



Disease-related and treatment-related unfavorable events in the management of low-risk papillary microcarcinoma of the thyroid by active surveillance versus immediate surgery

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Active surveillance is emerging as a viable clinical alternative to immediate surgery in the management of low-risk papillary thyroid microcarcinoma (PMC). While indolent PMC may be present in up to 10% of the United States population, only a small proportion of this subclinical disease evolves into clinically significant disease (1-3). Instead, the vast majority of lesions are asymptomatic and detected incidentally by imaging studies (neck US, CT, MRI) done for unrelated reasons (4). Active surveillance has arisen as an attractive alternative management strategy because the natural history of PMC is one of slow growing or stable tumors with low rates of lymph node metastasis, and extremely low risk of distant metastasis and disease-related mortality. Even more importantly, a delayed surgical approach has proven to be a very effective salvage therapy for the few patients who demonstrate structural disease progression (5). Several recent reports continue to demonstrate that active surveillance is associated with excellent clinical outcomes (5-8).

The article by Oda *et al.* titled “*Incidences of Unfavorable Events in the Management of Low-Risk Papillary Microcarcinoma of the Thyroid by Active Surveillance Versus Immediate Surgery*” makes a significant contribution to our understanding of the risks and benefits of an active surveillance approach to the management of PMC (9). In particular, the authors examined 2,153 patients diagnosed with low-risk PMC in Kuma Hospital in Japan, who chose either active surveillance or immediate surgery. They present an update with regard to both oncologic outcomes as well as

unfavorable events after a median follow up of 47 months in a cohort of low-risk PMC patients evaluated and treated by a very experienced disease management team.

Unfavorable events in the management of low-risk PMC can be classified as either disease-related or treatment-related. Disease-related unfavorable events include tumor invasion into surrounding structures (e.g., recurrent laryngeal nerve), development of lymph node or distant metastases, and rates of persistent or recurrent disease. On the other hand, treatment-related unfavorable events include surgical hypoparathyroidism, or intraoperative injury of the recurrent laryngeal nerve resulting in vocal cord paralysis. While not evaluated in the current study, another unfavorable event that may be experienced by patients with PMC undergoing active surveillance includes the psychological burden of living with a known malignancy. Further research on the impact of an active surveillance approach on quality of life is needed to address this issue.

Disease-related unfavorable events

Table 1 shows the rate of disease-related unfavorable events in the active surveillance group as a whole, the active surveillance patients that converted to surgery, and the immediate surgery group. Oda *et al.* reported that 94 of 1,179 patients in the active surveillance group eventually underwent surgery (9). Of these, 51 of 94 (54%) delayed surgeries occurred due to patient preference, and 33 of 94 (35%) occurred because of disease progression. Six patients

Table 1 Incidence of disease-related unfavorable events in all patients undergoing active surveillance, active surveillance patients converted to delayed surgery, and immediate surgery patients

Disease-related unfavorable event	Active surveillance		Immediate surgery (N=974)
	Entire cohort (N=1,179)	Delayed surgery (N=94)	
Tumor invasion (e.g., RLN)	None	None	None
Distant metastasis	None	None	None
Recurrent disease	n/a	1* (1.1%)	5** (0.5%)
Disease-related death	None	None	None

*, the 1 instance of disease recurrence in the delayed surgery group occurred in lymph nodes in the lateral neck; **, of the 5 instances of disease recurrence in the immediate surgery group, 3 occurred in the contralateral lobe and 2 occurred in lymph nodes in the lateral neck. RLN, recurrent laryngeal nerve; n/a, not applicable.

(0.5% of 1,179) had new lymph node metastases, and one patient who underwent delayed surgery had a recurrence in the lateral neck (0.1% of 1,179). In contrast, 974 patients chose immediate surgery, of which 5 patients (0.5% of 974) had a neck recurrence. No patients developed distant metastasis and there were no disease-related deaths.

The similar rates of disease-related unfavorable events in the active surveillance group that converted to surgery compared to the immediate surgery group can be attributed to the natural history of low-risk PMCs and to the skill of the clinicians in selecting proper patients for observation and understanding when observation should be abandoned in favor of delayed surgery. Therefore, appropriate patient selection and exclusion of inappropriate patients is crucial to the success of an active surveillance approach. Brito *et al.* discuss a clinical framework for risk stratification of patients undergoing consideration for active surveillance (10). They outline a number of tumor/neck ultrasound characteristics, patient characteristics, and medical team characteristics that define a patient's eligibility for active surveillance. Upon assessment, patients should be classified as ideal, appropriate, or inappropriate for active surveillance, and this process should be repeated at subsequent follow up visits. Proper application of this clinical framework requires an experienced multidisciplinary team, an engaged and willing patient, and confident sonographic evaluation of tumor location and lymph node status.

Treatment-related unfavorable events

Oda *et al.* compared the rate of treatment-related unfavorable events in patients undergoing active surveillance versus immediate surgery groups (9). When evaluating

treatment related unfavorable events, the authors found that immediate surgery was associated with a significantly higher rate of transient vocal cord paralysis (4.1% *vs.* 0.6%, *P* value <0.0001), transient hypoparathyroidism (16.7% *vs.* 2.8%, *P* value <0.0001), and permanent hypoparathyroidism (1.6% *vs.* 0.08%, *P* value <0.0001) than the active surveillance group as a whole. They found similar rates of permanent vocal cord paralysis between the two groups (0.2% *vs.* 0%, *n.s.*). When comparing patients that underwent immediate surgery with those that underwent delayed surgery, no significant differences were seen with regard to transient vocal cord paralysis (4.1% *vs.* 6.4%), permanent vocal cord paralysis (0.2% *vs.* 0%), or permanent hypoparathyroidism (1.6% *vs.* 1.1%). The rate of transient hypoparathyroidism was significantly higher after delayed surgery than with immediate surgery (35.1% *vs.* 16.7%, *P*<0.0001) (*Table 2*).

Overall, this provides support for the fact that delayed surgery is not a higher risk procedure than immediate surgery, whether it is performed for reasons of disease progression or patient preference. It is unclear whether the higher rates of transient hypoparathyroidism seen in the delayed surgery group occurred in patients that underwent delayed surgery for reasons of disease progression or patient preference, or if disease progression resulted in a greater proportion of patients undergoing total thyroidectomy as opposed to hemithyroidectomy. However, it is reassuring that there is no increase in permanent hypoparathyroidism in the delayed surgery group. It is important to note that all surgical complication rates reported by Oda and colleagues are those of experienced, high-volume head and neck surgeons at Kuma Hospital, and can be expected to be higher in both groups when performed by low volume

Table 2 Incidence of treatment-related unfavorable events in patients undergoing active surveillance, active surveillance converted to delayed surgery, and immediate surgery

Treatment-related unfavorable events	Active surveillance		Immediate surgery (N=974)
	Entire cohort (N=1,179)	Delayed surgery subgroup (N=94)	
Temporary vocal cord paralysis [n, (%)]	7 (0.6)	6* (6.4)	40 (4.1)
Permanent vocal cord paralysis [n, (%)]	0 (0)	0 (0)	2 (0.2)
Temporary hypoparathyroidism [n, (%)]	33 (2.8)	33 (35.1)	163 (16.7)
Permanent hypoparathyroidism [n, (%)]	1 (0.1)	1 (1.1)	16 (1.6)

*, one case of temporary idiopathic vocal cord paralysis that occurred contralateral to the PMC was excluded from analysis. PMC, papillary thyroid microcarcinoma.

surgeons (11).

Conclusions

A few important lessons can be learned from this important publication:

- (I) When implemented appropriately, an active surveillance approach does not increase disease-related unfavorable events compared to immediate surgery. A successful active surveillance management program must include proper initial patient selection, ongoing monitoring, and appropriate termination of active surveillance and conversion to surgery if clinically significant disease progression is identified.
- (II) Delayed surgery in patients with disease progression does not increase the risk of clinically significant treatment-related unfavorable events such as permanent hypoparathyroidism or vocal cord paralysis, when performed by experienced surgeons.

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