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Scientific Article

Impact of the COVID-19 Pandemic on Hypofractionated Radiation Therapy Use for Breast Cancer in Japan: A Nationwide Study

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Purpose: Hypofractionated radiation therapy (RT) was recommended for several cancer sites to reduce outpatient visits during the COVID-19 pandemic. This study aimed to identify the impact of the pandemic on hypofractionated RT for breast cancer in Japan.
Methods and Materials: The monthly number of courses for hypofractionated and conventional RTs was counted using sample data sets from the National Database of Health Insurance Claims and Specific Health Checkups of Japan, a nationwide database accumulating insurance claims data comprehensively. Changes in the number of hypofractionated and conventional RTs were estimated using an interrupted time-series analysis.
Results: The number of hypofractionated RT courses gradually increased before the pandemic in contrast to that of conventional RT courses, which gradually decreased. However, conventional RT remained outnumbered by hypofractionated RT throughout the observation period. After the outbreak of the pandemic, the use of hypofractionated RT significantly increased in April 2020 (1312 courses; 95% CI, 801-1823) but decreased in October 2020 (−601; 95% CI, −1111 to −92). Subgroup analysis by age and the number of beds in medical institutions revealed similar trends.
Conclusions: Although conventional RT for breast cancer has been gradually replaced by hypofractionated RT, it remains predominant. The use of hypofractionated RT increased briefly early in the COVID-19 pandemic; however, this increase was not sustained, unlike in other countries. Considering the benefits of hypofractionated RT for breast cancer, its use should be encouraged in Japan.

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This study was based on the data from National Database (NDB) of Health Insurance Claims and Specific Health Checkups of Japan. The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form, eg, publications). At the time of request data were provided by the Ministry of Health, Labour, and Welfare (MHLW), but now NDB are owned and maintained by the MHLW.

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Introduction

The COVID-19 pandemic has greatly impacted cancer care. Health care providers were forced to deviate from their standard of care to prevent infections and deal with the shortage of resources. Several experts issued practice recommendations for cancer care during the pandemic to support health care providers in making difficult decisions during the crisis. In these, hypofractionated radiation therapy (RT) in several cancer sites was proposed to reduce patient visits, resulting in a reduction in potential exposure to SARS-CoV-2.[1-5] To date, previous studies in various countries, including the United Kingdom,[6-8] Spain,[9] the United States,[10,11] Canada,[12-14] India,[15] and Brazil,[16] have reported an increase in the use of hypofractionated RT during the pandemic. However, most of these were single-center studies [8,9,11,13-15] or questionnaire surveys with relatively low response rates,[10,16] with low generalizability of their results. Additionally, regional differences in the use of hypofractionation likely stem from differences in health care systems, local guidelines for RT, and professional cultures.[17] In particular, the Asia-Pacific region, including Japan, lags in the use of hypofractionated RT.[17]

We aimed to identify changes in the uptake of hypofractionated RT for breast cancer during the pandemic using data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB).

Materials and Methods

Data source

We used sample data sets from the NDB administered by the Ministry of Health, Labour, and Welfare (MHLW). The characteristics of the database have been described previously.[18-20] The features of the sample data sets were as follows: (1) data sets were created by MHLW 4 times a year (January, April, July, and October); (2) data were randomly sampled from the NDB at a sampling rate of 1% for the medical outpatient claims and of 10% for medical inpatient and diagnosis procedure combination claims; and (3) personally identifiable information was excluded from the data sets. Sample data sets from January 2015 to January 2021 were obtained from the MHLW for this study.

Target treatments and extraction procedures

The targeted treatments for breast cancer include hypofractionation and conventional RTs. Outpatient claims were used because RT after breast-conserving surgery is performed on an outpatient basis. In Japan, adjuvant RT to the whole breast is administered as a conventional regimen, such as 50 Gy administered in 25 fractions at a dose of 2 Gy per fraction over 5 weeks. Additionally, a moderate hypofractionated RT regimen, such as 42.56 Gy administered in 16 fractions at 2.66 Gy per fraction over 22 days, is also recommended. Under the health care system in Japan, from April 2014, an additional payment for hypofractionation can be claimed when irradiation of the whole breast at 2.5 Gy or more per fraction is performed. Using this additional payment, the insurance claims for hypofractionated and conventional RT for breast cancer were extracted (Appendix E1).

Creating the time-series data

Using the extracted insurance claims, the time-series data for each RT were created as follows: (1) we counted the number of claims for each month; and (2) the counted number was multiplied by 100 (the reciprocal of the extraction rate). This number roughly corresponded to the number of RT courses each month (Appendix E2).

Statistical analysis

We performed an interrupted time-series analysis using the seasonal autoregressive integrated moving average (SARIMA) model based on the method by Schaffer et al.[21] All statistical analyses were performed using R version 4.2.0, an open-source software package. First, we determined the SARIMA components $(p, d, q) \times (P, D, Q)s$, with the lowest Akaike's information criterion. The number of seasonality (s) was determined to be 4 because our time-series data were created 4 times per calendar year (in January, April, July, and October). In this step, all 25-point time-series data were used, and step-change variables during the pandemic were included in the model as external regressors. The step-change variables took the value of 1 for each month during the pandemic and 0 otherwise. The estimates of the step-change variables represent the changes in numbers for each month during the pandemic period. Second, the number during the pandemic was predicted using only prepandemic points (21 points), which is a counterfactual number, assuming that the pandemic did not occur. In this step, the SARIMA components are applied to those determined in the first step. The observed and counterfactual numbers with 95% CIs were plotted in the same graph (Figs. 1, 2, and 3). Subgroup analysis by age category (<50 and ≥50 years) was performed because the clinical practice guidelines of the Japanese Breast Cancer Society recommended moderate hypofractionated RT only for women aged >50 years until June 2022. Moreover, subgroup analysis by the number of beds in the medical institutions (<600 and ≥600 beds) was performed, which equalized the observed number of hypofractionated RT courses for breast cancers between groups.

Ethical statement

The sample data sets from the NDB were used in this study. These data sets were anonymized when created in the MHLW. Therefore, informed consent was not required. This study was approved by the Research Ethics Committee of the Chiba Foundation for Health Promotion and Disease Prevention (approval number R3-4) and conducted in accordance with the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Biological Research Involving Human Subjects.

Results

We analyzed 20,452,831 medical outpatient claims. Of the 226 insurance claims extracted for hypofractionated RT and the 1469 claims for conventional RT, the information on the number of beds was missing from 6 and 36 claims, respectively. Therefore, these claims were excluded from subgroup analysis by the number of beds in medical institutions.

The trends in the number of conventional and hypofractionated RT courses for breast cancer are shown in Fig. 1. Throughout the observation period, the number of conventional RT courses exceeded the number of hypofractionated RT courses. However, the number of hypofractionated RT courses gradually increased, whereas that of conventional RT courses gradually decreased, suggesting that conventional RT was gradually replaced by hypofractionated RT. This trajectory was more pronounced in the age group of ≥50 years, as presented in Fig. 2. The subgroup analysis by the number of beds in medical institutions revealed that conventional RT was predominant, and the number of hypofractionated RT courses gradually increased throughout the observation period in medical institutions with <600 beds (Fig. 3A) as well as those with ≥600 beds (Fig. 3B). However, the number of hypofractionated RT courses relative to the number of conventional RT courses was apparently higher in medical institutions with ≥600 beds than that in those with <600 beds, indicating that hypofractionated RT is more likely to be selected in medical institutions with a larger number of beds.

The changes in the number of conventional and hypofractionated RT courses for breast cancer during the pandemic are shown in Table 1. The number of hypofractionated RT courses significantly increased in April 2020 (1312; 95% CI, 801-1823) but decreased in October 2020 (−601; 95% CI, −1111 to −92). Subgroup analysis by age indicated similar results; the number increased in April 2020 in both age groups of <50 (705; 95% CI, 513-897) and ≥50 years (526; 95% CI, 58-994), but decreased in October 2020 in the age group of ≥50 years (−898; 95% CI, −1349 to −447). The subgroup analysis by the number of beds revealed that the number increased in April 2020 in medical institutions with ≥600 beds (800; 95% CI, 308-1292), but not in those with <600 beds. However, Fig. 3A reveals an increased trend in the number of hypofractionated RT courses in April 2020 in medical institutions with <600 beds.

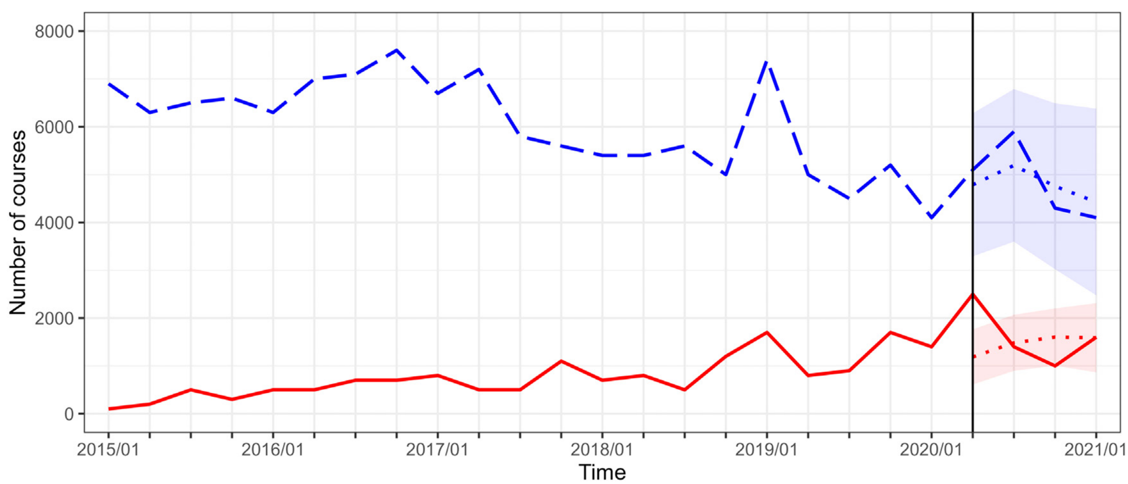

Figure 1 Trends in the number of hypofractionated and conventional fractionated radiation therapy (RT) courses for breast cancer in all women. The observed numbers for hypofractionated and conventional fractionated RT courses are indicated by solid and dashed lines, respectively. The counterfactual numbers during the COVID-19 pandemic are indicated by dotted lines, and 95% CIs for hypofractionated and conventional fractionated RT are denoted by shading. The data are presented 4 times per calendar year: in January, April, July, and October.

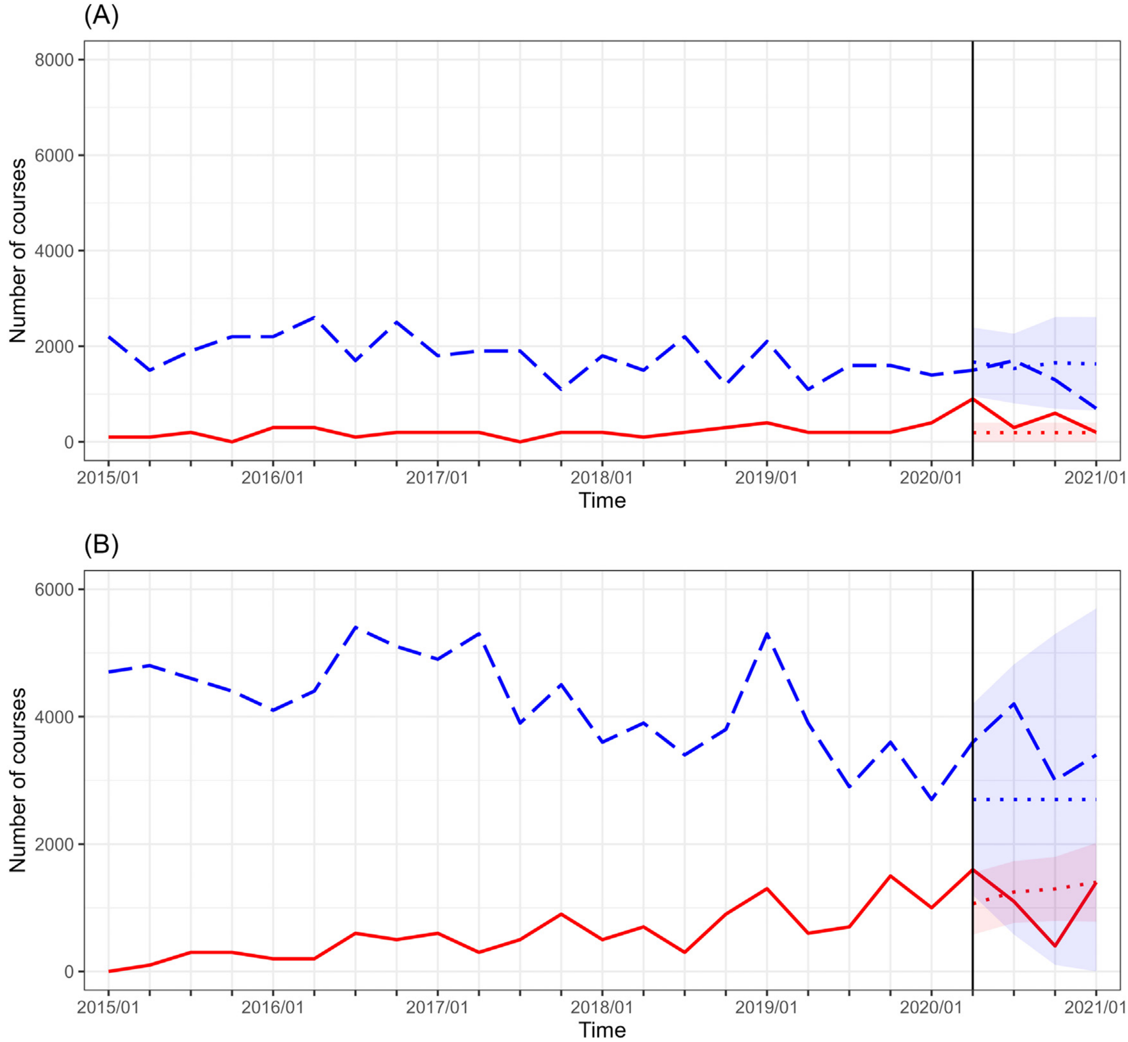

Figure 2 Subgroup analysis by age. (A) <50 years; (B) ≥50 years. The observed numbers for hypofractionated and conventional fractionated radiation therapy (RT) courses are indicated by solid and dashed lines, respectively. The counterfactual numbers during the COVID-19 pandemic are indicated by dotted lines, and 95% CIs for hypofractionated and conventional fractionated RT are denoted by shading. The data are presented 4 times per calendar year: in January, April, July, and October.

Discussion

This study revealed the changes in the fraction patterns delivered for breast cancer before and after the onset of the COVID-19 pandemic in Japan using sample data sets from the NDB.

The number of hypofractionated RT courses increased in April 2020, indicating that hypofractionation for breast cancer was used early during the pandemic to reduce outpatient visits. However, this increase was temporary. In a study performed in Manitoba, Canada, the number of RT fractions for all cancers was disproportionately reduced compared with the number of first radiation treatments; this trend continued until the end of the observation period (June 30, 2021).[12] A population-based study in England, the United Kingdom, reported that most RT regimes for breast cancer were administered at 40 Gy in 15 fractions (moderate hypofractionation) before the pandemic. After the first UK lockdown, the frequency of the RT regimen of 26 Gy in 5 fractions (ultrahypofraction) increased sharply, and the number of ultrahypofractionated RT regimes exceeded that of moderate RT regimes.[6] Furthermore, the use of ultrahypofractionated RT remained predominant until the end of the observation period (June 28, 2020). The uptake of hypofractionated RT was not sustained in Japan, unlike in Canada and the United Kingdom, possibly for the following reasons. First, randomized controlled trials (RCTs) were conducted in Canada and the United Kingdom to evaluate the efficacy of hypofractionated RT for breast cancer.[22-28] However, no RCTs were conducted in Japan. Therefore, concerns about acute and late adverse reactions due to a large-

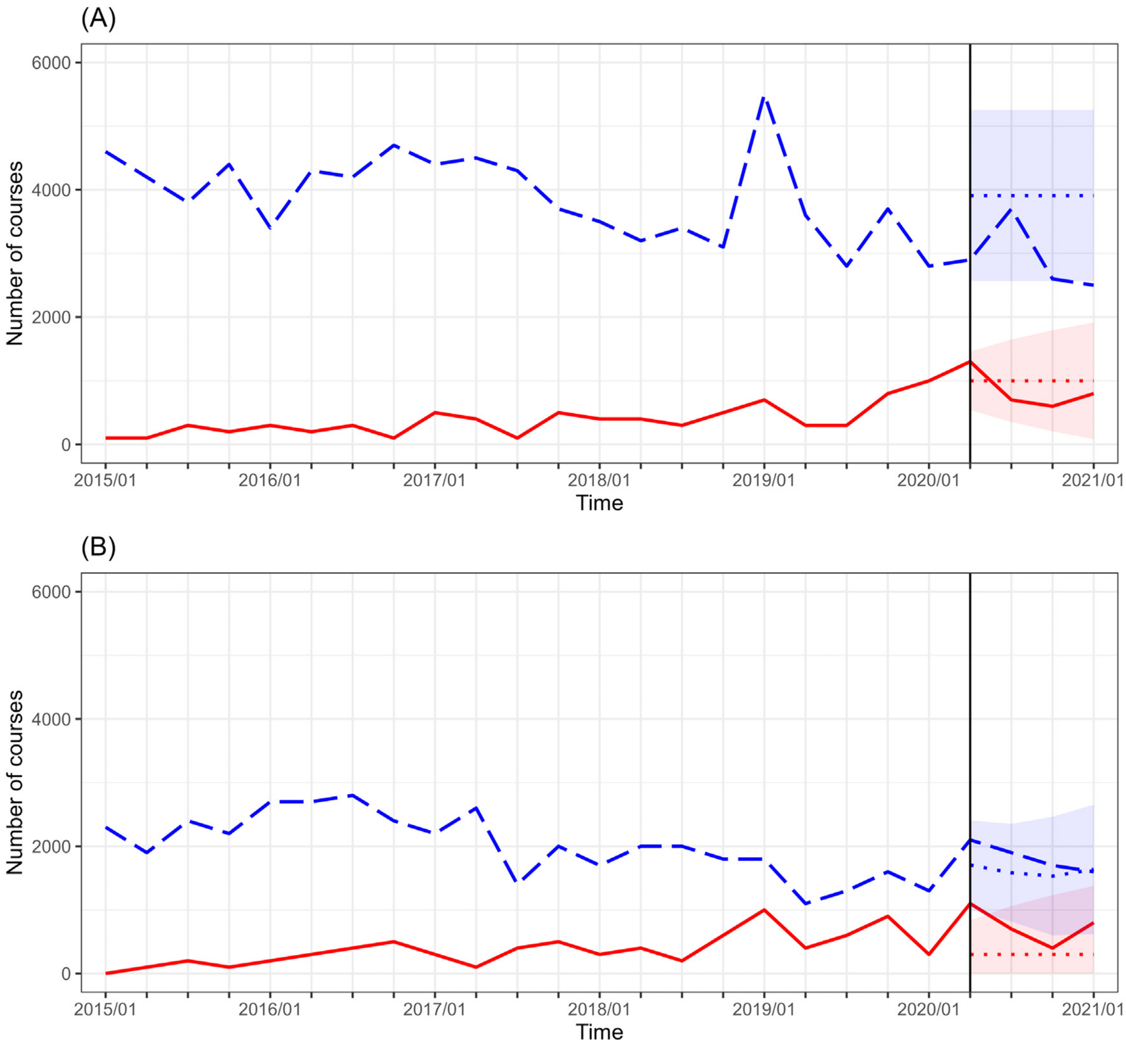

Figure 3 Subgroup analysis by the number of beds in medical institutions. (A) <600 beds; (B) ≥600 beds. The observed numbers for hypofractionated and conventional fractionated radiation therapy (RT) courses are indicated by solid and dashed lines, respectively. The counterfactual numbers during the COVID-19 pandemic are indicated by dotted lines, and 95% CIs for hypofractionated and conventional fractionated RT are denoted by shading. The data are presented 4 times per calendar year: in January, April, July, and October.

fraction dose, considering the difference in physique between Japanese and Western women, may have prevented the continued use of hypofractionation. Second, the public health insurance system in Japan adopts a pay-per-fraction scheme. Additional payments for hypofractionation can be claimed when irradiation of the entire breast at 2.5 Gy or more per fraction is performed. However, because the total payment for conventional RT for breast cancer is higher than that for hypofractionated RT, providers do not promote hypofractionated RT. In contrast, in the United Kingdom, a per-attendance tariff for national RT commissioning was moved away in March 2020, which is likely to have supported providers in rapidly adopting ultrahypofractionated RT.[6] Third, all Japanese citizens are covered by the public health insurance system; however, many have also private health insurance. Private health insurance coverage for RT is often contingent on a total radiation dose of >50 Gy. Therefore, patients with such private health insurance may prefer conventional to hypofractionated RT.

The number of hypofractionated RT courses for breast cancer gradually increased before the pandemic, indicating that hypofractionation gradually gained acceptance in Japan. The clinical practice guidelines for breast cancer in Japan were revised in 2022, when the age limit for hypofractionated RT for breast cancer was lifted. Until then, hypofractionated RT was recommended only for women aged >50 years. Hence, it is reasonable that the increase in use of hypofractionated RT before the pandemic was more pronounced among women aged >50 years than that among their younger counterparts. Subgroup analysis by the number of beds revealed that the relative number of hypofractionated RT courses to the number of conventional RT courses was higher in medical institutions with

Table 1 Estimated changes in the number of hypofractionated and conventional radiation therapy courses for breast cancer during the COVID-19 pandemic

Radiation therapy	Time	Changes in number	95% CI Lower limit	95% CI Upper limit	*P* value
All					
Hypofractionated radiation therapy	2020/04	1312*	801*	1823*	<.001*
	2020/07	−75	−644	494	.796
	2020/10	−601*	−1111*	−92*	.021*
	2021/01	4	−676	684	.991
Conventional radiation therapy	2020/04	302	−1008	1612	.652
	2020/07	494	−1519	2507	.631
	2020/10	−629	−2566	1309	.525
	2021/01	−246	−2257	1764	.810
<50 y					
Hypofractionated radiation therapy	2020/04	705*	513*	897*	<.001*
	2020/07	105	−87	297	.285
	2020/10	405*	213*	597*	<.001*
	2021/01	5	−187	197	.961
Conventional radiation therapy	2020/04	−178	−812	456	.582
	2020/07	154	−490	798	.639
	2020/10	−381	−1319	557	.426
	2021/01	−948*	−1821*	−76*	.033*
≥50 y					
Hypofractionated radiation therapy	2020/04	526*	58*	994*	.027*
	2020/07	−135	−635	366	.598
	2020/10	−898*	−1349*	−447*	<.001*
	2021/01	−19	−642	605	.953
Conventional radiation therapy	2020/04	900	−468	2268	.197
	2020/07	1500	−435	3435	.129
	2020/10	300	−2070	2670	.804
	2021/01	700	−2037	3437	.616
<600 beds					
Hypofractionated radiation therapy	2020/04	300	−118	718	.159
	2020/07	−300	−891	291	.320
	2020/10	−400	−1123	323	.279
	2021/01	−200	−1035	635	.639
Conventional radiation therapy	2020/04	−1010	−2242	223	.108
	2020/07	−210	−1442	1023	.739
	2020/10	−1310*	−2542*	−77*	.037*
	2021/01	−1410*	−2642*	−177*	.025*
≥600 beds					
Hypofractionated radiation therapy	2020/04	800*	308*	1292*	.001*
	2020/07	400	−295	1095	.259

(*continued on next page*)

Table 1 (*Continued*)

Radiation therapy	Time	Changes in number	95% CI Lower limit	95% CI Upper limit	*P* value
	2020/10	100	−752	952	.818
	2021/01	500	−483	1483	.319
Conventional radiation therapy	2020/04	384	−268	1035	.248
	2020/07	298	−457	1053	.439
	2020/10	157	−681	996	.731
	2021/01	−57	−1040	925	.909

*Statistical significance.
Outpatient insurance claims were used.

≥600 beds compared with those with <600 beds. This suggests that hospitals with large bed capacity are more likely to select hypofractionated RT for breast cancer treatment than those with small capacity. The reason for this is not clearly understood in this study. One possible reason is that institutions with large number of beds have full-time radiation oncologists who may encourage the use of hypofractionated RT.

Conventional fractionated RT continued to be predominant throughout the observation period. This pattern was different from that observed in Western countries. For example, in the United Kingdom, moderate hypofractionated RT for breast cancer was commonly administered even before the pandemic.[6] Our results are consistent with those of previous studies that showed regional differences in the use of hypofractionated RT. Considering the advantages of hypofractionated RT for breast cancer, such as comparable efficacy with conventional fractionated RT,[22-30] reduction in the time and financial burden of outpatient visits and treatments, and efficient use of medical resources, it should be encouraged. A single-arm clinical trial in Japan confirmed the safety of moderate hypofractionated RT (42.56 Gy in 16 fractions) after breast-conserving surgery,[31] and a trial to confirm the safety of ultrahypofractionated RT (26.0 Gy in 5 fractions) is ongoing in Japan.[32] These data are expected to encourage the use of hypofractionated RT for breast cancer in Japan. Additionally, the payment system for the public health insurance system should be revised, and the total dose requirements for private medical insurance must be eliminated.

Although the uptake of hypofractionated RT increased in April 2020, it decreased significantly in October 2020. A previous study reported that the number of breast-conserving surgeries decreased significantly in July and October 2020, whereas the number of total mastectomies did not change.[19] Because RT is performed after breast-conserving surgery in general, we concluded that the use of RT decreased with a time lag from the reduction in breast-conserving surgery.

This study had some limitations. First, the RT regimen could not be determined from insurance claims. We extracted target claims using the additional payment for hypofractionation that is claimed when an irradiation to whole breast at 2.5 Gy or more per fraction is performed. Therefore, we could not distinguish between moderate hypofractionated and ultrahypofractionated RTs. Second, the use of hypofractionated RT at other sites could not be determined because the additional payment was only applied to whole-breast irradiation throughout the observational period. Third, we could not distinguish between curative and palliative RTs. However, when the target claims were extracted, those with disease codes corresponding to the International Classification of Diseases, 10th revision, codes C78.X (secondary malignant neoplasm of the respiratory and digestive organs) and C79.X (secondary malignant neoplasm of other and unspecified sites) were excluded, as shown in Appendix E1. Therefore, data on curative RT are thought to be extracted. Fourth, although we performed subgroup analyses for age and the number of beds in medical institutions, we could not analyze other factors that may influence the use of hypofractionated RT. For example, breast cancer stage and existence of chest wall or axillary irradiation may influence the use of hypofractionation. However, these data could not be analyzed because they were not included in the sample data sets of the NDB. Moreover, we were not able to characterize the clinical effects of hypofractionated RT, such as local control of breast cancer, toxicity, quality of life, and economic impact on the patients, for the same reason. However, to the best of our knowledge, this study is the first to identify changes in the patterns of fractionation regimes for breast cancer using data from the NDB. The use of the NDB allowed us to determine changes in Japan, resulting in high generalizability. The application of an interrupted time-series analysis using the SARIMA model is another strength.

In conclusion, the uptake of hypofractionated RT for breast cancer briefly increased early in the pandemic, but this increment was not sustained in Japan. Considering the benefits of hypofractionated RT for breast cancer, its use should be encouraged.

Disclosures

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101555.

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