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Natural history of papillary thyroid microcarcinoma: Kinetic analyses on tumor volume during active surveillance and before presentation ☆

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ABSTRACT

Background: We report on the growth of papillary microcarcinoma during active surveillance and before clinical presentation.

Methods: We conducted a retrospective study of 169 patients with papillary microcarcinoma who were enrolled in active surveillance at our hospital between 2000 and 2004. Patients were followed for a median of 10.1 years using serial ultrasonography (median, 12 examinations), used to calculate the tumor doubling time. To contextualize tumor growth rates during active surveillance, we calculated the hypothetical tumor doubling time before clinical presentation. To resolve the limitations in tumor doubling time, tumor doubling rates were inversely transformed into doubling rates.

Results: The doubling rates (per year) during active surveillance (median: 0.0) were >0.5, 0.1 to 0.5, −0.1 to 0.1, and <−0.1 in 5, 38, 97, and 29 cases, respectively. The proportions of tumors with rather rapid growth, slow growth, stable, and a decrease in size were 3%, 22%, 57%, and 17%, respectively.

Conclusion: Tumor growth of papillary microcarcinomas varies from rather rapid growth to a decrease in size during active surveillance.

Introduction

The incidence of thyroid cancer has increased in many countries in recent decades without an associated increase in mortality.[1–3] The increase primarily has been due to the increased detection of small papillary thyroid carcinoma (PTC) with imaging studies. Several research groups[1–3] have suggested an overdiagnosis and overtreatment of small PTCs. PTCs ≤1 cm are called papillary microcarcinomas (PMCs) of the thyroid, which account for approximately 50% of the recent thyroid cancer cases.[2,3] Previously, we reported that only a small proportion of patients with low-risk PMCs exhibited disease progression during active surveillance (AS), as did another Japanese study.[4,5] In addition, those PMCs exhibiting disease progression were treated successfully with rescue surgery without further disease progression.[4–6] Given the safety of AS, the 2015 guidelines of the American Thyroid Association [7] endorse AS as an alternative to thyroidectomy in patients with low-risk PMCs.[7] AS is superior to immediate operative treatment because of the greater incidence of adverse events and the 4.1-fold increase in medical costs that result from operative intervention at this stage.[8,9]

In a previous study,[10] we determined that only 8% of low-risk PMCs enlarged >3 mm in size at 10-year AS. This increase in size was strongly associated with a younger age at presentation. Tuttle et al.[11] studied tumor growth kinetics on 291 patients with PTCs ≤1.5 cm who underwent AS for a median of 25 months. The cumulative incidence of a tumor growth of >3 mm was 3.8% at 5 years, which was comparable to the Japanese reports.[5,10] Tumor volumes were calculated using 3-dimensional measurements. The cumulative incidence of volume increase by >50% was 24.8% at 5 years.

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Table 1
Characteristics of 169 adult patients with low-risk PMC who were enrolled in AS from January 2000 to December 2004 at Kuma Hospital.

Variable	Total	Retained in AS	Conversion to surgery
No. of patients	169	146	23
Age at diagnosis (years)	55 (24–79)	56 (24–79)	54 (29–65)
Sex, no. (%)			
Female	150 (89)	130 (89)	20 (87)
Male	19 (11)	16 (11)	3 (13)
Tumor size (mm)*	7 (3–10)	7 (3–10)	7 (4–10)
Duration of AS (years)*	10.1 (1.57–13.5)	10.5 (1.57–13.5)	4.2 (1.71–108)
No. of ultrasonographic examinations*	12 (3–26)	13 (3–26)	8 (5–21)
Tumor size increase ≥3 mm	7	0	7
Appearance of LN¶ met.	2	0	2
Tumor doubling time (year)			
Positive value, no.	85 (50.3%)	70 (48%)	15 (65%)
Value*	9.98 (0.75 ≥ 100)	12.8 (0.79 ≥ 100)	3.34 (0.75–146)
Negative value, no.	84 (49.7%)	76 (52%)	8 (35%)
Value*	−15.5 (>−100 to −0.08)	−17.5 (>−100 to −0.08)	−2.69 (−16.3 to −1.77)
Doubling rate per year†	0.00 (−12.8 to 1.32)	−0.01 (−12.8 to 1.27)	0.064 (−0.566 to 1.33)
Death	1	0	1

Note: The doubling rate is defined as the inversion of the TDT (ie, 1/TDT); the 1 death was a result of pancreatic cancer
* Median (range)
¶ *LN met*., lymph node metastasis

The median tumor doubling time (TDT) was 2.2 years. The decrease in volume of the tumor by >50% was reported in 6.5% of patients, although this was not discussed in detail.

The tumor decreased in size in some of our patients with PMCs during AS.[4] Tumor growth is best analyzed and expressed as TDT[12]; however, TDT has 2 major limitations. Therefore, we propose the "doubling rate," which is the inverse of TDT. Tumor growth before presentation is unknown. Herein, we estimated tumor growth before presentation using a hypothesis described in the Discussion of the present article.

The aim of this study was to examine the natural history of PMCs by comparing the observed growth rates with the estimated values before presentation.

Patients and methods

Between January 2000 and December 2004, 169 consecutive patients (aged 24–79 years) with low-risk PMC were enrolled in our program of AS at our hospital.

Tumor size at presentation ranged from 3 mm to 10 mm (median: 7 mm). All of the patients had a malignant diagnosis on ultrasound-guided fine-needle aspiration cytology. None of them had worrisome features, such as nodal or distant metastasis, substantial extrathyroidal extension, or aggressive cytology. Patients with tumors attached to the trachea or located along the course of the recurrent laryngeal nerve were excluded. Since 1993, patients with low-risk PMCs have been informed of the following 2 management options: (1) immediate operative intervention or (2) AS.[6] The patients included in this study chose to proceed with AS. Patients were followed for a median of 10.1 (range: 1.57–13.5) years using serial ultrasonographic examinations (median, 12 [range, 3–26] examinations; Table 1). Ultrasonographic examinations were performed 6 months after the diagnosis and approximately once a year thereafter by sonographers trained specifically in neck ultrasonography. If the tumor increased by ≥3 mm or lymph node metastasis occurred, rescue surgery was recommended.

TDT was calculated based on serial measurements of tumor size. The maximum diameter (D_1) and the diameter in the direction perpendicular to the maximum diameter (D_2) were measured. Tumor depth was often not reliable because of ultrasound shadowing. Tumor volume (V) was calculated using the ellipsoid equation ($\pi/6 \times D_1 \times {D_2}^2$).[13] Time (T) is the time interval between presentation and measurement. TDT was calculated as previously described.[14]

$$a = \left(n\sum_{k=1}^{n} T_k \times \log(V_k) - \sum_{k=1}^{n} T_k \times \sum_{k=1}^{n} \log(V_k) \right) \Big/ \left(\sum_{k=1}^{n} {T^2}_k - \left(\sum_{k=1}^{n} T_k \right)^2 \right)$$

Then, TDT = (log 2)/α. This can easily be performed using the Doubling Time & Progression Calculator (available from: http://www.kuma-h.or.jp/english/). The tumor in 1 patient became undetectable during AS. The size of the tumor was considered to be 1 mm for the calculation.

Some of the PMCs had negative TDTs, because they exhibited a decrease in size. Although TDT is a valid method to describe tumor growth rate, there is the issue of discontinuity among positive and negative TDT values. To address this problem, doubling time (DT) was converted to the inverse of DT (ie, 1/DT) as suggested by Barbet et al.[12] We propose calling this value "doubling rate" because it means the number of doublings that occur in a unit time (eg, per year). Negative values indicated the number of halvings per unit time.

Statistical analysis

The statistical tests used to compare the differences between the groups were the Mann-Whitney U test for skewed variables and the Wilcoxon signed-rank test for paired skewed variables. All statistical analyses were conducted using StatFlex version 6.0.

The present study was approved by the Ethical Committee at Kuma Hospital.

Results

After enrollment, 23 (14%) of the 169 patients subsequently underwent conversion to operative resection (Table 1). Reasons for the operative intervention included tumor enlargement ≥3 mm in 7 patients, recognition of presumed lymph node metastasis in 2, enlargement of associated nodules in 2, Graves' disease in 1, and changes in patient preference in 1. The reason for operative intervention was unknown in 10 patients. None of the patients had both tumor enlargement and nodal metastasis. One patient died of pancreatic cancer 3.5 years after thyroid surgery.

Table 2
Doubling rate in 146 patients retained in active surveillance and among 23 patients who had conversion to operative intervention.

Patients group	No. of patients	Doubling rate per year			
		>0.5 Rather rapid growth	0.1–0.5 Slow growth	−0.1 to 0.1 Stable	<−0.1 Decrease in size
Retained in AS	146	1 (1%)	31 (21%)	89 (61%)	25 (17%)
Conversion to operative intervention	23	4 (17%)	7 (30%)	8 (35%)	4 (17%)
All patients	169	5 (3%)	38 (22%)	97 (57%)	29 (17%)

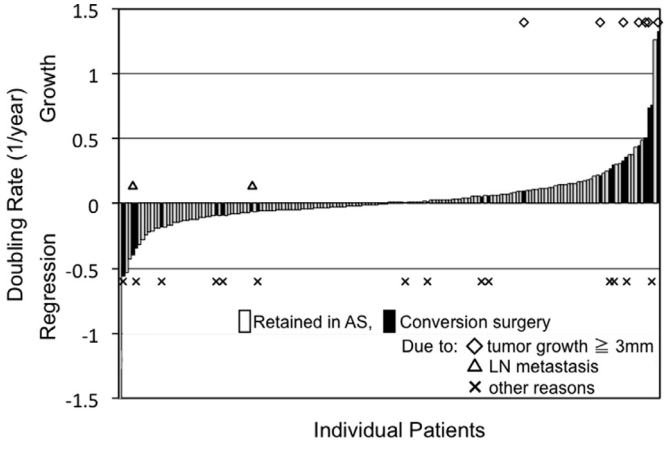

Fig. 1. Doubling rates indicating tumor growth (positive values) or a decrease in size (negative values) during active surveillance (AS) for each patient; clear columns represent patients retained in AS; solid columns and + indicate patients who underwent conversion from AS to operative intervention. LN, lymph node.

A total of 85 patients (50.3%) had positive TDTs that varied greatly (median, 10.0 years), whereas 84 patients (49.7%) had negative TDTs that also varied greatly (median, −15.5 years; Table 1).

Doubling rates during AS for each patient ranged from −12.8 to 1.32 (median, 0.0) per year (Table 1). Using doubling rates, the tumor volume kinetics of all patients are shown in Fig. 1. This figure also shows patients who remained in AS and those who underwent operative intervention owing to tumor growth ≥3 mm, nodal metastasis, or other reasons. Tumor volume kinetics were divided into 4 categories: rather rapid growth, slow growth, stable, and decrease in size, using cutoffs for doubling rates of 0.5, 0.1, and −0.1 per year. Doubling rates were >0.5, 0.1 to 0.5, −0.1 to 0.1, and <−0.1 for 5, 38, 97, and 29 PMCs, respectively (Table 2). Thus, only 3% of PMCs exhibited rather rapid growth, 22% exhibited slow growth, 57% were stable, and 17% exhibited decrease in size. Because their tumors increased ≥3 mm, 4 of 5 patients with rather rapid growing tumors and 3 of 38 patients with slowly growing tumors underwent operative intervention. The 2 patients with nodal metastases were either stable or had exhibited a decrease in size of the primary tumor. Patients who underwent operative intervention for other reasons had varying doubling rates (Fig. 1).

Doubling rates according to age at presentation (≤40, 41–60, and >60 years) are shown in Table 3 and Fig. 2. The proportion of the patients with rather rapidly growing or slowly growing tumors decreased with age (40% to 17%; $P = .019$); however, 5 rather rapidly growing tumors were seen in middle-aged or elderly patients. Tumors that decreased in size were the most frequently observed in the middle-aged group (21%). Thus, tumor growth patterns differed considerably among the 3 age groups.

Discussion

We reported a greater incidence of PMC progression during AS in younger patients at presentation.[10] Tuttle et al.[11] conducted AS

Table 3
Doubling rate during AS according to age at presentation.

Age, year	No. of patients	Doubling rate per year			
		>0.5	0.1–0.5	−0.1 to 0.1	<−0.1
≤40	20	0 (0%)	8 (40%)	9 (45%)	3 (15%)
41–60	87	4 (5%)	21 (24%)	44 (51%)	18 (21%)
≥61	62	1 (2%)	9 (15%)	44 (71%)	8 (13%)
All patients	169	5 (3%)	38 (22%)	97 (57%)	29 (17%)

Note: When the doubling rates of >0.5 and 0.1–0.5 are combined as growing tumors and doubling rates of −0.1 to 0.1 and <−0.1 are combined as tumors that are stable in size or are decreasing in size, the proportion of the patients with growing tumors decreased with age from 40% to 17% ($P = .019$).

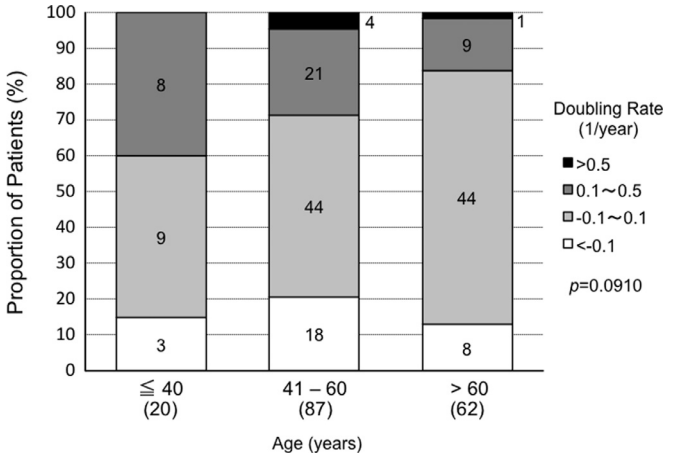

Fig. 2. Proportions of patients with a doubling rate of >0.5, 0.1 to 0.5, <−0.1 to 0.1, and <−0.1 according to age at presentation; figures indicate number of patients in each category; when the doubling rates of >0.5 and 0.1 to 0.5 are combined as growing tumors and doubling rates of −0.1 to 0.1 and <-0.1 are combined as tumors that are stable in size or are decreasing in size, the proportion of the patients with growing tumors decreased with age from 40% to 17% ($P = .019$).

in 291 patients with PTCs ≤1.5 cm and confirmed an association between tumor growth and a young age at presentation. These authors reported an increase in tumor volume of >50% in 36 patients. These PTCs had a median TDT of 2.2 years. TDTs for stable tumors or those that decreased in size were not reported.

Collins et al.[12] postulated that the growth of human tumors is exponential and suggested that tumor growth rate is best described as TDT. Previous studies[14–16] reporting time-dependent changes in serum calcitonin and thyroglobulin in patients with medullary and papillary thyroid carcinoma and the TDT of these values support this concept. Thus, doubling time is a validated method to analyze and express tumor growth. Despite its strengths, TDT has 2 major limitations. First, if some tumors exhibit a decrease in tumor volume (Fig. 3, *A*), their TDTs are expressed as negative values, which causes discontinuity, as shown in Fig. 3, *B*. To address this, Barbet et al.[15] used 1/TDT values for statistical analysis. Second, the magnitude of the TDT values is opposite to the magnitude of tumor growth or decrease in size (Fig. 3, *B*). The 1/TDT equation appears to overcome these limitations

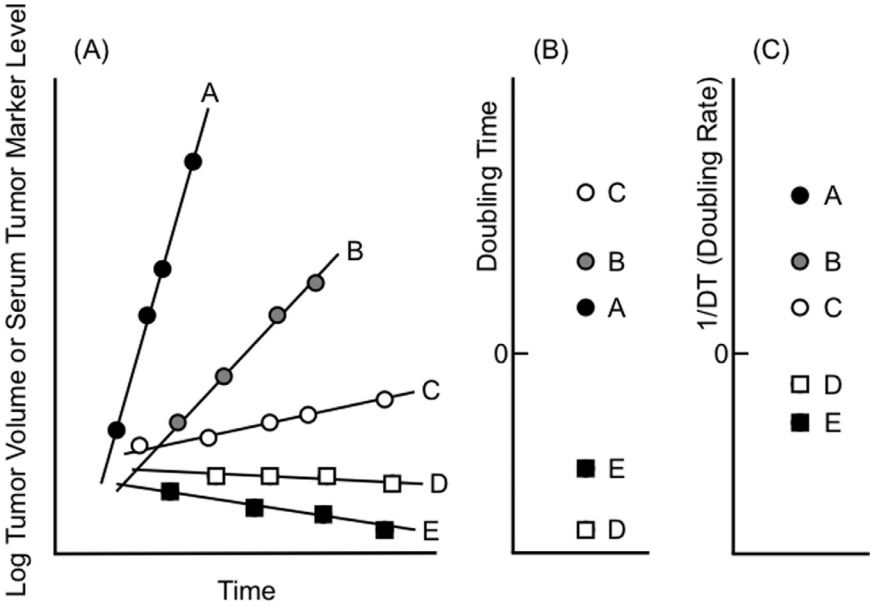

Fig. 3. Kinetic analysis of changes over time in tumor volume or levels of serum tumor marker. (*A*) Slopes for the regression analysis of the 5 sets of sample data. (*B*) Doubling times. (*C*) Doubling rates (the inverse of the doubling time [ie, 1/doubling time]). Note the orders and magnitudes of the values of the 5 sample cases in these 3 analyses.

satisfactorily (Fig. 3, *C*). We propose calling this value the doubling rate because it indicates the number of doublings or halvings that occur per unit of time. Using doubling rates, we were able to show tumor growth and decreases in size in 1 figure (Fig. 1).

As for the future of the natural history of PMCs, we have estimated the lifetime probability of PMC disease progression using age–decade-specific disease progression rates at 10 years obtained from our AS data.[17] Our estimates suggested that the probability of disease progression greatly decreases with age at presentation.

We also calculated the hypothetical TDT, an estimate of TDT before presentation, using age and tumor size at presentation, assuming that a single cancer cell (10 μm in diameter) was present at birth and grew at a constant rate, and thus predicted what the actual time of the origin of the tumor should be after birth. Therefore, the actual growth rate should be more rapid than the estimate. One might argue that the growth of the tumor may not have been constant; however, if there were slow growth periods, there should have also been rapid growth periods for the tumor to grow to the size at presentation. Therefore, the hypothetical TDT indicates the least tumor growth rate before presentation necessary for a cancer cell to grow to the size at presentation.

Estimated doubling rates before presentation (converted from the inverse of the hypothetical TDTs) ranged from 0.4 to 1.1 (median, 0.5) per year, which were greater than those observed during AS (median, 0.0 [range, −12.8–1.32]; Fig. 4; $P < .001$). This hypothetical argument suggests strongly that a rapid growth phase precedes presentation in the vast majority of cases.

Figure 5 is a schematic depicting the observed range of tumor growth and regression (line A) and the hypothetical growth of cancer arising at birth (line B). If the cancer arises after birth, tumor growth should be more rapid (line C). Tumor growth in the prepresentation period (close to presentation) should not be much different from the observed growth rate. Therefore, there should have been a period when the tumor grew more rapidly (line D). We think line D a most likely tumor growth pattern before presentation.

Mazzaferri et al.[18] reported that PTCs showed a unique biologic behavior associated with age at the time of operation. Younger patients had greater recurrence rates but excellent survival. Elderly

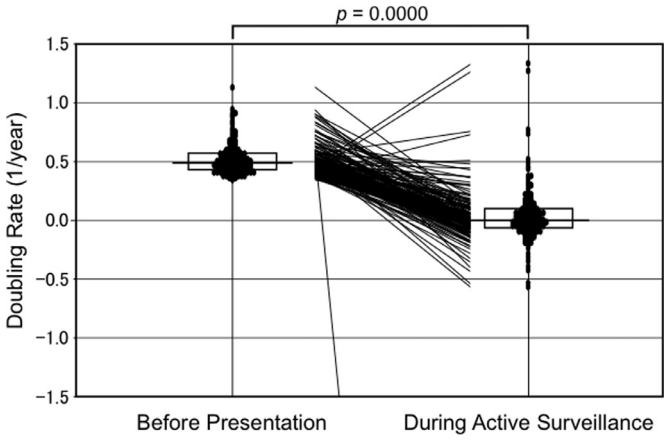

Fig. 4. Comparison of the doubling rate during active surveillance and the doubling rate converted from the hypothetical doubling time before presentation in each patient. *Solid circles* indicate the values. The changes in these values are represented by the lines. The boxes in the box-and-whisker plots represent the second and the third quartiles.

patients had greater recurrence and greater mortality rates. The reasons for these conflicting findings in younger patients with PTC are not clear. The natural history of PMCs described in this paper may be applicable to some clinical PTCs, especially in younger patients; however, further studies are needed to confirm this association.

Our study has several limitations. First, this is a retrospective analysis of the changes in the sizes of PMCs during AS. Second, ultrasonographic evaluations were performed by multiple examiners over a long period of time. Therefore, interobserver variations may have existed in the measurements, but the multiple examinations (median, 12 examinations) over a long period of time (median, 10.1 years) for each patient should have minimized the error in calculating TDTs. Finally, we selected 169 consecutive patients to minimize the selection bias of patients; however, larger cohorts of

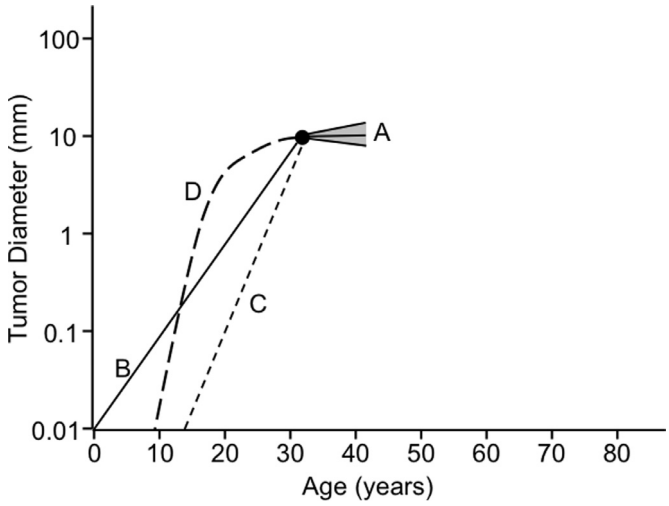

Fig. 5. Comparison of the hypothetical tumor volume doubling time and the most likely growth curve before presentation with the observed growth or decrease in size of PMCs during active surveillance. *Solid circle*, at presentation. (*A*) Range of the observed tumor growth or decrease in size. (*B*) The growth line to calculate the hypothetical tumor doubling time. (*C*) Growth line of a tumor with an origin after birth. (*D*) The most likely growth curve before presentation.

patients with PMCs and longer surveillance times may allow for a more detailed analysis.

Conclusion

According to our novel calculation of doubling rate, only 3% of tumors reported in this study of 169 consecutive patients exhibited rather rapid growth, whereas 22%, 57%, and 17% exhibited slow growth, stable disease, and a decrease in size, respectively, during AS. The estimated doubling rates before presentation converted from a hypothetical TDT were significantly greater than the doubling rates calculated during AS, suggesting that there is a rapid growth period before presentation.

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Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Discussion

Dr Ashok R Shaha (New York, NY): Dr Miyauchi, I would like to congratulate you and your institution for doing remarkable work and pioneering the whole idea about observation more than 20 years ago. Every time you present here, you bring some new information, which is quite interesting and quite complex also.

I am interested in regression of the thyroid tumors. At least we generally feel that tumors don't get smaller, and that's the whole idea of monitoring the patient and seeing what happens. Is this regression related to needle biopsy causing some infarction? Or did it become bigger because during the needle biopsy there was some bleeding and it appeared to measure 1 centimeter, and over a period of time it resolved to 5 millimeters? I am just curious to know about this.

The understanding of the tumor volume is very critical. It's not just the diameter. Dr Mike Tuttle, who you know very well, and our group did the study looking at the tumor volume and the tumor doubling time, which I think you have popularized in medullary cancer, thyroid cancer, and now in active surveillance.

Rather than using the words "active surveillance," it may be a good idea to use the term "before intervention." What we are

really trying to do is defer the intervention. At the age of 25, we know that probably the patient will come to surgery. Again, this is just a philosophy, but something that I have been thinking about. Perhaps what we are doing today is deferring the intervention, monitoring the patient, and operating at an appropriate time. Thank you very much.

Dr Akira Miyauchi: Thank you, Dr Shaha. Very nice comment and question.

I do not know the reason why a tumor may show shrinkage. One possibility might be the fine-needle aspiration. That is very likely 1 of the possibilities. But I think it may be a natural cause too.

You commented on Michael Tuttle. He did a very similar study on changing tumor volume. If you read his paper carefully, you see that it included some tumor shrinkage. So that is not only our own cases but some of your cases at Memorial Sloan-Kettering also showed tumor shrinkage.

Dr Larry Kim (Chapel Hill, NC): I also want to thank you for the work you have done showing that active surveillance again is safe. It's really revolutionary.

Your hypothesis is that there's this period of rapid growth and then stabilization, and sometimes even shrinkage. That really flies in the face of what we intuitively think about tumor growth as sort of a constant doubling. My first question is whether you have any sort of biological hypothesis to explain this?

And then my second question is why don't we catch these tumors during that growth phase more commonly? It seems like sometimes you would catch them during that rapid growth phase more often.

Dr Akira Miyauchi: Thank you for your comment and questions. Why do tumors show shrinkage? I do not know. But this is our observation. Our work shows that tumor growth deceleration and shrinkage is a real phenomenon, at least for papillary micro cancer. But thyroid cancer might show a similar phenomenon. Of course, we do not have many chances to observe the natural course of a larger tumor, but probably the same thing may occur.

Dr Quan-Yang Duh (San Francisco, CA): Dr Miyauchi, you always teach us something when you are on the podium. Thank you very much for presenting this.

You are the one that taught us about doubling time. And we learned that most of the time it is constant. But you are also the one that taught us that when we follow the patient, if the doubling time changes, that means something. If it's shortened, you know something happened to the tumor. And one would expect that's probably related to some mutation or something that occurred.

So if you consider growth, like you say, before you find the tumor, and you are not proposing that there is also some kind of dynamic changes in doubling time, do you have some hypothesis of what it is that changes the tumor doubling time?

Dr Akira Miyauchi: When we observed the changing tumor size or tumor marker trend, we saw that some cases showed rapid increase in the growth rate. That can be seen in papillary cancer and also medullary thyroid cancer.

Typically, this is very easy to understand if it is a change in differentiation or anaplastic change. But at the same time, we see decreasing growth rate after more than 5 or 10 years in some. That is another issue. But I do not know why it occurs.

Dr Quan-Yang Duh (San Francisco, CA): Do you think the potential regression could be related to the vascular supply of the tumor?

Dr Akira Miyauchi: Well, I think these questions remain for you to study.

Dr Sareh Parangi (Boston, MA): Dr Miyauchi, we are really grateful that you come here to AAES to present this work.

I have a question about what your experience is now with the screening of children after the Fukushima disaster in Japan. Do you think we will have an opportunity to answer some of your wonderful theories in those being studied?

Dr Akira Miyauchi: Today I talked about the only adult patients. Probably small papillary thyroid cancers in children might be different. My speculation is that in children it might show rather rapid growth but it will stop. Why in children does papillary thyroid cancer have a good prognosis?

Most of the childhood thyroid cancer tends to have distant metastasis at presentation. But they rarely die. Why? Probably it stops growing spontaneously. Rapid growth—but then stops. This is my speculation.