Surgery ■■ (2017) ■■–■■

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/ymsy

American Association of Endocrine Surgeons

Estimation of the lifetime probability of disease progression of papillary microcarcinoma of the thyroid during active surveillance

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ARTICLE INFO

Article history:
Accepted 21 March 2017

Background. We reported that a minority of patients with low-risk papillary microcarcinoma of the thyroid showed disease progression during active surveillance and that older patients had significantly lower disease progression rates than younger patients. Here, we estimated lifetime (≤85 years old) probabilities of disease progression during active surveillance according to the age at presentation based on age decade-specific disease progression rates.

Methods. From 1993–2013, 1,211 low-risk papillary microcarcinoma patients aged 20–79 years underwent active surveillance at Kuma Hospital. We calculated the disease progression rate at the 10-year point of active surveillance for each age-decade group (20s to 70s) with the Kaplan-Meier method. The lifetime disease progression probability for each age group was calculated as (1 – cumulative probability of progression-free survival calculated with age decade-specific disease progression rates) until the patients reached their 80s (i.e., 85 years on average).

Results. The age decade-specific disease progression rates at 10 years of active surveillance were 36.9% (20s), 13.5% (30s), 14.5% (40s), 5.6% (50s), 6.6% (60s), and 3.5% (70s); the respective lifetime disease progression probabilities were 60.3%, 37.1%, 27.3%, 14.9%, 9.9% and 3.5% according to the age at presentation.

Conclusion. The estimated lifetime disease progression probabilities of papillary microcarcinoma during active surveillance vary greatly according to the age at presentation. (Surgery 2017;160:XXX-XXX.)

Papillary thyroid cancer (PTC) accounts for ≈90% of all thyroid cancers. The incidence of PTCs <2 cm in size was reported to be disproportionately increased compared with larger PTCs and other types of thyroid cancer, without an increase in mortality from thyroid cancer.[1,2] Several research groups have thus suggested that there has been an overdiagnosis and overtreatment of small PTCs.[1-3] The question of how to manage patients with small PTCs has therefore become a major clinical issue.

PTCs that are ≤1 cm are called papillary microcarcinomas (PMCs) of the thyroid. In 1993 we proposed and initiated an active surveillance trial for patients with low-risk PMCs without worrisome features. We observed that only a small minority of the patients at our institution (Kuma Hospital in Kobe, Japan) showed disease progression and that these patients were successfully treated with a rescue surgery without mortality from thyroid cancer.[4-6] The cancer Institute Hospital in Tokyo started a similar trial 2 years after the start of our trial, and they reported similar promising data.[7] Given the safety of the active surveillance management of low-risk PMCs, the 2015 American Thyroid Association (ATA) guidelines made 2 major changes.[8] They decided to no longer require a fine-needle aspiration biopsy for thyroid nodules ≤1 cm even if the nodules show suspicious ultrasound features, unless they are associated with obvious aggressive features.[8] The ATA guidelines also now acknowledge that "an active surveillance management approach can be considered as an alternative to immediate surgery" in patients with low-risk PMCs.[8]

We reported that at the 10-year point of active surveillance, 8% and 3.8% of our patients with low-risk PMCs showed tumor enlargement by ≥3 mm and a novel appearance of nodal metastasis, respectively.[5] If these rates remain constant over time, as many as 32% and 15.2% of the patients would show tumor enlargement and nodal metastasis after 40 years of active surveillance, respectively. However, we showed that the disease progression rates are significantly lower in older patients than in younger patients,[5] and thus

Presented at the 37th annual meeting of the American Association of Endocrine Surgeons from April 2–4, 2017, Orlando, FL.

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https://doi.org/10.1016/j.surg.2017.03.028

the risk of disease progression would decrease over time. Here, we estimated the lifetime (≤85 years old) probabilities of disease progression during active surveillance according to the patients' age at presentation based on age decade-specific disease progression rates.

Patients and Methods

From January 1993 to December 2011, 1,211 patients who were evaluated as having low-risk PMCs at Kuma Hospital, Japan, chose active surveillance as the alternative to immediate surgery. All had a malignant diagnosis on ultrasound-guided fine needle aspiration cytology. None of them had worrisome features, such as distant or nodal metastasis, significant extrathyroid extension, or aggressive cytology. We cautiously excluded patients with tumors attaching to the trachea or located on the course of the recurrent laryngeal nerve from the candidate for the active surveillance. Since 1993 we have informed and proposed to the patients with low-risk PMCs 2 management options: immediate surgery or active surveillance. The present patients chose active surveillance. The patients included 1,088 females and 123 males with a median age of 56 years (range 20–79 years), and they were followed for a median period of 6.2 years (range 0.5–23.0 years). All patients were followed with an ultrasound examination 6 months after the enrollment and once a year thereafter. Tumor enlargement was defined as increase in tumor size by ≥3 mm. Nodal metastasis was diagnosed with ultrasound-guided fine-needle aspiration cytology and the measurement of the washout of the needle used for the aspiration.[9] Disease progression (DP) was defined as tumor enlargement and/or nodal metastasis.

During the surveillance, 72 patients showed tumor enlargement, 18 patients showed novel nodal metastasis, and 4 of these patients showed both. The numbers of patients in the age-decade groups were as follows: 20s ($n = 37$), 30s ($n = 129$), 40s ($n = 220$), 50s ($n = 350$), 60s ($n = 308$), and 70s ($n = 167$). The period of surveillance and the numbers of patients with tumor enlargement, nodal metastasis and DP in each age group are shown in Table I.

We used the Kaplan-Meier method to calculate the cumulative rates of tumor enlargement, nodal metastasis and DP at the 10-year time point of active surveillance for each age group. Here we express these age decade-specific progression rates for the age groups as R_{20s}, R_{30s}, and so on.

Hypotheses on disease progression

We used 3 hypotheses to describe the possible lifetime rates of disease progression. The assumption that PMCs progress strictly according to the decade-specific rates calculated in this article is referred to hereafter as "Hypothesis A."

The patients who show DP during the initial 10-year period undergo surgical treatment and are thus removed from the active surveillance program thereafter. The assumption that the remaining patients therefore have only tumors that lack a progressive nature and do not progress in the succeeding surveillance is referred to hereafter as "Hypothesis B."

Hypothesis B may be possible at least for some of the remaining patients, but applying it to all of the remaining patients might be too optimistic. The actual probability might be values that are between the values estimated with Hypothesis A and those estimated with Hypothesis B. This assumption referred to hereafter as "Hypothesis C."

Lifetime probability of progression according to Hypothesis A

According to Hypothesis A, the lifetime probability of progression for each age group was calculated by the following formula: 1 – the cumulative probability of progression free survival calculated with decade-specific progression rates (R values) until the patients reached their 80s. For example, the lifetime probability of disease progression for patients in their 50s at presentation (55 years old on average) was calculated as: $1 - (1 - R_{50s}) \times (1 - R_{60s}) \times (1 - R_{70s})$.

DP trends over time according to Hypothesis A

With a similar concept, we calculated the trends of DP over the years of active surveillance according to the patients' age at presentation for the decade-periods of surveillance until the patients reached their 80s (85 years old on average). For example, the DP rate at 30 years of active surveillance for patients in their 20s at presentation (25 years old on average) was calculated as: $1 - (1 - R_{20s}) \times (1 - R_{30s}) \times (1 - R_{40s})$.

Lifetime probability of progression according to Hypothesis B and C

According to Hypothesis B, the lifetime probability of DP is the same as the observed cumulative rate of DP at the 10-year time point of surveillance. According to Hypothesis C, the probability values are calculated as (the value of Hypothesis A + the value of Hypothesis B) / 2.

Results

The observed cumulative rates of tumor enlargement at the 10-year time point of active surveillance for the age groups decreased with age from 22.0% for the patients in their 20s to 2.8% in the 70s (Fig 1, Table II). The estimated lifetime probability of tumor

Table I.
Patients who had tumor enlargement, nodal metastasis or disease progression during active surveillance according to the age group at the presentation

Age group	No. of patients	Active surveillance (y)	Patients who had:		
			Tumor enlargement	Novel nodal metastasis	Disease progression
20s	37	5.5 (0.8–14.8)	6 (16%)	4 (11%)	9 (24%)
30s	129	5.8 (0.6–21.6)	12 (9.3%)	3 (2.3%)	14 (11%)
40s	220	5.9 (0.5–23.0)	20 (9.1%)	5 (2.3%)	25 (11%)
50s	350	6.8 (0.8–22.7)	17 (4.9%)	4 (1.1%)	19 (5.4%)
60s	308	6.5 (1.2–20.4)	13 (4.2%)	1 (0.3%)	14 (4.5%)
70s	167	5.8 (1.6–18.0)	4 (2.4%)	1 (0.6%)	5 (3.0%)

Tumor enlargement was defined as increase in tumor size by ≥3 mm. Disease progression was defined as tumor enlargement and/or novel appearance of nodal metastasis. Data are median (range).

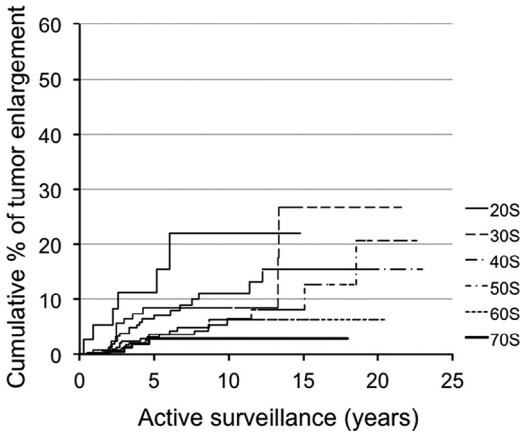

Fig 1. Proportion of patients whose PMC enlarged by ≥3 mm during active surveillance according to their age at presentation.

Please cite this article in press as: Akira Miyauchi, et al., Estimation of the lifetime probability of disease progression of papillary microcarcinoma of the thyroid during active surveillance, Surgery (2017), doi: 10.1016/j.surg.2017.03.028