Comparison of the costs of active surveillance and immediate surgery in the management of low-risk papillary microcarcinoma of the thyroid

Hitomi Oda1), Akira Miyauchi1), Yasuhiro Ito1), Hisanori Sasai2), Hiroo Masuoka1), Tomonori Yabuta1), Mitsuhiro Fukushima1), Takuya Higashiyama1), Minoru Kihara1), Kaoru Kobayashi1) and Akihiro Miya1)

1) Department of Surgery, Kuma Hospital, Center for Excellence in Thyroid Care, Kobe 650-0011, Japan
2) Department of Head and Neck Surgery, Kuma Hospital, Center for Excellence in Thyroid Care, Kobe 650-0011, Japan

Abstract. The incidence of thyroid cancer is increasing rapidly in many countries, resulting in rising societal costs of the care of thyroid cancer. We reported that the active surveillance of low-risk papillary microcarcinoma had less unfavorable events than immediate surgery, while the oncological outcomes of these managements were similarly excellent. Here we calculated the medical costs of these two managements. We created a model of the flow of these managements, based on our previous study. The flow and costs include the step of diagnosis, surgery, prescription of medicine, recurrence, salvage surgery for recurrence, and care for 10 years after the diagnosis. The costs were calculated according to the typical clinical practices at Kuma Hospital performed under the Japanese Health Care Insurance System. If conversion surgeries were not considered, the ‘simple cost’ of active surveillance for 10 years was 167,780 yen/patient. If there were no recurrences, the ‘simple cost’ of immediate surgery was calculated as 794,770 yen/patient to 1,086,070 yen/patient, depending on the type of surgery and postoperative medication. The ‘simple cost’ of surgery was 4.7 to 6.5 times the ‘simple cost’ of surveillance. When conversion surgeries and recurrence were considered, the ‘total cost’ of active surveillance for 10 years became 225,695 yen/patient. When recurrence were considered, the ‘total cost’ of immediate surgery was 928,094 yen/patient, which was 4.1 times the ‘total cost’ of the active surveillance. At Kuma Hospital in Japan, the 10-year total cost of immediate surgery was 4.1 times expensive than active surveillance.

Key words: Papillary microcarcinoma, Active surveillance, Surgery, Medical economics, Cost

Researchers have reported a rapid increase in the incidence of thyroid cancer in many countries; e.g., an approximately three-fold increase over a 34-year period in the U.S. [1] and a 15-fold increase over an 18-year period in Korea [2]. These increases are due mostly to the increase in the detection of papillary carcinomas ≤2 cm in size. The incidences of papillary carcinoma >2 cm and other types of thyroid cancer have remained stable. Papillary carcinomas ≤1 cm, which are called papillary microcarcinomas (PMCs), account for 39% of the cases of thyroid cancer in the U.S. [1] and 43.1% of the cases in Korea [3].

Although the incidence of thyroid cancer has increased, mortality from thyroid cancer has remained stable. In light of all of the above data, several research groups have suggested that the overdiagnosis and overtreatment of small papillary carcinomas has occurred [1, 2]. Almost all patients with a newly diagnosed thyroid cancer are treated surgically, and the number of the patients with vocal cord paralysis and hypoparathyroidism postoperatively has increased [2]. Medical costs are another important issue. Lubitz et al. warned that the $1.6 billion societal cost of thyroid cancer care in the U.S. in 2013 could increase to $3.5 billion by 2030 if the recent trend of the increase in the incidence continues [4]. Medical costs are a very important issue for any society, and it is also a major concern for individual patients.

In 1993 at a meeting of Kuma Hospital physicians, Akira Miyauchi proposed an observation clinical trial for low-risk PMC based on the following hypothesis: most PMCs remain small, and observation or surveillance without immediate surgery could identify the
small minority of PMCs that may cause harm in the future; performing surgery only for the PMCs that show slight progression might not be too late. This proposal was approved and the clinical trial started the same year.

We reported the outcomes of our clinical trial in several papers [5-10]. The active surveillance of 1,235 patients with low-risk PMCs revealed that only 8% of the patients showed an increase in tumor size by ≥3 mm, and only 3.8% of the patients showed novel nodal metastases at 10 years of observation [8]. The patients who had slight progression of the disease were successfully treated by a salvage surgery.

Our most recent study of 2,153 patients with low-risk PMCs comparing the outcomes of 974 patients who chose immediate surgery with those of 1,179 patients who chose active surveillance clarified that although the surgical and surveillance management modalities had similarly excellent oncological outcomes, the incidences of unfavorable events such as vocal cord paralysis and hypoparathyroidism were significantly higher in the surgical group compared to the surveillance group [10]. In the present study, we calculated and compared the medical costs for these two management modalities for the diseases according to a model created from the actual flow of the managements of those 2,153 patients with low-risk PMCs.

Materials and Methods

In the present study, we created a model of the flow of the two management modalities, i.e., immediate surgery and active surveillance, for patients with low-risk PMC based on our previous study [10] of 2,153 patients with low-risk PMCs (Fig. 1). In that study, 41% of the immediate surgery group underwent a total thyroidectomy with central node dissection and 59% underwent a hemithyroidectomy with paratracheal dissection. After surgery, 0.51% (5 patients) of the 974 patients who underwent an immediate surgery developed local recurrence, mostly nodal metastases in the lateral neck compartment. They were successfully treated by a salvage surgery. In the active sur-

![Fig. 1 A model of the flow of the management according to the initial intention of active surveillance or immediate surgery.](image-url)
We calculated the medical costs of these surgical and surveillance management modalities for 10 years of care per patient. The medical costs include the costs of the initial diagnosis step, the costs of the surgeries and the costs of the follow-up care. The costs of the surgery include all medical costs of the preoperative examinations, surgery, anesthesia, pathological examination and admission based on typical clinical practices at Kuma Hospital, based on the Japanese Health Care Insurance System.

Our definitions of high- and low-risk PMC are the following: High-risk PMC is PMC having one or more of the following: lymph node or distant metastasis, extrathyroid extension, high-grade cytology, or growth during a previous observation. We cautiously included tumors located near the recurrent laryngeal nerve or attached to the trachea in the high-risk category. Low-risk PMC is defined as PMC having none of these features.

The standard protocols for the managements of low-risk PMC are shown in Table 1. Following the diagnosis, patients who chose active surveillance were followed up with an ultrasound examination 6 months later and once a year thereafter. Patients who chose immediate surgery were seen more frequently for preoperative evaluations and for postoperative consultations in the first year, and were seen once a year thereafter. However, patients who needed medications were seen every 6 months, since the maximum length of a prescription for l-thyroxine or vitamin D in the Japanese Health Care Insurance System is 6 months.

| Management time * | Active surveillance group | Surgery group (With LT4) | Surgery group (Without LT4) |
|-------------------|---------------------------|-------------------------|----------------------------|
| At presentation   | C, BT, US, FNA            | C, BT, US, FNA          | C, BT, US, FNA             |
| Management for surgery | No                        | Yes                     | Yes                        |
| 1 m               | No                        | C, BT, LT4              | C, BT                      |
| 3 m               | No                        | C, BT, LT4              | C, BT                      |
| 6 m               | C, BT, US                 | C, BT, LT4              | No                        |
| 1 yr annually     | C, BT, US                 | C, BT, US, LT4          | C, BT, US                  |
| Every 6 m         | No                        | C, BT, LT4              | No                        |

Time *, The time after the diagnosis for the active-surveillance group and after surgery for the surgery group. LT4, prescription of l-thyroxine with or without vitamin D; C, consultation; BT, blood tests; US, ultrasound examination; FNA, fine needle aspiration cytology. The management for the surgery patients included preoperative examinations, additional consultations, seeing an anesthesiologist and the admission for surgery. The patients who had a conversion surgery were managed with the standard protocols for surgical patients following the conversion.
The costs of the major clinical practices, examinations and surgeries are shown in Table 2. These values are based on the actual clinical practice at Kuma Hospital under the Japanese Health Care Insurance System. The fees for any clinical practices performed under this system are the same regardless of the experience of the surgeon, the type of hospital and the location of the hospital. The costs of the initial diagnosis step, total thyroidectomy and hemithyroidectomy including all necessary costs in the perioperative period, and the follow-up visit with ultrasound examination were 21,280 yen, 308,100 yen, 241,800 yen, and 14,650 yen respectively (U.S. dollar, US$ 193, $2,801, $2,198, and $133, respectively). For patients who need l-thyroxine (100 μg/day) and l-thyroxine and vitamin D (as alfacalcidol 2 μg/day), additional costs are incurred (3,700 yen/year and 10,900 yen/year, respectively) (US$ 34 and $99, respectively). The cost for alfacalcidol was calculated with the cost for a low-cost generic medicine by Sawai Pharmaceutical Co., Ltd, Osaka, Japan. In the present paper, the USS values were calculated at the exchange rate of US$ 1 = 110 Japanese yen.

We calculated the total costs of the ‘active surveillance’ and ‘immediate surgery’ management modalities for 10-year care from the costs of the treatments and management modalities, weighed by the frequencies of the events described above and as summarized in Fig. 1. The values are given on an intention-to-treat (ITT) basis.

Results

If there were no conversion surgeries, ‘the simple cost’ of active surveillance for 10 years was calculated as 167,780 yen (US$ 1,525)/patient (Table 3). However, with the model shown in Fig. 1 (i.e., 8% conversion surgery cases and 0.08% local recurrence cases), ‘the total cost’ of active surveillance for 10 years was calculated as 225,695 yen (US$ 2,052)/patient.

For the immediate surgery with 10 years of postoperative follow-up care, if there were no recurrences, ‘the simple cost’ for the patients with total thyroidectomy was calculated as 1,014,070 yen (US$ 9,219) and 1,086,070 yen (US$ 9,873) depending on the presence or absence of permanent hypoparathyroidism (Table 3), and ‘the simple cost’ for the patients with hemithyroidectomy was 794,770 yen (US$ 7,225) and 947,720 yen (US$ 8,616) depending on the necessity of l-thyroxine (Table 3). Thus, the simple cost of immediate surgery is 4.7 to 6.5 times the simple cost of active surveillance. When the proportion of the type of thyroid surgeries and the incidence of recurrence were included in the calculation, the ‘total cost’ of immediate surgery and 10-year follow-up care became 928,094 yen (US$ 8,437)/patient.

Thus, the total costs for these management modalities for 10 years per patient on an ITT basis were 225,695 yen (US$ 2,052) for active surveillance and 928,094 yen (US$ 8,437) for immediate surgery. The use of immediate surgery for PMC patient management was 4.1 times more expensive than active surveillance.

Table 2  The costs of major clinical activities, examinations and surgical treatments

| Item                     | Cost (Japanese yen) | Cost (US$) |
|--------------------------|---------------------|------------|
| Initial diagnosis        | 21,280              | 193        |
| Visiting physician       | 2,820               | 26         |
| Blood tests              | 8,960               | 81         |
| US                       | 3,500               | 32         |
| FNAC                     | 6,000               | 55         |
| Thyroid surgeries        |                     |            |
| TT with CND              | 308,100             | 2,801      |
| Hemi with PD             | 241,800             | 2,198      |
| CT with MND              | 348,100             | 3,165      |
| Follow-up care           | 14,650              | 133        |
| Visiting physician       | 2,190               | 20         |
| Blood tests              | 8,960               | 81         |
| US                       | 3,500               | 32         |
| Additional cost for prescription / year | |  |
| l-thyroxine *            | 3,700               | 34         |
| l-thyroxine and vitamin D ** | 10,900             | 99         |

Blood tests included serum TSH, FT4, thyroglobulin and thyroglobulin-antibody. The costs of thyroid surgeries included all costs for preoperative examinations, general anesthesia, surgery, pathological examinations and admission fees during the perioperative period. * l-thyroxine 100 μg/day for 1 year. ** Vitamin D as alfacalcidol 2 μg/day for 1 year. Costs in USS are calculated at the exchange rate of US$ 1 = 110 Japanese yen. CND, central node dissection; CT, completion total thyroidectomy; FNAC, fine-needle aspiration cytology; Hemi, hemithyroidectomy; MND, modified radical neck dissection; PD, paratracheal dissection; TT, total thyroidectomy; US, ultrasound examination.
Discussion

The rapid increase in the incidence of thyroid cancer over the past three decades has brought about several serious problems in many developed countries. Some researchers have called this phenomenon an endemic [2]. The increase was mostly due to the increase in the incidental detection of small papillary carcinomas by imaging studies for other purposes or by screening studies for thyroid diseases. The subsequent problems include: [1] A clinical issue: how should PMCs be treated? [2] The increase in the number of patients with postoperative complications, and [3] Economic issues at both the societal level and for individual patients. For example, Ahn et al. reported an increase in thyroid cancer patients with surgical complications in Korea [2]. Lubitz et al. warned of a significant possible expansion of the societal medical costs for thyroid cancer in the U.S. [4].

At Kuma Hospital, we have been conducting an active surveillance clinical trial for low-risk PMC since 1993. We reported that the oncological outcomes of the active-surveillance and immediate-surgery patient groups were similarly excellent, but the incidences of unfavorable events were significantly higher in the immediate-surgery group than the active-surveillance group, although the surgeries were done by highly experienced endocrine surgeons in a center hospital for thyroid diseases [10].

In the present paper, we report that at Kuma Hospital in Japan, the total cost of the immediate surgery with postoperative care for 10 years was 4.1 times more expensive compared to the total cost of the active surveillance for 10 years, calculated on an ITT basis. With the present data, one might think that the income of a hospital or a surgeon decreases if an active surveillance management is taken instead of an immediate surgery for low-risk PMC. However, we, the doctors of Kuma Hospital, think that our priority should be patients’ good health and happiness. These data and the data on the incidences of unfavorable events clearly show that active surveillance is much better than immediate surgery for individual PMC patients in view of individual healthcare and individual economics as well. In the present flow model, we did not include transient and permanent vocal cord paralysis. If these were included, the cost difference would be slightly larger, since these unfavorable events occurred basically following thyroid surgery.

If the present data are adapted to societal healthcare economics, the difference in societal medical costs becomes huge. In Japan the number of new thyroid cancer patients in 2015 was 17,900. We speculate that more than 35% of these patients had low-risk PMC, since our data on thyroid cancer patients treated surgically in the period from February 2005 to August 2013 at Kuma Hospital (where we try to avoid unnecessary surgery) showed that 22% of the patients had low-risk PMC. For example, if 6,265 patients with low-risk PMC were managed with active surveillance instead of immediate surgery, the total cost saving would have been 4,401 million yen (US$ 40.0 million).

The number of new thyroid cancer patients in 2013 in the U.S. was 60,220. Davies and Welch reported that 39% of thyroid cancers were PMC [1], indicating 23,485 new patients with PMC. The number of new thyroid cancer patients in Korea in 2011 was 40,568 [2]. Lee and Shin reported that 43.1% of their thyroid cancer series were PMC [3], indicating 17,484 new patients with PMC. If these patients with PMC were managed with active surveillance instead of immediate surgery, the total cost saving in these countries would have been substantially more than that in Japan. Of course these are simple applications of the

| Table 3 Costs of simple active surveillance and simple immediate surgery with 10 years of follow-up care |
| --- |
| Medicine | Cost for 10 years (Japanese yen) | Cost for 10 years (US$) |
| Active surveillance | no | 167,780 | 1,525 |
| Hemithyroidectomy | no | 794,770 | 7,225 |
| | l-thyroxine | 947,720 | 8,616 |
| Total thyroidectomy | l-thyroxine | 1,014,070 | 9,219 |
| | l-thyroxine & vitamin D | 1,086,070 | 9,873 |

The costs include the costs of the initial diagnosis step, all costs for surgery cases, follow-up care for 10 years, and prescription medicine when necessary. The costs of medicines were calculated at l-thyroxine 100 μg/day and alfacalcidol 2 μg/day for vitamin D.
data obtained in the present study, which were calculated from the model based on our previous clinical practice that was done under the Japanese Health Care Insurance System. Each country has a different medical care system with a different cost system for clinical practices. These differences are very significant. Therefore, the cost analyses on active surveillance versus immediate surgery should be done according to the medical care system of each country. However, if one accepts our model shown in Fig. 1 and adjusts the cost data in Table 2 according to a particular country’s medical system, the total costs for active surveillance and immediate surgery with 10-year care can be calculated accordingly.

In conclusion, our comparison of the costs of active surveillance and immediate surgery in the management of low-risk papillary microcarcinoma of the thyroid revealed that at Kuma Hospital in Japan, the total cost of immediate surgery for 10-year management was approximately 4.1 times the total cost of active surveillance with 10-year follow-up care, calculated according to the flow of the management model created based on our previous study.

Disclosure

The authors state that there are no conflicts of interest related to this study.

References

1. Davies L, Welch HG (2014) Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 140: 317-322.
2. Ahn HS, Kim HJ, Welch HG (2014) Korea’s thyroid-cancer “epidemic” — screening and overdiagnosis. N Engl J Med 371: 1765-1767.
3. Lee JH, Shin SW (2014) Overdiagnosis and screening for thyroid cancer in Korea. Lancet 384: 1848.
4. Lubitz CC, Kong CY, McMahon PM, Daniels GH, Chen Y, et al. (2014) Annual financial impact of well-differentiated thyroid cancer care in the United States. Cancer 120: 1345-1352.
5. Ito Y, Uruno R, Nakano K, Takamura Y, Miya A, et al. (2003) An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 13: 381-388.
6. Ito Y, Miyauchi A (2007) A therapeutic strategy for incidentally detected papillary microcarcinoma of the thyroid. Nat Clin Pract Endocrinol Metab 3: 240-248.
7. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, et al. (2010) An observation trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 34: 28-35.
8. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, et al. (2014) Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid 24: 27-34.
9. Ito Y, Miyauchi A (2015) Nonoperative management of low-risk differentiated thyroid carcinoma. Curr Opin Oncol 27: 15-20.
10. Oda H, Miyauchi A, Ito Y, Yoshioka K, Nakayama A, et al. (2016) Incidences of unfavorable events in the management of low-risk papillary microcarcinoma of the thyroid by active surveillance versus immediate surgery. Thyroid 26: 150-155.