

Hospital financial implications of subcutaneous versus intravenous trastuzumab plus pertuzumab in Japan: a micro-costing and threshold analysis

Junichi Mase

junichi.mase@gmail.com

Gifu Prefectural General Medical Center <https://orcid.org/0009-0008-3036-2412>

Mana Tsukada

Gifu Prefectural General Medical Center

Toko Nakamura

Gifu Prefectural General Medical Center

Hiroyuki Kinomura

Gifu Prefectural General Medical Center

Keiko Ishihara

Gifu Prefectural General Medical Center

Hiroyuki Ohno

Gifu Prefectural General Medical Center

Shota Mano

Gifu Prefectural General Medical Center

Atsuko Ogiso

Gifu Prefectural General Medical Center

Nobuhisa Matsuhashi

Gifu University Hospital: Gifu Daigaku Igakubu Fuzoku Byoin

Yasuko Nagao

Gifu Prefectural General Medical Center

Manabu Futamura

Gifu University Hospital: Gifu Daigaku Igakubu Fuzoku Byoin

Research Article

Keywords: HER2-positive breast cancer, subcutaneous administration, fixed-dose combination, micro-costing analysis, hospital costs

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11168431/v1>

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Abstract

Background

In Japan, the outpatient oncology chemotherapy management fee is substantially lower for subcutaneous (SC) administration than for intravenous (IV) administration of trastuzumab plus pertuzumab (HP). Concerns that this revenue gap could disadvantage hospitals have delayed the adoption of the fixed-dose SC formulation, but its actual financial effect is unknown.

Methods

This was a single-center, retrospective observational study. We modeled a standard 17-cycle adjuvant course using fiscal year (FY) 2025 and FY2026 fee schedules, itemized material costs, and labor costs based on nurse wages and total visit times from 815 administrations. Uncertainty was assessed by probabilistic sensitivity analysis using 10,000 Monte Carlo simulations with patient-level bootstrapping, one-way sensitivity analysis, two-way sensitivity analysis, threshold analysis, and scenario analysis.

Results

In FY2025, SC reduced annual fee revenue by 75,000 yen but reduced material costs by 99.4% and labor costs by 78,001 yen, resulting in an improvement of the annual administration-process balance by 51,077 yen. SC was favorable in all 10,000 simulations, and the FY2026 advantage was 77,577 yen. In FY2025, IV was favorable only when the nurse wage was below 932 yen/h or the visit-time saving was below 35.2 min. SC remained favorable during concomitant IV chemotherapy, and switching 100 patients receiving HP alone improved the annual balance by 5.1 million yen in FY2025.

Conclusions

For HP alone, switching from IV to SC improved the administration-process balance despite lower fee revenue, and the advantage remained robust even under reasonable wage and time-saving assumptions.

Introduction

Combination anti-human epidermal growth factor receptor 2 (HER2) therapy with trastuzumab plus pertuzumab (HP) is the standard treatment for early and metastatic HER2-positive breast cancer [1, 2] and is widely used in Japanese clinical practice [3]. The subcutaneous (SC) formulation, approved in Japan in 2023, has shown pharmacokinetic non-inferiority to intravenous (IV) administration, with equivalent efficacy and safety. Both antibodies can be administered in approximately 5 min [4], and 85% of patients preferred SC [5]. Evidence from studies conducted outside Japan indicates that SC anti-HER2 therapy can reduce the workload of healthcare professionals and costs. A multinational time-and-motion

study revealed that the working time of healthcare professionals per administration was shortened by 13 to 17 min [6]. An Irish cost-minimization analysis estimated savings of approximately 1,600 euros per treatment course [7], whereas a Swedish single-institution study reported more than 1,100 hours of departmental working time and 600,000 euros saved in 1 year [8]. These international findings cannot be directly applied to Japan because both costs and reimbursements differ between countries. Under Japan's National Health Insurance fee schedule, the outpatient oncology chemotherapy management fee, which reimburses the administration process, is substantially higher for IV administration than for SC administration. For a 17-cycle annual course of HP alone under the fiscal year (FY) 2025 fee schedule, switching from IV to SC reduces the fee revenue by 75,000 yen per patient. This substantial revenue difference has repeatedly raised concerns among hospital administrators that adopting SC will worsen their finances. Such concerns are understandable: fees are clearly stated on each claim and easily compared per process, while the corresponding costs for supplies and staff time are calculated as aggregate hospital expenditures and are seldom itemized per process. Therefore, decision-making based only on items that can be evaluated individually, such as service fees and drug costs, makes it difficult to assess more efficient routes of administration for the drug. Although the cost-effectiveness of adjuvant HP has been evaluated in Japan [9], no detailed analysis has compared the costs of SC and IV HP administration under the Japanese fee schedule. The FY2026 revision subsequently made the outpatient oncology chemotherapy management fee applicable throughout the SC treatment course [10]. Therefore, we examined two questions: first, whether switching to SC actually worsens the administration-process balance after material and labor costs are included; and second, whether the conclusion remains applicable to institutions with different wage structures and workflows from ours. To address these questions, we performed a detailed micro-costing analysis using the total visit times from 815 HP administrations.

Materials and Methods

Study design and ethical considerations

This single-center retrospective observational study was conducted in the Department of Breast Surgery at Gifu Prefectural General Medical Center. The center's Ethics Committee approved the study (approval no. 1037), which was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived, and an Ethics Committee-approved opt-out procedure was used for the retrospective visit-time data. Using these data, we compared the costs associated with IV and SC HP administration from the hospital perspective.

Model overview and perspective

We modeled a 17-cycle standard postoperative adjuvant course over a 1-year time horizon, applying a micro-costing approach from the hospital perspective. Costs are reported in Japanese yen; no discounting was applied because the time horizon was 1 year. The administration-process balance was

defined as the outpatient oncology chemotherapy management fee revenue minus the material and labor costs. Consultation, testing, and medication costs were excluded. Accordingly, the resulting balance represents only the administration process and should not be interpreted as the overall profitability of the institution or the complete treatment course. We limited the analysis to administration-related revenue and costs to isolate the financial effect of switching from IV to SC while assuming the same HP treatment regimen. The reporting followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 statement [11].

Visit-time data

The model used the total visit times from 815 HP administrations (IV, 389; SC, 426) delivered to 79 patients with HER2-positive breast cancer between January 2024 and December 2025. The total visit time was defined as the time from automatic reception check-in to the completion of billing and was extracted from electronic medical record timestamps. This “door-to-door” definition was adopted because it accounts for the time patients spend in outpatient care, such as at the reception desk, in the chemotherapy unit, and at the accounts desk, and includes time spent visiting other departments and undergoing tests. Furthermore, since both endpoints are automatically recorded for every visit, it helps avoid recall bias and observer bias. In addition, because occasional lengthy visits may skew the distribution of visit times, the median, rather than the mean, was used as the base-case input. For HP alone, the median total visit times were 285.0 min for IV and 183.0 min for SC. The difference was consistent in both the within-patient and between-period analyses. The inputs and other model parameters are summarized in Table 1.

Table 1
Base-case model inputs and sources

Input	IV	SC	Source / range examined
Time horizon and cycles	17 cycles / 1 year	17 cycles / 1 year	Standard adjuvant course; varied 15–19
Total visit time per administration (HP alone), median, min	285.0	183.0	Measured, 815 administrations in 79 patients; patient-level bootstrap
Nurse hourly wage, yen	2,699	2,699	MHLW job tag; FY2025 Basic Survey on Wage Structure; varied $\pm 20\%$
Management fee, FY2025, points/year	8,700	1,200	FY2025 fee schedule
Management fee, FY2026, points/year	8,717	3,867	FY2026 revision (Chuikyo, 647th general assembly)
Material cost per administration, yen	2,844	16	List prices, itemized in Table 2; varied $\pm 10\%$
The administration-process balance was defined as management fee revenue minus the sum of material and labor costs; consultation fees, examination fees, and drug costs were excluded. One point = 10 yen.			
<i>FY fiscal year, HP trastuzumab plus pertuzumab, IV intravenous, MHLW Ministry of Health, Labour and Welfare, SC subcutaneous</i>			

Outpatient oncology chemotherapy management fee

The outpatient oncology chemotherapy management fee was calculated as follows. FY2025: IV, 800 points $\times 3 + 450$ points $\times 14 = 8,700$ points per year (87,000 yen); SC, 200 points $\times 6 = 1,200$ points per year (12,000 yen). FY2026: IV, 801 points $\times 3 + 451$ points $\times 14 = 8,717$ points per year (87,170 yen); SC, 351 points $\times 3 + 201$ points $\times 14 = 3,867$ points per year (38,670 yen) [10]. One point equals 10 yen. In FY2025, this fee was applicable for SC administration only for the initial six administrations; however, in the FY2026 revision, the fee became applicable throughout the entire course, and a specific fee for SC administration was newly established [10].

Material costs

The tax-inclusive list prices of consumables specific to each administration route were totaled and converted to 17-cycle costs. IV items comprised a peripheral IV catheter, dressing, infusion set, connector, normal saline, and alcohol swab. SC items comprised a hypodermic needle and alcohol swab.

Labor costs

Annual labor costs were estimated from total visit time for HP alone (IV, 285.0 min; SC, 183.0 min), 17 cycles, and a standard nurse wage of 2,699 yen/h based on the Ministry of Health, Labour and Welfare job information site [12] and the FY2025 Basic Survey on Wage Structure [13]. The same hourly wage was applied to both routes; regional and facility-specific variations were addressed through a one-way sensitivity analysis ($\pm 20\%$) and a two-way sensitivity analysis covering a range from levels below the lowest regional minimum wage to levels well above the observed values. Nurses, who primarily manage administration, were used to represent the professions involved in outpatient chemotherapy. Total visit time includes periods during which staff do not directly attend the patient. Nevertheless, the base case assumed, in principle, one staff member per patient throughout the visit, and sensitivity analysis examined the effect of this upper-bound assumption.

Sensitivity, threshold, and scenario analyses

Following economic evaluation recommendations [14, 15], robustness was assessed using five methods. First, probabilistic sensitivity analysis comprised 10,000 Monte Carlo simulations combining patient-level bootstrapping of median visit time with a uniform distribution ($\pm 20\%$) for the nurse wage; we calculated the 95% uncertainty interval (UI) and probability favoring SC. Using a patient-level bootstrap method that resamples patients with replacement rather than individual administrations, we preserved the correlation between repeated visits by the same patient. Second, one-way sensitivity analysis varied the visit-time saving over its bootstrap 95% UI, nurse wages by $\pm 20\%$, cycles from 15 to 19, and material costs by $\pm 10\%$; fees and materials were recalculated for each cycle count. Third, the two-way sensitivity analysis jointly varied the nurse wage and per-visit time savings. The annual SC – IV balance difference equaled material-cost saving + [nurse wage (yen/h) $\times$ time saving (min/visit) $\times$ 17/60] – management-fee revenue reduction. Zero defined the break-even frontier, where positive values favored SC and negative values favored IV. Fourth, the threshold analysis fixed either time saving or wage at its observed value and solved for the value of the other input that made the annual difference zero. Fifth, scenario analysis was performed to examine combination regimens with docetaxel or eribulin. As cytotoxic anticancer drugs are administered intravenously, the management fees and material costs for the HP route were assumed to be unchanged, and only the reduction in labor costs attributable to the observed visit-time differences was calculated. Probabilistic, two-way, threshold, and scenario analyses used both FY2025 and FY2026 fee schedules. A one-way sensitivity analysis is reported for FY2025, which has a smaller base-case advantage. Base-case and threshold results were calculated directly from closed-form formulas without simulation. The reproducibility of the probabilistic analysis was ensured by using a fixed random number seed. Analyses were conducted using R 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria) in RStudio 2026.08.0 + 187 (Posit, Boston, MA, USA), and Python 3 was used to independently reproduce the formula-based results.

Results

Material costs

The material cost per administration was 2,844 yen for IV (peripheral IV catheter, 220; dressing, 112; infusion set, 2,093; connector, 150; normal saline, 267; alcohol swab, 2) and 16 yen for SC (hypodermic needle, 14; alcohol swab, 2). Thus, SC reduced the per-administration material cost by 99.4%. When the same route-specific consumables were applied across the modeled adjuvant course, the annual material costs over 17 cycles were 48,348 yen for IV and 272 yen for SC (Table 2).

Table 2			
Medical consumable cost per administration for the intravenous and the subcutaneous route			
Item	IV group (yen per administration)	SC group (yen per administration)	Difference (yen)
Peripheral IV catheter / hypodermic needle	220	14	-206
Dressing	112	–	-112
Infusion set	2,093	–	-2,093
Connector	150	–	-150
Normal saline	267	–	-267
Alcohol swab	2	2	0
Total per administration	2,844	16	-2,828 (-99.4%)
Annual total (17 cycles)	48,348	272	-48,076
Costs are based on the standard list price (tax included). Dashes indicate items not used. The IV group used a peripheral IV catheter (220 yen), and the SC group used a hypodermic needle (14 yen).			
<i>IV intravenous, SC subcutaneous</i>			

Labor costs

Assuming a nurse wage of 2,699 yen/h [12, 13], the estimated annual labor costs were 217,944 yen for IV and 139,943 yen for SC. The shorter total visit time with SC therefore produced an annual labor-cost saving of 78,001 yen.

Administration-process balance

Under the FY2025 fee schedule, annual fee revenue was 87,000 yen for IV and 12,000 yen for SC, 75,000 yen lower with SC. Annual material-plus-labor expenditure was 266,292 yen for IV and 140,215 yen for SC. The administration-process balance was therefore – 179,292 yen for IV and – 128,215 yen for SC, an annual improvement of 51,077 yen (Table 3, Fig. 1a, b). Under the FY2026 fee schedule, when the management fee became billable throughout the SC course [10], annual fee revenue was 87,170 yen for IV and 38,670 yen for SC, and the balances were – 179,122 and – 101,545 yen, respectively, increasing the difference to 77,577 yen. Both balances are negative because consultation fees and drug revenue were excluded; therefore, these figures do not represent the profitability of the entire treatment course.

Table 3

Annual administration-process cost and economic impact of intravenous and subcutaneous administration (17-cycle adjuvant model, micro-costing method)

Item (yen per patient per year)	IV, FY2025	SC, FY2025	Difference (FY2025, SC – IV)	IV, FY2026	SC, FY2026	Difference (FY2026, SC – IV)
Outpatient oncology chemotherapy management fee	87,000	12,000	–75,000	87,170	38,670	–48,500
Billing points per year	8,700 pts	1,200 pts	–7,500 pts	8,717 pts	3,867 pts	–4,850 pts
Total expenditure	266,292	140,215	–126,077	266,292	140,215	–126,077
Material cost	48,348	272	–48,076	48,348	272	–48,076
Labor cost	217,944	139,943	–78,001	217,944	139,943	–78,001
Administration-process balance	–179,292	–128,215	+ 51,077	–179,122	–101,545	+ 77,577
Administration-process balance = outpatient oncology chemotherapy management fee – (material cost + labor cost). Consultation fees, drug revenue, and examination fees are excluded; therefore, the balance reflects the administration process alone and not the overall profitability of the institution.						
FY2025 fee schedule: IV, 800 points for administrations 1–3 and 450 points for administrations 4 and beyond (8,700 points/year); SC, 200 points for administrations 1–6 and not billable thereafter (1,200 points/year). After the FY2026 revision: IV, 801 points × 3 + 451 points × 14 = 8,717 points/year; SC, 351 points × 3 + 201 points × 14 = 3,867 points/year (Central Social Insurance Medical Council, 647th General Assembly). One point = 10 yen.						
Labor cost was estimated as the total visit time for HP alone (IV, 285.0 min; SC, 183.0 min) × 17 cycles × a standard nurse hourly wage of 2,699 yen (MHLW job tag and the FY2025 Basic Survey on Wage Structure).						
<i>FY fiscal year, HP trastuzumab plus pertuzumab, IV intravenous, MHLW Ministry of Health, Labour and Welfare, SC subcutaneous</i>						

Probabilistic, one-way, and two-way sensitivity analyses and threshold analysis

In the probabilistic sensitivity analysis, the median SC advantage across 10,000 simulations was 51,077 yen per year (95% UI, 29,576–76,003) in FY2025 and 77,577 yen per year (95% UI, 56,076–102,503) in FY2026. SC was favorable in all 10,000 simulations. In the one-way sensitivity analysis, visit-time savings (95% UI based on the bootstrap method, 80.5–123.0 min) and nurse wages had the largest effect. When time savings were varied within the bootstrap 95% UI, the annual benefit ranged from 34,636 to 67,136 yen; when the hourly wage was varied by ± 20%, the benefit ranged from 35,477 to 66,677 yen. The effects of the number of cycles (15–19; 45,245–56,910 yen) and material costs (± 10%; 46,270–55,885

yen) were smaller. However, the SC – IV balance difference remained above zero throughout every examined range, including variations in the cycle number and material costs (Table 4, Fig. 2). Therefore, changes in a single variable within the predefined ranges did not alter the conclusions of the base case. In this analysis, the two factors with the greatest impact were examined individually, and in the subsequent two-way sensitivity analysis, they were examined in combination. The remaining input variables were examined within their predefined ranges.

Table 4
Uncertainty and threshold analyses of the administration-process balance

Analysis	Basis	Estimate	95% UI or range
Administration-process balance under FY2025, yen per patient per year			
Base case	–	51,077	–
Probabilistic sensitivity analysis	10,000 simulations	51,077	29,576–76,003
Visit-time saving varied	95% UI (80.5–123.0 min)	–	34,636–67,136
Nurse wage varied	± 20%	–	35,477–66,677
Cycles per year varied	15–19 ^a	–	45,245–56,910
Material cost varied	± 10%	–	46,270–55,885
Administration-process balance under FY2026, yen per patient per year			
Base case	–	77,577	–
Probabilistic sensitivity analysis	10,000 simulations	77,577	56,076–102,503
Threshold at which the advantage of SC administration disappears			
Nurse hourly wage, FY2025	–	932 yen/h	actual 2,699 yen
Time saving per administration, FY2025	–	35.2 min	actual 102.0 min
Two-way frontier (wage × saving), FY2025	–	95,026 yen·min/h	actual 275,298
Nurse hourly wage, FY2026	–	15 yen/h	actual 2,699 yen
Time saving per administration, FY2026	–	0.6 min	actual 102.0 min
Two-way frontier (wage × saving), FY2026	–	1,496 yen·min/h	actual 275,298
Scenario: concomitant cytotoxic phases, yen per administration^b			

Analysis	Basis	Estimate	95% UI or range
Administration-process balance under FY2025, yen per patient per year			
HP plus docetaxel	time saving 81.5 min	+ 3,666	–
HP plus eribulin	time saving 101.0 min	+ 4,543	–
Projection per 100 patients per year (HP alone), yen			
FY2025	–	+ 5.11 million	–
FY2026	–	+ 7.76 million	–
Values are the difference in the administration-process balance, SC minus IV; a positive value favors SC administration. Probabilistic sensitivity analysis drew 10,000 seeded Monte Carlo simulations combining a patient-level bootstrap of the visit-time medians with a uniform distribution ($\pm 20\%$) for the nurse wage; SC administration was favorable in 100% of the simulations. The one-way rows vary a single input at a time under the FY2025 fee schedule. The threshold rows give the value at which the difference becomes zero, alongside the value actually observed; the two-way frontier is the product of nurse wage and time saving below which the balance favors IV administration (Fig. 3). Dashes indicate quantities that do not apply.			
^a Fee revenue and material cost were recalculated from the point schedule at each cycle count (IV, 800 [801] points for cycles 1–3 and 450 [451] thereafter; SC, 200 points for cycles 1–6 only in FY2025 and 351 points $\times$ 3 plus 201 points thereafter in FY2026).			
^b The cytotoxic agent continues to be infused intravenously; therefore, the management fee and material cost remain unchanged by the route of HP; the advantage equals the labor saving alone (visit-time difference $\times$ nurse wage).			
<i>FY fiscal year, HP trastuzumab plus pertuzumab, IV intravenous, SC subcutaneous, UI uncertainty interval</i>			

In the two-way sensitivity analysis, the break-even product of nurse hourly wage and time saving was 95,026 yen·min/h in FY2025 and 1,496 yen·min/h in FY2026 (Fig. 3). Products above the relevant value favored SC, whereas those below favored IV. The higher the wage, the less time is needed to offset the lower fee revenue generated by SC. At the lowest FY2025 regional minimum wage of 1,023 yen/h [16], the required time saving per administration was 92.9 min; however, the observed value of 102.0 min exceeded this value. The observed combination (2,699 yen/h, 102.0 min) favored SC under both schedules.

In the threshold analysis, when time savings were fixed at 102.0 min, the break-even nurse wages were 932 yen/h in FY2025 and 15 yen/h in FY2026. When the hourly wage was fixed at 2,699 yen/h, the break-even time savings were 35.2 and 0.6 min, respectively. Each threshold applies only when the other input

variable is fixed at its observed value; therefore, these values should not be interpreted as universal criteria.

Scenario analysis and facility-specific projections

Since cytotoxic anticancer drugs, such as docetaxel or eribulin, were administered intravenously when used in combination with HP, there were no differences in the management fees and material costs based on the HP administration route. SC shortened median total visit time by 81.5 min for docetaxel and 101.0 min for eribulin, corresponding to labor cost savings of 3,666 and 4,543 yen per administration, respectively. Therefore, the economic advantage of SC was maintained even during combination chemotherapy. Thus, SC was favored in every uncertainty analysis: in all 10,000 probabilistic simulations, across all prespecified one-way ranges, at the observed wage–time combination under both fee schedules, and in both concomitant-chemotherapy scenarios. For an institution treating 100 patients with HP alone annually, switching to SC improved the financial balance by 5.11 and 7.76 million yen in FY2025 and FY2026, respectively. The nursing workload and time occupied by chemotherapy chairs were reduced by 2,890 hours. Assuming 2,000 working hours per full-time equivalent employee, the reduction achieved by this model was equivalent to approximately 1.4 full-time equivalent person-years.

Discussion

The central finding of this study is that switching the route of HP administration from IV to SC does not worsen, but rather improves, the financial performance of the administration process at Japanese medical institutions. Although the difference in management fees for FY2025 clearly favors IV and could be a factor discouraging the adoption of SC, a comparison based only on reimbursement amounts overlooks the additional materials and time required for IV. In this model, savings in materials and labor costs exceeded the decrease in management fee revenue associated with SC; consequently, the administration-process balance improved in FY2025 and improved further in FY2026. Specifically, the 75,000 yen decrease in management fee revenue in FY2025 was offset by savings of 48,076 yen in material costs and 78,001 yen in labor costs, resulting in a net improvement of 51,077 yen. In FY2026, while the decrease in revenue narrowed to 48,500 yen, cost savings remained unchanged, resulting in an improvement of 77,577 yen. Because these route-specific differences recur over 17 cycles, modest changes per administration accumulate into meaningful annual effects for both patients and facilities. The negative balance estimated for both routes should not be interpreted as a loss on the complete treatment course because consultation fees, examinations, and drug revenue were outside the scope of the analysis. To our knowledge, this is the first micro-costing analysis of this question under Japan's fee-for-service system to quantify uncertainty and the first economic analysis of HP to incorporate the FY2026 revision. While previous models in Japan [9] and internationally [17] have examined the cost-effectiveness of the drugs themselves, this study focuses on the method of administration. This distinction is important because even the same drug regimen can be delivered through pathways that vary substantially in terms of staff time, supplies, and facility utilization.

Generalizability based on sensitivity and threshold analyses

A single-facility cost analysis may depend on the facility's wages and workflow. Therefore, rather than assuming that the base case applies uniformly, we used two-way and threshold analyses to identify the conditions under which the results would be reversed. The two-way analysis shows that the time savings required for SC to be advantageous depend on the hourly wage. For example, at the lowest regional minimum wage of 1,023 yen/h in FY2025, SC requires a time saving of at least 92.9 min per administration; the observed savings of 102.0 min met this condition. Therefore, each facility can use Fig. 3 to determine where its own combination of hourly wage and time savings falls relative to the break-even frontier. This enables facility-specific interpretations that are not solely dependent on the wages and workflows measured at our hospital. Probabilistic analysis complements this by addressing the sampling uncertainty. Even when visit time and wages were simultaneously varied across 10,000 simulations, the lower limit of the 95% UI (29,576 yen in FY2025) remained positive, indicating that it is unlikely that these findings are the result of sampling variation within a single-facility cohort. Unlike the two-way frontier, each threshold for a single variable applies only when the other input remains constant. The 932 yen/h threshold was obtained by fixing time savings at 102.0 min, and the 35.2-min threshold was obtained by fixing the hourly wage at 2,699 yen/h; neither is a universal or standalone criterion. Nevertheless, the wage thresholds fall below the lowest regional minimum wage, and the time thresholds represent approximately one-third of the observed values, which is smaller than the time savings reported in previous studies on SC anti-HER2 therapy [6–8]. Under the FY2026 fee schedule, savings in material costs alone nearly offset the difference in management fees, and the thresholds drop to 15 yen/h and 0.6 min, respectively. Taken together, these analyses suggest that the superiority of SC is likely to persist, despite moderate differences in wages and workflows among Japanese facilities.

Scenario analyses also confirmed the superiority of SC when combined with chemotherapy. As management fees and material costs remained constant across HP routes owing to IV cytotoxic anticancer drugs, the comparison during this period depended on labor cost reductions resulting from shorter visit times. These positive results indicate that even if SC is introduced at the start of treatment, it is unlikely to result in economic disadvantages during the combination therapy or HP-alone phase. As HP is typically initiated in combination with cytotoxic chemotherapy, the combination therapy phase is the stage at which facilities newly adopting SC first experience the economic impact of the switch. The finding that no disadvantages arise at this stage removes a potential barrier to initiating SC at the start of treatment.

Relationship to international evidence and policy implications

The results of this study are consistent with cost-minimization analyses conducted in Ireland and Sweden [7, 8] and with multinational evidence on healthcare professionals' working hours [6]. However, because the endpoints differ, caution should be exercised when directly comparing the figures. While a

multinational time-and-motion study measured healthcare providers' actual working time and reported a reduction of 13 to 17 min per visit [6], this model evaluated the total visit time from arrival to checkout, with an observed difference of 102.0 min. These two approaches address different questions. The actual working time approximates the incremental staffing requirement, whereas the time from arrival to checkout approximates the occupancy of outpatient infrastructure such as IV chairs. If the time saving were limited to this level of actual working time, it would fall below the FY2025 threshold of 35.2 min; therefore, the conclusion for FY2025 would depend on the value the facility places on the freed-up chair time. In contrast, because the threshold for FY2026 is 0.6 min, the conclusion is not influenced by the choice of time definition. Japan is distinctive because the lower fee for SC creates a reimbursement disparity that disadvantages the more efficient route when only revenue is considered. The fact that SC administration remained advantageous, even with this structure, supports the robustness of this conclusion. A system that pays higher fees for administration routes that take more time may create incentives that counter patients' time-related benefits and healthcare providers' operational efficiency. The FY2026 revision narrowed this fee disparity, and this analysis quantitatively demonstrates how these changes reinforce the balance favoring the SC route. As medical reimbursement rates are revised every two years, the thresholds reported in this study serve as a transparent foundation for anticipating the impact of future revisions. Because the break-even frontier shifts in proportion to the difference in management fees, any future narrowing or widening of the fee gap between IV and SC can be directly mapped to the required combination of wage costs and time savings. Facility-level projections also demonstrate that even a slight difference per patient has important operational implications. Specifically, in a medical department treating 100 patients annually, the choice of treatment pathway can shift the balance of revenues and expenses by approximately 5–8 million yen and reduce the nursing workload and the occupancy rate of IV chairs by an amount equivalent to approximately 1.4 person-years. At this scale, the annual financial difference is likely to be sufficient to support additional staff. The 2,890 hours freed up may, in practical terms, be even more important than the financial balance. Constraints in outpatient chemotherapy units generally stem not from consumable budgets but from IV chair time and nursing time; the capacity freed up by SC administration can be redirected toward an increasing patient load and other time-intensive regimens without the need to add chairs or staff members. Viewing the choice of administration route as a capacity-based decision rather than a comparison of management fees may provide a more appropriate managerial perspective.

Limitations

This study has several limitations. First, the data were collected from a single healthcare facility, and workflows, staffing levels, and wages may differ across facilities. Although two-way and threshold analyses define the applicable conditions, they cannot replicate every possible process. Second, because the total visit time was valued at the nurse wage, unoccupied waiting time was also counted as labor, resulting in an upper-bound estimate of the absolute cost. However, the same method was applied to both administration routes, and even when the time saving was reduced to two-thirds of the observed value, the conclusions for FY2025 remained unchanged. Nevertheless, future studies should directly measure the actual staff-related labor time. Third, material costs were based on list prices, including

taxes, and may differ from the purchase prices specific to each medical institution. Therefore, estimates of absolute expenditures should be interpreted in light of local procurement systems. Fourth, labor costs were evaluated based solely on nurses' wages; the time spent by pharmacists and physicians on the aseptic preparation of each of the two IV medications was not measured or accounted for individually. As these tasks are associated with IV administration rather than SC administration, their exclusion makes the main conclusion more conservative.

Additional costs resulting from extravasation or infusion reactions were also excluded from the analysis. As these are primarily associated with IV administration, their inclusion could potentially favor SC administration over IV administration. Drug costs and waste were also excluded; therefore, the conclusions were limited to the administration process. In the scenario analysis, we assumed that administration-related costs would remain equivalent even with combination therapy, as cytotoxic therapy continues to be administered intravenously. Furthermore, the projected 100 cases were an arithmetic calculation based on the case composition of HP alone, rather than a direct observation of 100 patients. Finally, while the base case assumed 17 cycles of adjuvant therapy, the conclusions remained unchanged when recalculated for 15–19 cycles.

Conclusion

Under Japan's medical fee-for-service system, switching the administration route of HP from IV to SC improved the financial outcome of the modeled administration process by 51,077 yen/patient/year in FY2025 and 77,577 yen in FY2026. SC administration was advantageous in all 10,000 probabilistic simulations and across all specified one- and two-way ranges. A favorable effect was also observed with concomitant IV chemotherapy. These findings suggest that the adoption of a fixed-dose SC formulation should not be postponed solely because of lower management fees. Switching to SC administration has the potential to improve the efficiency of the administration process while reducing the time burden on patients and the workload of healthcare professionals.

Abbreviations

CHEERS, Consolidated Health Economic Evaluation Reporting Standards; FY, fiscal year; HER2, human epidermal growth factor receptor 2; HP, trastuzumab plus pertuzumab; IV, intravenous; SC, subcutaneous; UI, uncertainty interval

Declarations

Compliance with Ethical Standards

Funding

Conflict of interest

JM: Honoraria: AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly Japan, Exact Sciences, Gilead Sciences, Johnson & Johnson, Kyowa Kirin, MSD, Nippon Kayaku, Pfizer, and Taiho Pharmaceutical. NM: Grants: Abbott, Chugai Pharmaceutical, Covidien Japan, JMS, Johnson & Johnson, Kaken Pharmaceutical, Nippon Kayaku, Nippon Zoki Pharmaceutical, TERUMO, and Toray Medical, Research Fund: Ark Medical Solutions, Astellas Pharma, AstraZeneca, e-NA Biotec, EPS, MSD, Ono Pharmaceutical, PPD-SNBL, Syneos Health, Taiho Pharmaceutical, Takeda Pharmaceutical, and Tigerise. Honoraria: Abbott, Alfresa Pharma, AMCO, Asahi Kasei Therapeutics, Astellas Pharma, AstraZeneca, Bayer Yakuhin, Bristol Myers Squibb, Chugai Pharmaceutical, Covidien Japan, Daiichi Sankyo, EA Pharma, Eisai, Eli Lilly, Guardant Health Japan, Intuitive Surgical, Johnson & Johnson, Kaken Pharmaceutical, Kyowa Kirin, LTT Bio-Pharma, MC Medical, Merck Biopharma, Miyarisan Pharmaceutical, MSD, Novartis, Novo Nordisk Pharma, Olympus Marketing, Ono Pharmaceutical, Shionogi, Sysmex, Taiho Pharmaceutical, TAKATA Pharmaceutical, Takeda Pharmaceutical, TERUMO, Tsumura, Yakult Honsha, and Zeria Pharmaceutical. MF: Honoraria: AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly Japan, Exact Sciences, Gilead Sciences, Johnson & Johnson, Kyowa Kirin, MSD, Nippon Kayaku, Pfizer, and Taiho Pharmaceutical.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Ethics Committee of Gifu Prefectural General Medical Center, approval no. 1037) and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

For this type of study, formal consent is not required. Written informed consent was waived, and an opt-out procedure approved by the Ethics Committee was used.

Author contributions

Conceptualization: JM; data curation: JM, MT, TN; formal analysis: JM, HK; investigation: JM, MT, TN, KI, HO, SM; methodology: JM, HK; project administration: JM, AO, YN; supervision: NM, MF; writing of the original draft: JM; review and editing of the manuscript: all authors. All authors have read and approved the final manuscript.

Acknowledgments

We thank the staff of the Departments of Breast Surgery, Nursing, Pharmacy, and Medical Affairs at Gifu Prefectural General Medical Center for their assistance with data collection. DeepL was used for English translation and Paperpal for English proofreading.

Data availability

Anonymized datasets and the analysis scripts used to reproduce the figures in this study are available from the corresponding author upon reasonable request.

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Figures

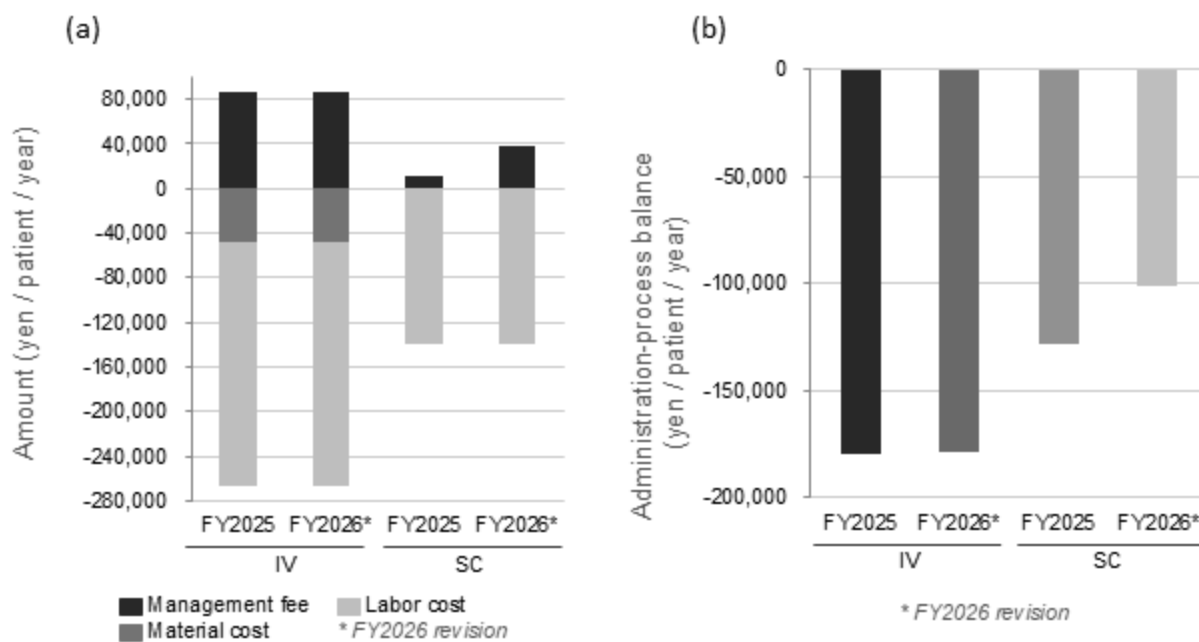


Figure 1

Annual administration-process cost components and balance by route. **a** Management fee revenue above zero and material and time-based labor costs below zero for each route in a 17-cycle postoperative adjuvant model. **b** Modeled balance per patient-year, which equals management fee revenue minus material and time-based labor costs. Labor costs are an upper-bound estimate obtained by valuing the total visit time at the hourly wage of a nurse. Asterisks indicate FY2026 values. FY, fiscal year; IV, intravenous; SC, subcutaneous

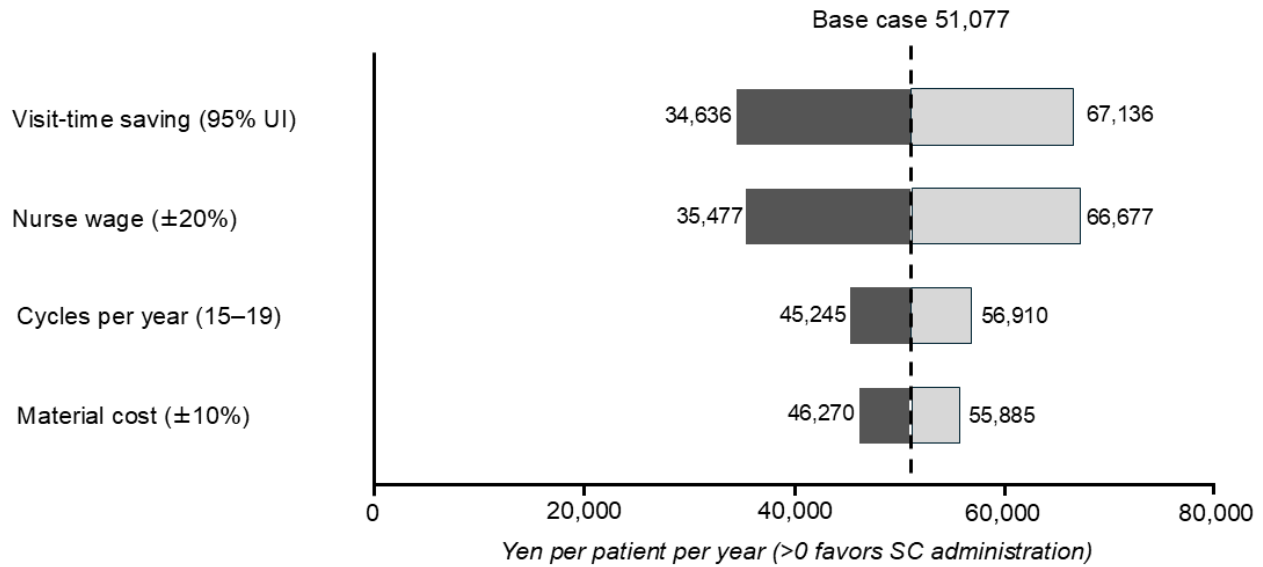


Figure 2

One-way sensitivity analysis for FY2025. Each bar shows the result when one input is varied over its prespecified range; the vertical dashed line marks the base case of 51,077 yen. The SC–IV difference remained positive throughout the examined range. Labor costs are upper-bound estimates based on the total visit time. FY, fiscal year; IV, intravenous; SC, subcutaneous; UI, uncertainty interval

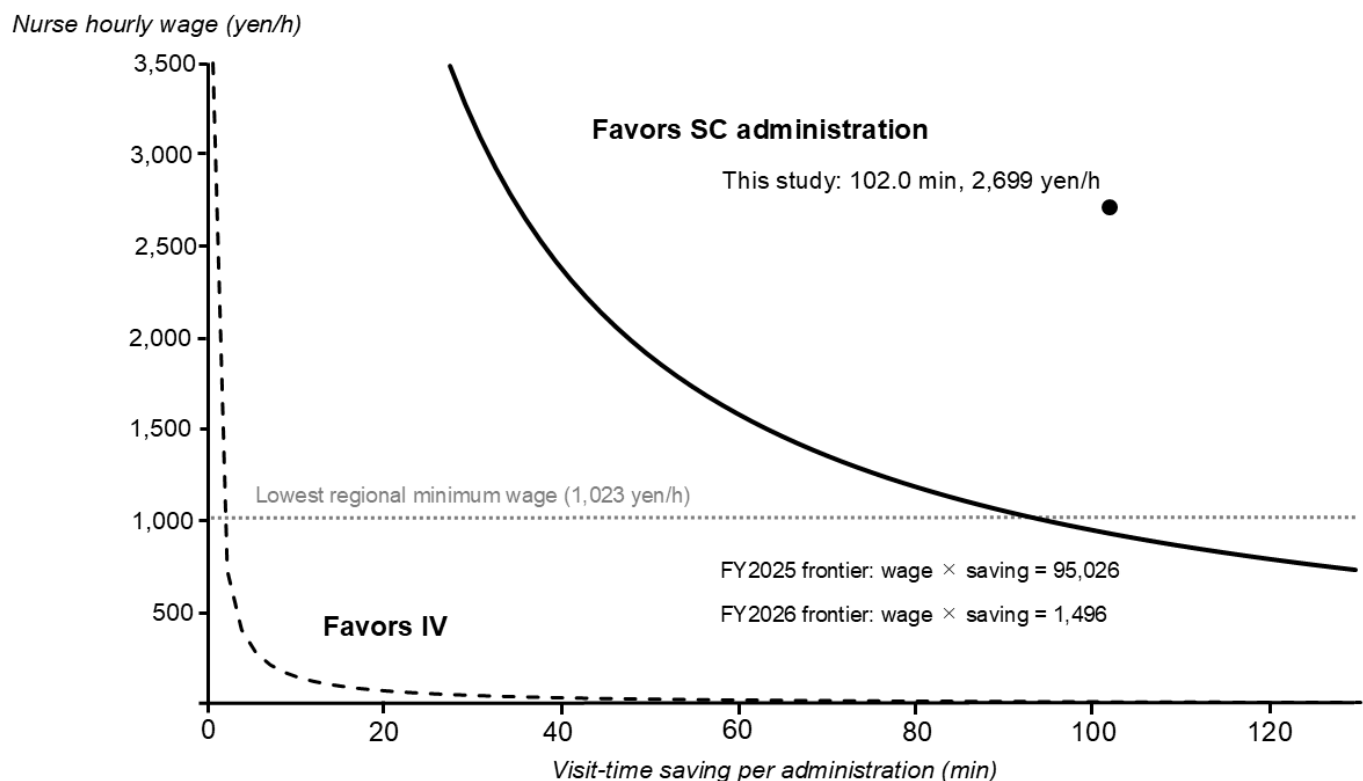


Figure 3

Joint effects of nurse wages and time saving. The two-way sensitivity analysis varied nurse hourly wages and visit-time savings per administration simultaneously. The solid line represents the FY2025 break-even frontier (wage × time saved = 95,026 yen·min/h), and the dashed line represents the FY2026 frontier (1,496 yen·min/h). Products above a frontier favor SC, and those below favor IV. The circle marks the combination observed in this study (2,699 yen/h; 102.0 min), and the horizontal dotted line marks the lowest FY2025 regional minimum wage (1,023 yen/h). FY, fiscal year; IV, intravenous; SC, subcutaneous