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Response to Letter to the Editor on Surgical Outcomes in Patients With Low-Risk Papillary Thyroid Microcarcinoma From MAeSTro Study: Immediate Operation Versus Delayed Operation Following Active Surveillance

A Multicenter Prospective Cohort Study

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We appreciate the interest of Dr Ziwen Liu and colleagues from China in our article on surgical outcomes between immediate operation (IOP) and delayed operation (DOP) after active surveillance (AS),[1] and the protocol of a Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (MAeSTro).[2]

The MAeSTro study was meticulously designed to observe the natural course of papillary thyroid microcarcinoma (PTMC) during AS and to compare the outcomes of patients who underwent IOP and DOP. For our study, a multidisciplinary MAeSTro team consisting of experts in the fields of endocrinology, endocrine surgery, otolaryngology, radiology, and preventive medicine was assembled from the 3 tertiary hospitals in Korea. For the early detection of a possible progression in participants who choose AS instead of surgery, their PTMCs are closely monitored according to the protocol. The detailed protocol for the MAeSTro study for low-risk PTMC patients was described in a previous study.[2]

In 3 referral hospitals, total thyroidectomy was recommended in accordance with the guidelines provided by the Korean Thyroid Association in 2016[3] and the American Thyroid Association in 2015.[4] The decision on the extent of thyroidectomy was based on several factors, including tumor size, extrathyroidal extension, lymph node metastasis, history of head and neck radiation, family history, presence of bilateral thyroid disease, and patient preference. Additionally, the occurrence of postoperative complications is influenced by the surgical extent and the expertise of the surgeon. The 3 tertiary hospitals involved in the MAeSTro study have dedicated centers for thyroid cancer with highly experienced surgeons and are high-volume hospitals. Because our study aimed to compare the surgical outcomes between IOP and DOP patients, it was thought that the bias from the surgeon's experience might be minimal.

Dr. Ziwen Liu and colleagues mentioned the effect of multifocality on tumor aggressiveness[5] In our study, the DOP group was significantly associated with a higher rate of multifocality than the IOP group (28.4% vs 40.9%; $P = 0.008$). Additionally, the patients in the DOP group with progression had a higher rate of multifocality than the IOP group (28.4% vs 48.7%; $P = 0.008$). However, there was no significant difference between the DOP groups (48.7% in DOP with progression vs 37.6% in DOP without progression; $P = 0.237$), showing a lack of association between multifocality and progression. Sugitani et al[6] reported no evidence suggesting an association between tumor multifocality and tumor enlargement or the appearance of lymph node metastasis. As a result, they suggested that the patients with multifocal PTMC can also be candidates for AS. Given these, further study is needed to establish a definitive and conclusive association.

It is difficult to accurately evaluate the number of patients with multifocal PTMC before surgery because of the inability to pathologically evaluate all nodules preoperatively, particularly small nodules that may go undetected. Additionally, in the IOP group, there were 109 patients with multifocal PTMC, alongside 109 patients who underwent total thyroidectomy. However, it is important to note that the 109 patients who underwent total thyroidectomy were not consistent with the patients with multifocality. Among the 109 patients with multifocal PTMC in the IOP group, a total of 59 patients (54.1%) underwent total thyroidectomy, and 28 (51.9%) of the 54 patients with multifocal PTMC in the DOP group underwent total thyroidectomy. In the case of bilaterality, there was no significant difference between the IOP and DOP groups (n = 46, 12.0% in IOP vs n = 24, 18.2% in DOP; $P = 0.073$).

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As mentioned, when we designed this study protocol, the tumor volume (TV) change was not included in the definition of disease progression. However, considering recent studies[7–10] that indicate the sensitivity of TV change in detecting tumor progression, we further analyzed the clinicopathological features between the DOP groups. When a TV increase of 50% or more was included in the definition of disease progression, the rate of total thyroidectomy was significantly higher in the DOP group with disease progression than in the DOP group without disease progression (42.4% vs 26.0%; $P = 0.048$).[1] Based on these findings, it was suggested that surgical intervention could be considered when there is a TV increase of >50% in patients undergoing AS. However, further study is needed to evaluate the optimal timing for surgical intervention.

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