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Scientific Article

# Development of Machine-Learning Prediction Programs for Delivering Adaptive Radiation Therapy With Tumor Geometry and Body Shape Changes in Head and Neck Volumetric Modulated Arc Therapy

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**Abstract**

**Purpose:** During radiation therapy for head and neck cancer using volumetric modulated arc therapy, excessive dosing or underdosing occurs as a result of the decrease in tumor volume and changes in body weight. Adaptive radiation therapy (ART) is performed when significant changes are observed; however, the decision to implement ART depends on the oncologist's subjective judgment. The purpose of this study was to present objective indicators for ART and develop a program to predict the need for ART.

**Methods and Materials:** The study included 47 patients in the non-ART group and 21 patients in the ART group with shape changes. Patients who received ART could not be covered with the prescribed radiation therapy dose due to shape changes. For each patient, 1112 6-dimensional lists were created, including the number of irradiations, amount of change in the clinical target volume (CTV), rate of change in CTV, mean oral cavity dose, age, and body mass index. Support vector machine and k-nearest neighbor were used for machine learning. The random number of test data to be extracted varied from 1 to 9, and a mean accuracy score was calculated. These programs could predict the need for ART if the accuracy score was high.

**Results:** The classification accuracy of the list, including the amount of change in the CTV and rate of change in CTV up to 20 fractions, was 0.963 and 0.967 for support vector machine and k-nearest neighbor, respectively.

**Conclusions:** This program predicted the need for ART with more than 90% accuracy based on shape changes over time in cone beam computed tomography analysis for up to 20 fractions. This may provide significant support for objective decisions to implement ART based on the amount of change over time during treatment.



## Introduction

Radiation therapy for head and neck cancer may cause significant reduction in tumor volume and patient weight loss.[1,2] Mucositis is particularly painful and is likely to result in weight loss.[3] Changes in the shape occurring during the treatment plan development can cause fixture inconsistencies and over- or underdosing around the

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target.[4] Hence, image guided radiation therapy generally is used to ensure the accuracy of the irradiation position; however, replanning is necessary if significant changes occur. This change in plan is called adaptive radiation therapy (ART).[5] However, there are no clear indicators for ART, and its implementation depends on the subjective assessment of the staff in charge.

Zhao et al[6] reviewed 22 papers on the factors affecting tumor shape changes. They cited advanced stage, high pretreatment body mass index (BMI), and a combination of chemotherapy as high predictors of the evidence of shape change. Moderate predictors included xerostomia, mucositis, and high dose administered to the oropharynx and oral cavity. Ando et al[7] reported that the difference in daily food intake, depending on the presence or absence of teeth before the treatment, leads to variations in the responsiveness to liquid diets that change during treatment, resulting in different degrees of weight loss.

In this study, patients who underwent retrospective radical head and neck volumetric modulated radiation therapy (VMAT) were distinguished based on the implementation of ART.[8] In addition, an attempt was made to determine whether machine learning could accurately classify them. The factors for machine-learning classification and the amount of change in the target during treatment have been investigated in previous studies. Gudi et al[9] reported that machine learning indicated the need for ART in 70% of patients undergoing head and neck cancer treatment in the fourth week based on the degree of parotid volume. Ma et al[10] used machine learning to combine anatomic changes calculated from cone beam computed tomography (CBCT) and dose changes in radiation therapy for lung cancer. We aimed to develop a program that predicts the need for ART by combining the effects of changes in tumor shape and body shape with dose distribution and present the objective indicators for ART in the head and neck region. This study is an important report for ensuring that targets and organ at risk doses are secured in treatments using VMAT for head and neck cancer.

## Methods and Materials

### Target patients and irradiation methods

This study included 68 patients: 4, 36, 22, 4, 1, and 1 patient(s) with nasopharyngeal, oropharyngeal, hypopharyngeal, tongue cancer, maxillary sinus, and supragingival cancer, respectively. Patients underwent high-dose radiation therapy alone or with concurrent chemoradiotherapy, and the irradiation method used was VMAT within 3 arcs. All patients underwent CBCT from 1 to 5 fractions (fr) to identify any trends due to treatment positioning errors. Thereafter, depending on the radiation, CBCT was performed every 5 fr: at the 10th, 15th, and 20th irradiation sessions. All eligible patients underwent CBCT imaging at least 8 times. Patients suspected to have altered dose distribution based on the shape changes observed by the radiation therapy oncologist on the 20th or later CBCT image underwent replanning of CT; dose calculations were performed using the existing irradiation plan. Based on these results, the patients were divided into 2 groups: 47 patients in the non-ART group who completed radiation therapy without ART and 21 in the ART group who could no longer meet the dose constraints of the target or risk organs. Failure to achieve dose distributions was confirmed by radiation oncologists based on the findings of dose-volume histogram. Figure 1 presents a case in which ART was implemented, as the prescribed dose did not cover the target dose because of weight loss.

RayStation (version 10A; RaySearch Laboratories AB, Stockholm, Sweden) was used as the treatment-planning device. One dose fraction was 2 Gy, with prescribed doses of 66 to 70 Gy for high clinical target volume (CTV), 60 to 63 Gy for intermediate CTV, and 54 to 56 Gy for low CTV.[11,12] The linear accelerators used were TrueBeam and Clinac IX from Varian Medical Systems (Palo Alto, CA). Krishnappan et al[13] reported that the 2 linear accelerators were within the clinically acceptable limits, as the variation in the dose difference between the 2 devices was <3%.

### Calculation of the CTV change over time during the treatment period using CBCT

The changes in CTV between patients who required ART and that of those who did not were quantitatively compared. Deformable image registration (DIR) was performed on CBCT using MIM Maestro (version 6.9; MIM Software Inc, Cleveland, OH) with 3 different CTVs contoured on the planning CT. Oncologists confirmed the accuracy of DIR CTV. The Dice similarity coefficient (DSC) was calculated from the original CTV and DIR CTV. DSCs of CTVs were calculated for all CBCTs of all patients. Because the calculated DSCs were different for each patient, 3 DSCs of CTVs were normalized using the greatest DSC value for each type of CTV, which was considered the change in CTV.

### Creating a multidimensional list for machine learning

Six-dimensional lists were created for each patient, including the mean oral cavity dose calculated from dose-volume histogram, age, BMI, the number of irradiations (fr), DSC of CTV, and rate of change in DSC. The number of 6-dimensional lists created for a single patient was defined as the number of CBCT scans (8 times: 1-5, 10, 15, 20 [fr]) multiplied by the number of CTV at different prescribed dose levels that the patient was subjected to. For instance, a patient with 3 CTV levels for whom CBCT was performed 8 times would have 24 6-dimensional lists. The total number of 6-dimensional lists for all patients was 1112. These lists were differentiated into 408 lists for 21 patients with ART and 704 lists for 47 patients without ART.

### *Program environment and machine learning classification*

Python 3.7.6 (Centrum voor Wiskunde en Informatica, Amsterdam, the Netherlands) was used to develop 2 machine-learning programs. These programs used a support vector machine (SVM) classifier with a Gaussian kernel (radial basis function)[14,15] and a k-nearest neighbor (KNN) classifier.[16] Six-dimensional lists were used in this study. SVM is versatile and capable of high-dimensional classification. The algorithm of the KNN method is simple and user-friendly, and its prediction results are not black-boxed; therefore, we hypothesized that comparing the results of SVM with those of KNN will increase the reliability of SVM.

The following equation provided the data set for SVM:

$$(x_1, y_1), \ldots, (x_n, y_n), x_i \in R^d \text{and } y_i \in (-1, +1)$$

$x_i$ denotes the feature vector of the 6-dimensional list, and $y_i$ denotes the class label. The optimal hyperplane was defined as follows:

$$wx^T + b = 0$$

$w$ is the weight vector, $x$ is the input feature vector, and $b$ is the bias; $w$ and $b$ satisfy the following inequality for all elements:

$$wx_i^T + b \geq +1 \text{ if } y_i = 1$$

$$wx_i^T + b \leq -1 \text{ if } y_i = -1$$

In SVM, the optimal hyperplane separates the data and estimates $w$ and b that maximize the margin $1/||w||2$. KNN is a simple method that classifies the features of the

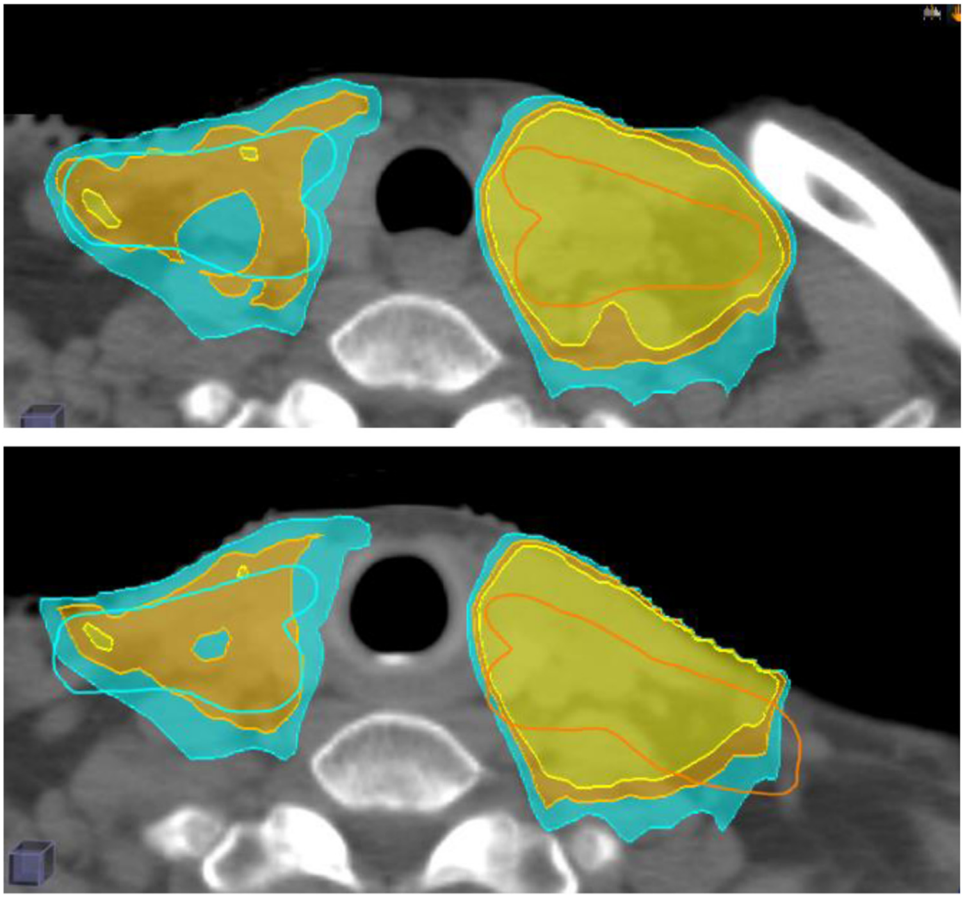

**Figure 1** Target and dose distribution on initial planning computed tomography (top), and target and dose distribution contoured by the oncologist after significant weight loss during treatment (bottom). The bottom figure shows the orange area was targeted for adaptive radiotherapy due to the presence of areas not covered by the yellow prescription dose curve.

input values into a large group belonging to the n data with the closest Euclidean distance, as shown to follow:

$$d(p,q)^2 = (q_1 - p_1)^2 + (q_2 - p_2)^2$$

Here, $p$ and $q$ are the coordinates of the 2 points, calculated as the positive square root of the sum of the squares of the differences in each axis.

The 6-dimensional list was split into learning and test data, with the test size varying from 10% to 90% at 10% intervals. The random state of the extracted test data varied from 1 to 9 at each test size, and the mean accuracy score was calculated. The SVM parameters were set to gamma = 0.05 and c = 10; the KNN parameters were set to n = 5. Owing to the risk of bias that may arise from insufficient data or overlearning, the size of data to be extracted, and the random number value, we varied the data size and randomness to ensure that the results were not biased or misleading. Risk of bias means the likelihood that features of the study design or conduct of the study will give misleading results.

Examining when the ART and non-ART groups would show differences revealed that although the total number of lists was reduced, DSC of CTVs in the 6-dimensional list reduced from 20 fr (1112 lists) to 15 fr (980 lists), 10 fr (840 lists), and 5 fr (700 lists), and changes in the mean accuracy scores were observed.

## Results

### Comparison of DSC of CTV in the ART and non-ART groups

We performed a *t* test to evaluate whether there was a difference in the DSCs of all level CTVs between the ART and non-ART groups. The *t* test was performed without distinguishing the level of CTV. All DSCs were calculated from DIR CTV on CBCTs performed at 5 fr, 10 fr, 15 fr, and 20 fr and the initial planning CTV. The *P* values were .374, .522, .059, and .007, respectively (Table 1). DSC decreased significantly at 15 fr, and a significant difference in DSC at 20 fr was confirmed ($P < .05$). Figure 2 presents the plots of DSCs in the ART and non-ART groups. The divergence of DSCs increased with the number of fr, and the DSCs of the ART group spread to the low-value side, indicating that many patients receiving ART experienced significant shape changes in the tumors or body shape after 15 fr of treatment.

### Comparison of other factors in the ART and non-ART groups

A *t* test was performed to determine whether there was a difference in the rate of change in DSC, BMI, mean oral cavity dose, and age with and without ART. The *P* values were .003, .710, .004, and .313, respectively (Table 1). Significant differences were observed in the rate of change in DSC and mean oral cavity dose ($P < .05$). Figure 3 presents the plots for these 4 factors distinguished by whether ART was implemented. A clear divergence is observed for the 2 factors with significant differences. There was no difference in BMI. Although there was no difference in the *P* value for age, the ART group was observed to be, on average, 3 years younger.

### Machine-learning classification and accuracy of the 6-dimensional lists

Table 2 presents the mean accuracy scores for the 6-dimensional lists with the test size varying from 0.1 to 0.9

**Table 1 DSC, rate of change in DSC, BMI, mean oral cavity dose, and age (mean and SD), differentiated by ART and non-ART groups**

| | ART | | Non-ART | | *t* test |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *P* |
| DSC | | | | | |
| 5 fr | 0.912 | 0.092 | 0.925 | 0.053 | .374 |
| 10 fr | 0.897 | 0.095 | 0.907 | 0.061 | .522 |
| 15 fr | 0.850 | 0.133 | 0.889 | 0.069 | .059 |
| 20 fr | 0.792 | 0.184 | 0.868 | 0.077 | .007 |
| Rate | −0.010 | 0.009 | −0.002 | 0.022 | .003 |
| BMI | 20.477 | 3.293 | 20.698 | 3.505 | .710 |
| Oral cavity mean dose | 3362.404 | 778.993 | 2899.307 | 1040.924 | .004 |
| Age | 60.846 | 12.732 | 63.034 | 11.340 | .313 |

*Abbreviations:* ART = adaptive radiation therapy; BMI = body mass index; DSC = Dice similarity coefficient; fr = fractions; SD = standard deviation. *P* values from results of the *t* test by ART and non-ART groups.

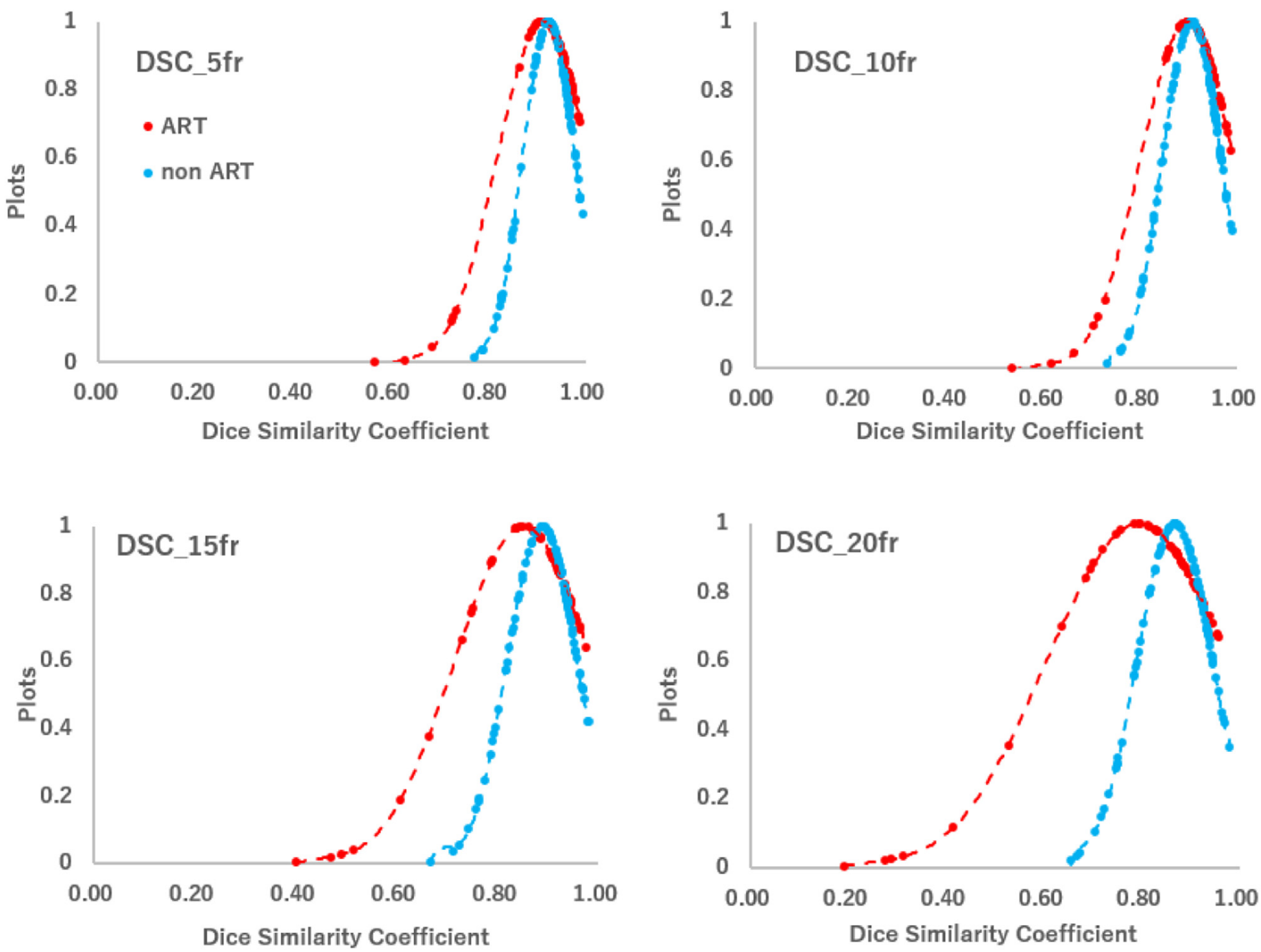


**Figure 2** The plots of Dice similarity coefficients (DSCs) calculated from deformable image registration clinical target volume (CTV) on cone beam computed tomography taken at 5, 10, 15, and 20 fractions (fr) and CTV on initial planning computed tomography.

and a varying random number of data extracted at each test size. The mean accuracy scores were calculated using lists up to the 20th treatment (CBCT imaging, 8 times; 1112 lists), 15th (CBCT imaging, 7 times; 980 lists), 10th (CBCT imaging, 6 times; 840 lists), and 5th (CBCT imaging, 5 times; 700 lists).

The minimum to maximum mean accuracy scores varied by test size for SVM including DSC were 0.843 to 0.998 for all listings up to 20 fr, 0.841 to 0.998 for listings up to 15 fr, 0.843 to 0.997 for listings up to 10 fr, and 0.871 to 1.0 for listings up to 5 fr.

The mean accuracy scores for KNN were 0.872 to 0.988 for listings up to 20 fr, 0.841 to 0.988 for listings up to 15 fr, 0.801 to 0.990 for listings up to 10 fr, and 0.773 to 0.993 for listings up to 5 fr.

SVM and KNN had the lowest accuracy scores at test size 0.9, with accuracy scores less than 90%, regardless of the total number of lists included in the list. Conversely, SVM and KNN showed accuracy scores greater than 90% in all cases when the test size was 0.7 or less. The SVM and KNN classifications of ART implementation were highly accurate if a highly biased test size was not selected.

## Discussion

In radiation therapy for head and neck cancer, weight loss caused by anticancer agents and mucositis can reduce the quality of life and affect the completion of radiation therapy and treatment prognosis.[17] Although head and neck cancer radiation therapy with VMAT has been shown to reduce pharyngeal and oral cavity doses, there is no established prevention or intervention for mucositis, as reported by Moslemi et al.[3] Hence, using machine learning to predict and prevent unacceptable dose distributions due to shape changes during treatment is very significant. Highly accurate prediction of tumor shape changes, such as in this study, and objective determination of the need

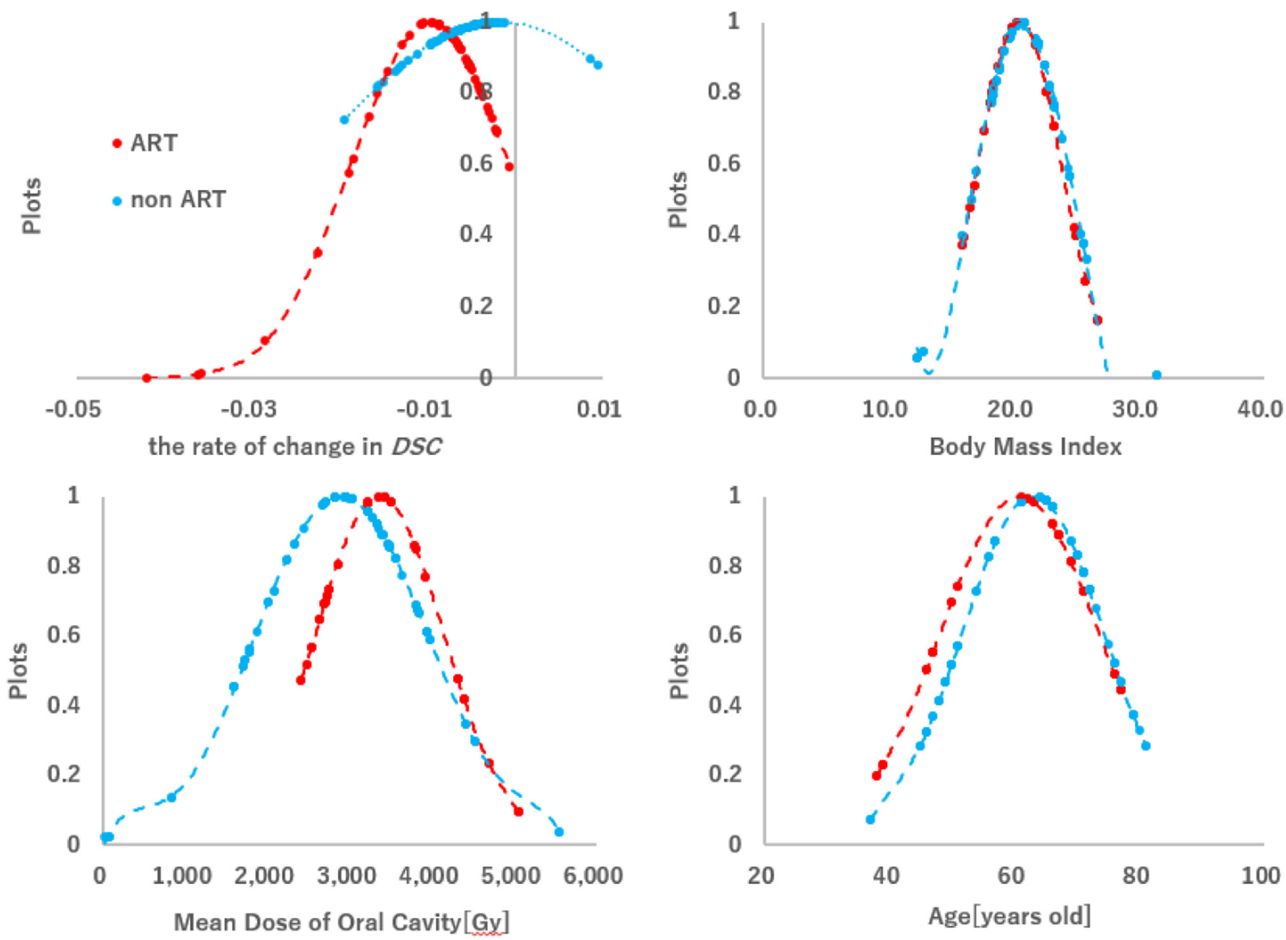


**Figure 3** Plots for the rate of change in Dice similarity coefficients (DSCs), body mass index, mean oral cavity dose, and age are displayed separately by adaptive radiation therapy (ART) status.

for ART during VMAT for head and neck cancer will greatly benefit medical staff and patients.

There was a large decrease in the *P* value between 10 fr and 15 fr in the DSC of CTV in the ART and non-ART groups, suggesting that many patients on ART have tumor and body shape changes at approximately 15 fr. Figure 2 shows a large divergence between 10 fr and 15 fr. Figen et al[5] report that ART was implemented in 31 patients among 291 patients, with an average timing of 15 fr; this finding is similar to the results of the present study.

Significant differences were observed in the rate of change in DSC ($P$ = .003) and the mean oral cavity dose ($P$ = .004), and a clear divergence was also observed (Fig. 3). The mean oral cavity dose was in the greater dose range for the ART group; this may be a significant weight loss factor due to mucositis symptoms. Mallick et al[18] also reported that radiation mucositis is more likely to be aggravated, and weight loss is more likely to occur at greater mean oral cavity doses.

BMI has been reported to be a predictor of weight loss by several investigators. Delayed nutritional support for patients with overweight is a major cause of weight loss.[19-21] Age and dental status also are related. According to Ando et al, [7,22] changes in eating patterns during treatment affect patients with teeth more than the patients without teeth, leading to weight loss. However, there was no difference in BMI ($P$ = .710) in this study, as shown in Table 1 and Fig. 3. This may be attributable to the racial differences among Asian patients, who participated in this study and had a greater body fat percentage than the people of European descent, although they had the same BMI, the referenced studies were from Western countries.[23]

Age is considered to be a factor in weight loss. Figure 3 shows that the patients in the ART group were approximately 3 years younger than those in the other groups. Matsuzaki et al[24] examined the effect of dental status on oral nutrition intake during IMRT treatment and reported that the patients with teeth showed significantly greater weight loss than the patients without teeth. They concluded that aging is likely to result in decreased bite strength and tooth loss and that older patients are less likely to experience weight changes, as they routinely consume soft foods. There was no significant difference in

**Table 2 Mean accuracy scores of SVM and KNN with the mean values of the various random numbers for each test size**

| SVM | Test size 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | Mean |
|---|---|---|---|---|---|---|---|---|---|---|
| Mean value (random number, 1-9) | | | | | | | | | | |
| 20 fr | 0.998 | 0.996 | 0.993 | 0.986 | 0.983 | 0.975 | 0.963 | 0.930 | 0.843 | 0.963 |
| 15 fr | 0.995 | 0.998 | 0.996 | 0.988 | 0.985 | 0.980 | 0.968 | 0.930 | 0.841 | 0.965 |
| 10 fr | 0.997 | 0.996 | 0.984 | 0.978 | 0.973 | 0.969 | 0.951 | 0.920 | 0.843 | 0.957 |
| 5 fr | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 0.987 | 0.959 | 0.871 | 0.980 |
| KNN | Test size 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | Mean |
| Mean value (random number, 1-9) | | | | | | | | | | |
| 20 fr | 0.987 | 0.985 | 0.988 | 0.988 | 0.987 | 0.981 | 0.970 | 0.943 | 0.872 | 0.967 |
| 15 fr | 0.988 | 0.985 | 0.988 | 0.987 | 0.988 | 0.988 | 0.980 | 0.941 | 0.841 | 0.965 |
| 10 fr | 0.984 | 0.990 | 0.989 | 0.989 | 0.988 | 0.987 | 0.973 | 0.913 | 0.801 | 0.957 |
| 5 fr | 0.993 | 0.991 | 0.989 | 0.989 | 0.989 | 0.980 | 0.965 | 0.883 | 0.773 | 0.950 |

*Abbreviations:* fr = fractions; KNN = k-nearest neighbor; SVM = support vector machine.
The mean value is maintained even when the number of fractions is small.

age between patients with and without ART ($P$ = .313) in our study; however, the results showed that the patients were younger in the ART group, which is similar to the results of the study by Matsuzaki et al.

Based on the aforementioned considerations, we determined that the rate of change in DSC, mean oral cavity dose, BMI, and age are 4 essential factors for machine-learning classification. Because SVM[25] and KNN[26] can ensure high classification accuracy even with high dimensionality, the 6-dimensional list with the addition of these 4 factors is an appropriate target. Table 2 shows that the mean values of the mean accuracy score for SVM and KNN were all >95% correct. The comparable results obtained for the 2 classification methods suggest that the classification results are highly reliable.

The mean accuracy scores of the 6-dimensional list including DSC up to 1 to 5 fr were almost identical to those of the 6-dimensional list including DSC up to 10, 15, and 20 fr. These results are shown in Table 2, indicating that for up to 5, 10, 15, and 20 fr, the values obtained by using SVM were 0.963, 0.965, 0.957, and 0.980, whereas those using KNN were 0.967, 0.965, 0.957, and 0.950, respectively. Therefore, patients who require ART tend to require it between the first and fifth treatment fractions.

This study used machine learning to discover trends in the ART group and constructed an objective trigger for ART and a program to predict the need for ART. However, CBCT is performed only once every 5 times to account for the patient dose based on subjective judgment; BMI and the mean oral cavity dose are only noted at a certain point in time (before treatment). There are limitations, such as changes in BMI and dose with the progression of treatment, that are not taken into account. In the future, it is necessary to perform DIR at each time point and collect DSC, changes in DSC, BMI, and mean oral cavity dose to make the data more robust.

However, classification by SVM or KNN of a 6-dimensional list created from information obtained before treatment and the amount of change in CTV over time is considered a sufficient quantitative indicator to suspect the possibility of ART owing to the high accuracy scores obtained. Because this study uses a generic program, it can be conducted at any facility. We believe we have proposed an innovative method based on a new machine-learning technique.

## Conclusion

This study created a 6-dimensional list from the DSC calculated using CTVs contoured on planning CT and CBCT, with the rate representing the amount of change in DSC, mean oral cavity dose, BMI, and age. In addition, we constructed a prediction program for ART using SVM and KNN, which are machine-learning methods with teaching data. This program would support decision-making processes regarding the implementation of ART.

The data used in our program had limitations, such as the accountability for the changes in BMI and dose as the treatment progressed. However, we quantitatively captured the changes in body shape and tumor geometry over the course of treatment and predicted the need for ART with greater than 90% accuracy. These results are significant in ensuring therapeutically effective radiation therapy doses for patients and enabling objective decision making for the implementation of ART decisions using machine learning.

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