Review Article

Clinical application of active surveillance in papillary thyroid microcarcinoma

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Abstract: Incidence of papillary thyroid carcinoma (PTC) has increased during last decades worldwidely, especially in Korea. There are reasonable evidences which the increase of incidence may be due to real increase of incidence. However, there are more evidences that this increase is due to increase of ultrasonography screening. Furthermore, majority of increase are increase of small papillary thyroid microcarcinoma (PTMC) and mortality from thyroid carcinoma is relatively stable even though incidence increase. Thus, suspicion of over-diagnosis and over-treatment has been raised. Concept of active surveillance has been proposed from Japanese surgeons under this circumstance. Gradually, management guidelines of leading societies are accepting concept of active surveillance. However, there are unsolved problems to imply active surveillance concept in clinical situation. In this article, we will discuss concept, application and problems of active surveillance.

Keywords: Carcinoma; thyroid neoplasm; surveillance

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Definition of active surveillance and background

Definition

Active surveillance is a treatment plan that involves closely watching a patient's condition but not giving any treatment unless there are changes in test results that show the condition is getting worse. Active surveillance may be used to avoid or delay the need for treatments such as radiation therapy or surgery, which can cause side effects or other problems. During active surveillance, certain exams and tests are done on a regular schedule. It may be used in the treatment of certain types of cancer, such as prostate cancer, urethral cancer, and intraocular (eye) melanoma (1).

Especially, prostate cancer is a good candidate for prostate cancer because of high incidence, good prognosis, higher detection rate by screening, and shorter needed surveillance time. Thus, many management guidelines including American Society of Clinical Oncology accepted concept of active surveillance in prostate cancer (1,2).

Active surveillance in papillary thyroid microcarcinoma (PTMC)

Worldwide increase of thyroid cancer incidence is closely related to introduction of active surveillance. Previously, AJCC (American Joint Committee on Cancer) staging for papillary thyroid carcinoma (PTC) regarded microscopic exrathyroidal extension as T3. Most guidelines support total thyroidectomy followed by radioactive iodine ablation for treatment of PTC (3). This kind of aggressive treatment policy inevitably causes increase of operative complication; especially hypoparathyroidism, worse quality of life and social cost increase. In USA, where inexperienced surgeons are doing many of thyroid surgery and medical cost is extremely high, these phenomenons are typical. Moreover, mortality from thyroid cancer remains stable even incidence of thyroid cancer increase (4).

Some Japanese surgeons proposed active surveillance; later decision of surgery with ultrasonography follow up

rather than immediate surgery.

First report on active surveillance was published in 2003 by Ito *et al*. from Kuma Hospital, Japan. They followed 56 PTMC patients without surgery (mean 46.5±21.5 months, 18–113 months) (5). During follow up period, 13 patients (23.3%) had increase of tumor size. Nine patients underwent operation due to final tumor size increase over 1 cm and two patients due to newly developed lateral neck lymph node metastasis. Other 47 patients underwent operation for various reasons. After this study, Ito *et al*. published active surveillance data from 1,235 PTMC patients in 2014 (mean follow up period 60 months, 18–227 months). A total of 191 patients out of 1,235 patients (15.4%) needed operation due to interval tumor size increase over 3 mm, becoming final tumor size over 12 mm or development of novel lymph node metastasis. However, after delayed surgery, one out of 191 patients had recurrence after 75 months of follow up. Thus they suggested delayed operation (after active surveillance) did not affect prognosis of patients (6). Sugitani *et al*. also reported similar results from follow up of 230 patients. 7% of the patients needed operation and no recurrence or death after delayed operation (7). These two reports became key evidence of accepting active surveillance as an alternative to immediate surgery in management guideline of American Thyroid Association (ATA), year 2016 (8). Management guideline from Korean Thyroid association in year 2016 also accepted concept of active surveillance (9). However, management guidelines from American Association of Clinical Endocrinologists and British Thyroid Association did not recommend active surveillance yet even though published in the same period (10,11). Maybe it is because of debates which will be discussed later in this article.

Application of active surveillance

Inclusion criteria

ATA management guideline suggested possible candidates for active surveillance as follows (8): (I) patients with very low risk tumors (e.g., papillary microcarcinomas without clinically evident metastases or local invasion, and no convincing cytologic evidence of aggressive disease); (II) patients at high surgical risk because of comorbid conditions; (III) patients expected to have a relatively short remaining life span (e.g., serious cardiopulmonary disease, other malignancies, very advanced age); (IV) patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery.

These inclusion criteria are a little bit ambiguous for clinical application. Thus, Brito *et al*. suggested more detailed inclusion criteria on the basis of tumor, patient and medical personnel characteristics (12). *Table 1* summarized their criteria. Overall, tumor size alone is not a criterion for active surveillance but various characteristics should be considered for active surveillance.

Follow up protocol

Solid follow up protocol is not made yet. In general, if patients meet inclusion criteria, clinicians should get an informed consent which explains benefits and harms from active surveillance. Especially if clinicians perform active surveillance as clinical trial, informed consent is crucial.

Intervals for ultrasonography exam are not clear neither. In Kuma hospital, they recommend ultrasonography exam 6 months after first diagnosis and then annual or biennial follow up if there is no change of tumor (13). Memorial Sloan-Kettering Cancer Center has more conservative protocol. They recommend 6 month interval follow up with ultrasonography for 2 years, and then annual or biennial follow up (12). Indication of delayed surgery during active surveillance is not clear neither. In Kuma Hospital, they recommend surgery in the following occasion (14): (I) increase if maximum tumor diameter over 3 mm; (II) novel development of lymph node metastasis; (III) final tumor size becomes larger than 12 mm.

Considerations for clinical implication

Definition of active surveillance is not giving up operation but having a follow up period to decide the best treatment plan for patients. Furthermore, active surveillance is still a clinical trial based strategy. Safety and cost effectiveness are also not proven consistently. Thus, informed consent and approval by Institutional Review Board is mandatory. Patient should have regular follow up. If it seems impossible, the patients should not be included in active surveillance. Haser *et al*. suggested consideration before active surveillance as follows (15): (I) to provide continuity of care as patients move or change physicians/hospitals; (II) to store ultrasonography data in a detailed and uniform format to identify and report changes readily; (III) to educate clinicians and patients about entry/exclusion criteria and follow-up; (IV) to evaluate patient quality of life during AS and conduct research on outcomes for patients undergoing AS.

Table 1 Selection criteria for active surveillance of PTMC

Subject	Tumor characteristics	Patients characteristics	Physician
Ideal	Single nodule	Age >60 years old	Experienced multidisciplinary team
	Round margin	Need of patients	High resolution ultrasonography
	Encased with thyroid parenchyma >2 mm	Understanding of possible future operation	Prospective trial
	No extrathyroidal extension	Cooperative for follow up plan	Patient follow up system
	No growth compared with previous imaging	Severe co-morbid condition	
	Clinical N0 or M0		
Appropriate	Multifocal PTMC	Middle age (18–59 years old)	Experienced endocrine surgeon or endocrine surgeon
	Subcapsular tumor without extrathyroidal extension far from recurrent laryngeal nerve	Strong family history	Neck ultrasonography routinely available
	Not circumscribed tumor	Plan of pregnancy	
	FDG avid PTMC		
	Background ultrasonographic findings that will make follow-up difficult		
Inappropriate	Aggressive variants	Age <18 years old	Inexperienced physician
	Close to recurrent laryngeal nerve	Not cooperative to follow up	Neck ultrasonography not routinely available
	Extrathyroidal extension	Patients want operation	
	Invasion to adjacent structure		
	N1 or M1		
	Already tumor growth over 3 mm		

Adapted and modified from reference (12). PTMC, papillary thyroid microcarcinoma.

Experiences from Asan Medical Center.

We included 192 PTMC patients into active surveillance from 2002 to 2012. They refused operation against medical advice or they had medical conditions (cancer of other organ or severe co-morbid condition etc.) which were not suitable for immediate operation (16). We excluded patients who had aggressive variants or risk factor of recurrence such as lymph node metastasis. Ultrasonography follow up was done with interval of 6 months or 12 months. Median follow period was 31.2 months. We defined tumor increase tumor size increase over 3 mm, novel lymph node metastasis or tumor volume increase over 50%. Twenty seven patients (14%) had tumor increase. Most of tumor increase was volume increase over 50% even though only 4 of 27 patients had increase of tumor size over 3 mm. One out of 192 patients had new lymph node metastasis. Delayed surgery was performed in 24 patients. Among them, 7 patients (29%) had lymph node metastasis after delayed surgery (*Tables 2,3*).

Problems associated with active surveillance

Lack of evidence

The most important problem is lack of evidence. Even in systematic review, the only evidence supporting active surveillance is only two retrospective papers from Japan (17). Nilubol *et al.* analyzed data of 61,253 patients from SEER (The Surveillance, Epidemiology, and End Results) data base. In their study, a total of 1,753 patients died from

thyroid cancer from 1988 to 2007. Among them, 7.7% of patients died from PTMC and 12.8% of patients died from PTC less than 2 over 1 cm (18). This reports suggested there are non-negligible number of death from PTMC after long term follow up. Thus, larger scale prospective trials are needed.

Selection criteria

If we can identify PTMC which are aggressive and progressive, problems associated with selection criteria will be solved. However, current technology cannot identify patients who are not suitable for active surveillance.

Until now, the most important risk factor of tumor progression is age of patients. Again from the study of Ito *et al*., in the patients group whose age was over 60 years old, tumor size increase over 3 mm, lymph node metastasis, and overall tumor size increase to 12 mm were observed in 4%, 0.5% and 2.5% respectively after 10 years follow up. However, in the patients group whose age was less than 40 years old, tumor progression was observed in 12.1%, 16.1%, 22.5% respectively, and 9.1%, 2.3%, and 4.9% in the patients group whose age was over 40 years old and less than 59 years old. It seems more likely to need operation in patients who need longer follow up period (6).

Fukuoka *et al*. reported differences of ultrasonography image between progressive PTMC and non-progressive PTMC during active surveillance. They found there were decrease of peritumoral vascular density and increase of density of intratumoral calcification in non-progressive PTMC during follow up period. However, it is not applicable for selection of patients before starting active surveillance because these findings were observed after some period during active surveillance (19). Hirokawa *et al*. also reported differences of pathologic findings between progressive PTMC and non-progressive PTMC during active surveillance. There were higher incidence of Ki-67 labeling index >5%, psammoma body in normal thyroid parenchyma and intrathyroidal metastasis (20). However these kinds of information are also not available before operation.

Quality of life

Another important consideration is quality of life. There are no published results about quality of life in patients with PTMC under active surveillance.

Table 2 Baseline clinical features of patients with PTMC in active surveillance at AMC

	Total (n=192)
Age at diagnosis (years)	51.3 (42.9–59.5)
<45	61 [32]
45–64	99 [52]
≥65	32 [17]
Sex (female)	145 [76]
Maximal tumor diameter at diagnosis (mm)	5.5 (4.2–6.9)
>5	114 [59]
Tumor volume at diagnosis (mm^3)	48.8 (23.1–100.6)
Hashimoto's thyroiditis	42 [22]
Reasons for active surveillance	
Refusal of patients	136 [71]
Co-morbidities	
Malignant disease	48 [25]
Cardiopulmonary disease	4 [2]
Systemic disease	4 [2]
Reasons for the decision of thyroid surgery	
Anxiety of patients	12 [50]
Tumor enlargement	8 [33]
Appearance of LN metastasis	1 [4]
Tumor location near posterior capsule	2 [8]
Co-existence of benign thyroid nodule	1 [4]

Continuous variables are presented as medians (interquartile ranges). Categorical variables are presented as numbers (percentages). PTMC, papillary thyroid microcarcinoma; AMC, Asan Medical Center.

Thus, at results from prostate cancer, which has been studied for, it seems that quality of life under active surveillance is not inferior than those of immediate surgery. Carter *et al*. reported that there were no differences in anxiety, depression and overall quality of life between active surveillance and immediate surgery in prostate cancer patients (21). Venderbos *et al*. also reported that anxiety and fear of prostate cancer patients under active surveillance decrease time dependently (22). However, parallel comparison is difficult because PTMC patients usually need longer follow up period due to relatively younger age of the patients. Furthermore, the

Table 3 Clinical features in patients with PTMC according to change in tumor sizeduring active surveillance

	Decreasing [n=33 (17%)]	Stable [n=132 (69%)]	Increasing [n=27 (14%)]	P
Age at diagnosis (year)	53.6 (41.6–60.3)	51.8 (43.5–59.7)	47.3 (41.2–58.7)	0.5[a]
<45	10 [30]	40 [30]	11 [41]	
45–64	16 [48]	71 [54]	12 [44]	0.8[b]
≥65	7 [21]	21 [16]	4 [15]	
Sex (female)	28 [85]	95 [72]	22 [81]	0.2[b]
Maximal tumor diameter at diagnosis (mm)[c]	6.0 (5.0–7.7)[d]	5.5 (4.5–6.7)[d]	4.5 (3.5–5.8)[e]	0.002[a]
>5 mm[c]	24 [73][d]	82 [62[d]	8 [30][e]	0.002[b]
Tumor volume at diagnosis (mm^3)[c]	79.6 (48.5–125.8)[d]	47.5 (26.5–100.6)[d]	23.0 (12.9–54.0)[e]	0.001[a]
Hashimoto's thyroiditis	7 [21]	29 [22]	6 [22]	0.9[b]

Continuous variables are presented as medians (interquartile ranges). Categorical variables are presented as numbers (percentages).[a], P value estimated by Kruskal-Wallis test; [b], P value estimated by Chi-square or Fisher's exact test; [c,d,e], post-hoc analysis was evaluated by Bonferroni correction method. PTMC, papillary thyroid microcarcinoma.

most frequent reason to decline active surveillance is anxiety of the patients (16,23).

Another concern for quality of life is possibility of increased complication with delayed surgery. Oda *et al*. compared postoperative complication of delayed surgery after active surveillance with those of immediate surgery. They reported temporary vocal cord palsy, temporary hypoparathyroidism, permanent parathyroidism, neck scar and hematoma formation were more frequently present in immediate surgery group. However, they compared incidence of complication in 1,179 active surveillance groups with those of immediate surgery. When we compared incidence of complication between 94 delayed surgery and 974 immediate surgery, it seemed that more complication occurred in delayed surgery group even though statistical analysis could not be made (*Table 4*) (24).

Delayed surgery may not be associated with increase of complication because most of delayed surgery should be hemi-thyroidectomy. However, we should keep in mind that we can meet more advanced thyroid cancer if we miss patients from regular follow up.

Cost-effectiveness

Cost-effectiveness analysis is another important concern because increase of socio-economical cost is one of the reasons for introduction of active surveillance.

Three cost-effectiveness analyses from Japan, Hong Kong and USA have been published. Active surveillance was cost-effective in Hong Kong and Japan while it was cost-effective in particular occasion in USA Lang *et al*. from Hong Kong reported that active surveillance is cost effective until 16 years after active surveillance. They assumed delayed surgery occurred 1 year after active surveillance and model patients was 40 years old female. After 17 years, cost of active surveillance increase but they showed it was still cost effective because quality of life index was superior (25). Oda *et al*. also reported 10 years cost effectiveness analysis in Japan. In their report, immediate surgery cost 4.1 times more than active surveillance (26). Venkatesh *et al*. from USA reported active surveillance is cost effective when health status utility is close to 1 (perfect health status, if close to 0, then general health status is close to death). If health status utility decreased or remaining life expectancy was longer, then immediate surgery (hemithyroidectomy) became more cost-effective (27).

These conflicting results may be generated from differences of each national health care system, medical resource consumption of patients or quality of life during active surveillance. However, it is obvious that operation after long term follow up makes active surveillance not cost-effective. Moreover, differences of medical cost in each country make these conflicts more complicated. Therefore, quality of life during active surveillance is the main factor to measure cost-effectiveness between active surveillance and immediate surgery. When decided to immediate surgery,

Table 4 Comparison of unfavorable events between active surveillance and immediate surgery

	Delayed surgery (original)	Delayed surgery (modified)	Immediate surgery	P value
No. of patients	1,179	94	974	
Unfavorable events				
Temporary VCP	7/1,179 (0.6%)	7/94 (7.4%)	40/974 (4.1%)	<0.0001
Permanent VCP	0/1,179 (0.0%)	0/94 (0.0%)	2/974 (0.2%)	Not significant
Temporary Hypo-P	33/1,179 (2.8%)	33/94 (35.1%)	163/974 (16.7%)	<0.0001
Permanent Hypo-P	1/1,179 (0.08%)	1/94 (1.1%)	16/974 (1.6%)	<0.0001
Recurrence	1/1,179 (0.1%)	1/94 (1.1%)	5/974 (0.5%)	Not significant
Death	3/1,179 (0.3%)	3/94 (3.2%)	5/974 (0.5%)	Not significant

P value is comparison between delayed surgery (original) column and immediate surgery. Statistical analysis is not available between modified delayed surgery group and immediate surgery group. Modified to calculate rate of adverse event only in delayed surgery patients. Adapted and modified from reference (24). VCP, vocal cord palsy; Hypo-P, hypo-parathyroidism.

minimal complication rate is mandatory because complication is the most important factor of less cost effectiveness and quality of life.

Conclusions

In conclusion, active surveillance is a possible alternative to immediate surgery for well selected PTMC patients. However, selection of patients is the most important factor in active surveillance. All patients who select active surveillance should be included in well-designed prospective clinical trial to answer unsolved problems in active surveillance.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aot.2017.08.01). The author has no conflicts of interest to declare.

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