17.6)	93.8	64.8	64.8	
Completeness of resection						**<0.001**
- Complete	367 (90.2)	35 (68.6)	98.1	94.9	93.4	
- Incomplete	40 (9.8)	16 (31.4)	87.2	81.4	78.5	
Radioiodine ablation						0.304

- Not given	151 (37.1)	19 (37.3)	96.7	94.4	94.4	
- Given	256 (62.9)	32 (62.7)	97.3	93.2	90.5	
External radiation therapy						**<0.001**
- Not given	351 (86.2)	34 (66.7)	97.7	95.7	94.5	
- Given	56 (13.8)	17 (33.3)	92.7	81.5	77.5	

Categorical variables are expressed as number (percentage)

*using Log-rank test

#by 7th edition *TNM* staging system

Table 2. A multivariate analysis of clinicopathological risk factors for cancer-specific survival

Covariates	ß-coefficient	Hazard ratio (95% confidence interval)	*p*-value
Age at diagnosis^			**0.006**
- 45 – 60 years		1	
- >60 years	1.107	3.027 (1.369 – 6.690)	
Tumor size+			**0.049**
- ≤ 4cm		1	
- > 4cm	0.281	2.043 (1.141 – 4.255)	
Tumor multifocality			0.357
- Absent		1	
- Present	0.294	1.342 (0.718 – 2.506)	
Extrathyroidal extension			0.394
- Absent		1	
- Present	0.335	1.398 (0.647 – 3.022)	
Nodal status#			
- None (N0/Nx)		1	
- N1a	1.003	2.726 (1.198 – 6.200)	**0.017**
- N1b	1.658	5.247 (2.987 – 9.216)	**<0.001**
DM on presentation			**0.002**
- Absent		1	
- Present	1.458	4.297 (1.726 – 2.506)	
Completeness of resection			0.389
- Complete		1	
- Incomplete	0.227	1.255 (0.586 – 2.689)	
External radiation therapy			0.172

- Not given		1	
- Given	0.531	1.701 (0.794 – 3.641)	

DM = distant metastases

#based on 7th edition *TNM* staging system

+when tumor size was entered as a continuous variable, HR (95%CI) became 1.184 (1.035 – 1.354), p=0.014

^when age was entered as a continuous variable, HR (95%CI) became 1.061 (1.027 – 1.095), p<0.001

Table 3. Clinicopathological factors and treatment predictive of disease-free survival^

	Number of patients (n=391)	Number of persistent/recurrent diseases (n=80)	Disease-free survival (%)			*p*-value*
			5-year	10-year	15-year	
Age at diagnosis						**0.015**
- 45 – 60 years	222 (56.8)	37 (46.3)	88.8	84.3	81.5	
- >60 years	169 (43.2)	43 (53.8)	83.6	74.6	73.4	
Sex						**<0.001**
- Male	104 (26.6)	33 (41.3)	78.9	68.8	65.6	
- Female	287 (73.4)	47 (58.8)	89.3	83.9	82.3	
Study period						**0.027**
- ≤ 1990	104 (26.6)	30 (37.5)	82.7	74.5	71.8	
- 1991 – 2000	123 (31.5)	30 (37.5)	85.6	76.8	75.2	
- ≥ 2001	164 (41.9)	20 (25.0)	89.5	86.4	86.4	
Preoperative ultrasound						**0.006**
- Not done	148 (37.9)	42 (52.5)	81.1	74.7	72.0	
- Done	243 (62.1)	38 (47.5)	90.0	84.8	84.8	
Tumor size						**<0.001**
- ≤ 4cm	332 (84.9)	57 (71.3)	88.9	84.1	82.0	

- > 4cm	59 (15.1)	23 (28.8)	74.6	62.6	60.2	
Tumor multifocality						0.299
- Absent	268 (68.5)	51 (63.8)	88.5	82.3	79.3	
- Present	123 (31.5)	29 (36.3)	82.0	76.3	76.3	
Extrathyroidal extension						**<0.001**
- Absent	240 (61.4)	32 (40.0)	91.5	87.7	85.6	
- Present	151 (38.6)	48 (60.0)	80.0	70.4	68.4	
Nodal status						**<0.001**
- None (N0/Nx)	243 (62.1)	21 (26.3)	95.8	93.1	91.0	
- N1a	44 (11.3)	12 (15.0)	79.5	74.4	74.4	
- N1b	104 (26.6)	47 (58.8)	70.3	56.3	53.1	
Completeness of resection						**0.002**
- Complete	358 (91.6)	67 (83.8)	89.0	83.0	80.5	
- Incomplete	33 (8.4)	13 (16.3)	66.7	60.5	60.5	
Radioiodine ablation						**0.011**
- None	151 (38.6)	21 (26.3)	91.0	88.2	86.1	
- Given	240 (61.4)	59 (73.8)	85.0	76.5	74.5	
External radiation therapy						**0.004**

- None	337 (86.2)	61 (76.3)	88.7	83.2	81.1	
- Given	54 (13.8)	19 (23.8)	77.8	66.5	64.4	

Categorical variables are expressed as number (percentage)

*using Log-rank test

^ patients presenting with distant metastases were excluded from analysis

Table 4. A multivariate analysis of clinicopathological risk factors for disease-free survival

Covariates	ß-coefficient	Hazard ratio (95% confidence interval)	*p*-value
Age at diagnosis^			0.800
- 45 – 60 years		1	
- >60 years	0.066	1.068 (0.643 – 1.773)	
Sex			0.137
- Male		1	
- Female	0.386	0.680 (0.409 – 1.131)	
Study period			0.143
- ≤ 1990		1	
- 1991 – 2000	0.189	0.827 (0.461 – 1.486)	
- ≥ 2001	0.514	0.598 (0.301 – 1.190)	
Preoperative ultrasound			0.664
- Not done		1	
- Done	0.419	0.664 (0.387 – 1.140)	
Tumor size+			**0.049**
- ≤4cm		1	
- >4cm	0.550	1.733 (1.030 – 3.058)	
Extrathyroidal extension			0.313
- Absent		1	
- Present	0.292	1.339 (0.760 – 2.360)	
Nodal status#			
- None (N0/Nx)		1	
- N1a	0.859	2.362 (1.010 – 5.523)	**0.047**
- N1b	1.478	4.383 (2.388 – 8.042)	**<0.001**

Completeness of resection			0.389
- Complete		1	
- Incomplete	0.281	1.325 (0.698 – 2.514)	
Radioiodine ablation			0.385
- None		1	
- Given	0.256	1.292 (0.725 – 2.301)	
External radiation therapy			0.869
- None		1	
- Given	0.054	1.056 (0.554 – 2.014)	

#based on 7th edition *TNM* staging system

+when tumor size was entered as a continuous variable, HR (95%CI) became 1.203 (1.077 – 1.343), *p* =0.001.

^when age was entered as a continuous variable, HR (95%CI) became 1.005 (0.983 – 1.027), *p*=0.763.
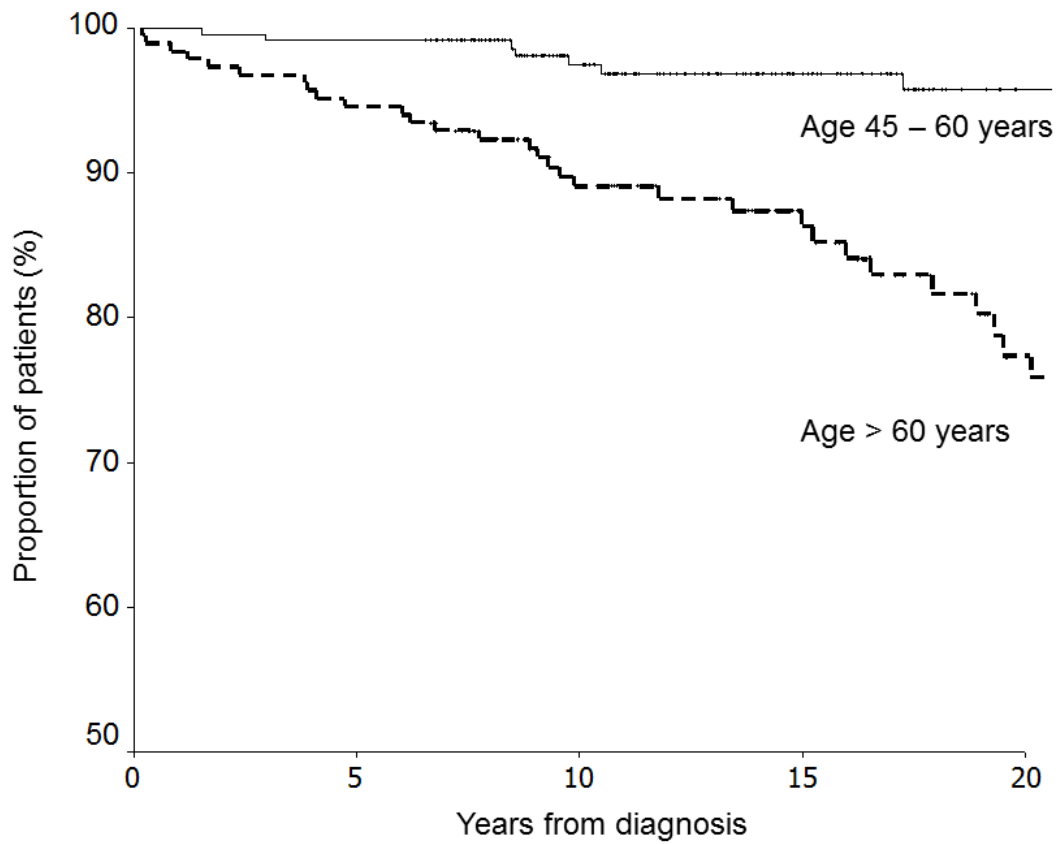
Figure 1a. Cumulative disease-specific survival curves of papillary thyroid carcinoma between those aged 45 – 60 years (n=224) and those aged > 60 years (n=183).
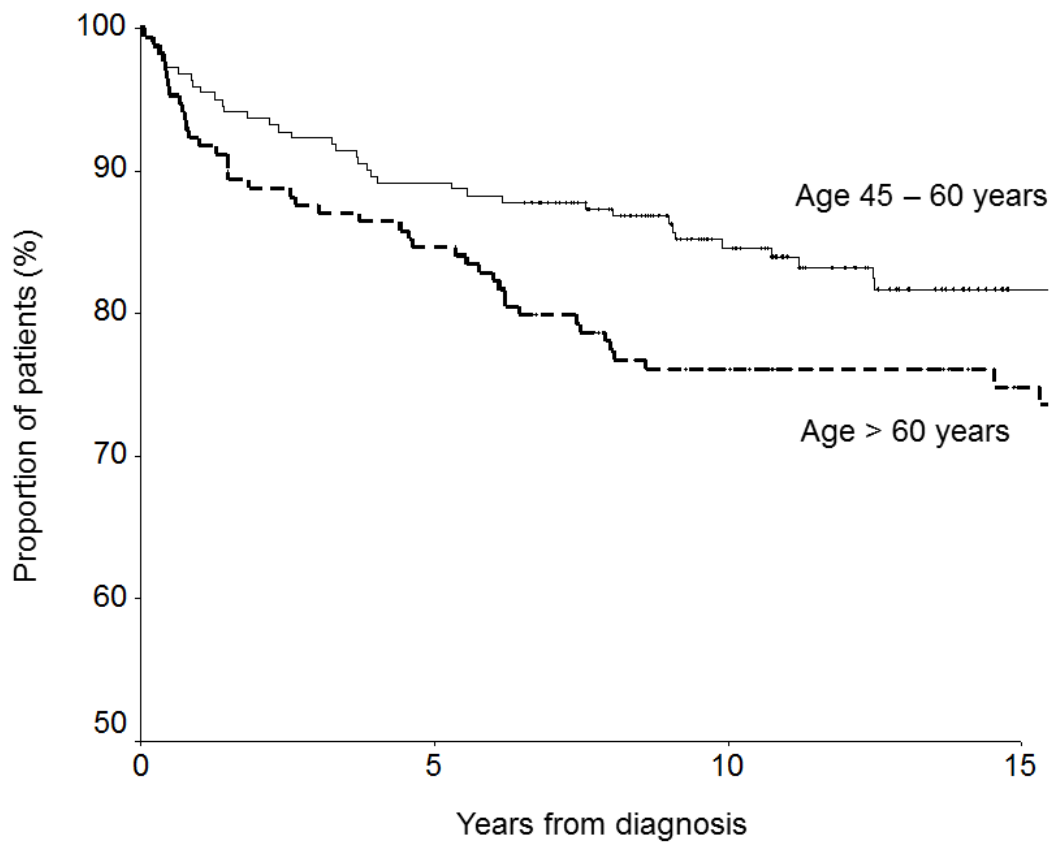
Figure 1b. Cumulative disease-free survival curves of papillary thyroid carcinoma between those aged 45 – 60 years (n=222) and those aged > 60 years (n=169). Those 16 patients presenting with distant metastases were excluded.