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Plan Complexity and Delivery Accuracy of Knowledge-based Volumetric Modulated Arc Therapy Plans with Single Optimization for Oropharyngeal Cancer

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Abstract. *Background/Aim: We investigated the plan complexity of volumetric modulated arc therapy (VMAT) with knowledge-based plan (KBP) for oropharyngeal cancer (OPC) with a single optimization and whether it could be used clinically. Materials and Methods: KBP model was configured using 55 consecutive OPC and nasopharyngeal cancer plans. Plan complexity as a characteristic of multi-leaf collimator (MLC) motion and γ pass rate (2%/2 mm criterion) were compared between clinical manual plan (CMP) and KBP for other 10 plans. Results: Plan complexity metrics that had significant differences ($p<0.05$) (CMP vs. KBP), were mean lateral displacement of MLC from central axis (15.82 mm vs. 18.90 mm), proportions of MLC aperture sizes of ≤5 mm (0.14 vs. 0.11), ≤10 mm (0.24 vs. 0.19), and ≤20 mm (0.41 vs. 0.34), and monitor units (578.68 vs. 505.04). The γ pass rate was 91.3% vs. 93.3%. Conclusion: Single optimized KBP for OPC had simple plan complexity features and comparable delivery accuracy to CMP, and could be clinically applied.*

Intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) using inverse planning have improved aspects of plan quality such as target coverage and sparing of normal tissue (1). Plan quality depends on the planner's or institution's experience and skill (2), which can result in large variations and compromise the effects of high-precision radiotherapy (3). The commercial knowledge-based plan (KBP) software RapidPlan, which is based on supervised machine learning, uses a dose-volume histogram (DVH) prediction model. The KBP was previously used to generate clinically acceptable VMAT plans for various treatment sites that were comparable or superior to clinical manual plan (CMP) (4-16).

We previously showed that KBP VMAT for prostate cancer with a single optimization was clinically acceptable (5), while it was suggested that despite being trained on past CMP cases, the KBP used a different plan complexity to the CMP, with lower multi-leaf collimator (MLC) travel and more closed or small MLC apertures (5). For the VMAT of head-and-neck cancer cases, our KBP model with manual objective constraints overcame the necessity of manual re-optimization to achieve clinical criteria for complicated anatomical sites (17), and was able to generate clinically acceptable plan quality with a single optimization (12). VMAT plans for the head-and-neck area are generally created with higher complexity MLC motion than those for the prostate, although this high complexity is not a negative feature of a treatment plan because it may be required to accommodate the complex geometry of the target and organs at risk (OARs) (18-20). If the KBP generates VMAT plans using more closed or small MLC apertures in head-and-neck cases, like the prostate cases (5), the delivery accuracy may be lower (19). The purpose of this study was to clarify the plan complexity characteristics of KBP VMAT for oropharyngeal cancer (OPC) with a single optimization and to verify their delivery accuracy with patient-specific quality assurance (QA). The influence of our KBP modeling method (12) on plan complexity is also discussed.

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Key Words: Knowledge-based treatment planning, plan complexity, delivery accuracy, volumetric modulated arc therapy, oropharyngeal cancer.

Materials and Methods

Patients and treatment planning. A total of 55 patients with OPC or nasopharyngeal cancer who underwent VMAT and IMRT between February 2014 and June 2018 were consecutively included in a case library, and the KBP model was trained using this database. A further 10 OPC patients who underwent VMAT between February 2014 and June 2018 and whose planning was not included in the model training were randomly selected as validation plans. CMP and single-optimized KBP VMAT were then compared for these 10 patients. Written informed consent was obtained from all patients, and our institutional ethics committee approved this study (Institutional Review Board number: 29-133).

For each patient, a total dose of 70 Gy in 35 fractions was prescribed to the planning target volume (PTV) (normalized at 95% of the prescribed dose), which consisted of the high-risk clinical target volume (CTV) (12, 21-23). All plans were created using 6 or 10 MV photon beams with 2 full arcs of VMAT (collimator angles: 5˚ and 85˚) on the Eclipse treatment planning system ver. 13.6 (Varian Medical Systems, Palo Alto, CA, USA) using the Analytic Anisotropic Algorithm for dose calculation of a TrueBeam (Varian) with a Millennium 120 MLC (12). The goals of the treatment plan in our institution were as follows: maximum dose (D_{max}) of the PTV <120% of the prescribed dose, mean dose (D_{mean}) of the PTV <105% (usually 103%-104%), dose recieved by 10% ($D_{10\%}$) of the PTV <110% of the prescription dose, D_{max} of the spinal cord <48 Gy, D_{max} of the brainstem <54 Gy, and median dose (D_{median}) <19 Gy or D_{mean} <25 Gy of at least one parotid gland. The planning and KBP modeling processes were explained in more detail in our previous report (12).

KBP validation. The following dose-volume parameters for the PTV and OARs were evaluated to compare the plan quality between CMP and single optimized KBP for the 10 validation OPC patients. 1. Doses received by 2% ($D_{2\%}$) and 50% ($D_{50\%}$) of the PTV; 2. Homogeneity index [HI; defined as $100 \times (D_{2\%} - D_{98\%})/D_{50\%}$, where $D_{98\%}$ is the dose received by 98% of the PTV] (24); 3. The 95% isodose conformity index (CI_{95}; defined as $V_{95\%}/V_{PTV}$, where $V_{95\%}$ is the volume covered by 95% of the prescribed dose and V_{PTV} is the PTV volume) (16); 4. Dose-volume parameters to brain stem as D_{max}; 5. Dose-volume parameters to spinal cord as D_{max}; 6. Dose-volume parameters to ipsilateral parotid as D_{median} and D_{mean}; 7. Dose-volume parameters to contralateral parotid as D_{median} and D_{mean}.

Plan complexity metrics. The plan complexity metrics for comparison between CMP and KBP were (5): mean field area (MFA), mean asymmetry distance (MAD), cross-axis score (CAS), closed leaf score (CLS), small aperture score (SAS) (25, 26), leaf travel (LT), modulation complexity score for VMAT (MCSv) (20, 27), and monitor units (MU). MFA is the weighted mean of the area between exposed open leaf pairs for all segments of the beam, each weighted value according to the number of MU. MAD is the mean lateral displacement (away from the central axis) of the center of the opening between each pair of MLC leaves. CAS is the proportion of MLC leaves within the jaw aperture that cross the central axis. CLS is the proportion of MLC leaf pairs within the jaw aperture that are entirely closed. SAS is the proportion of open MLC leaf pairs that are separated by less than the given threshold (2, 5, 10, and 20 mm in this study). LT is the averaged leaf moving distance over all in the field. MCSv is defined as the sum over all control points of the product of the aperture area variability (AAV), leaf sequence variability (LSV), and normalized MU (20, 27), with values ranging from 0 to 1 and lower values indicating more complex MLC modulation. The plan complexity parameters were calculated from the Digital Imaging and Communications in Medicine (DICOM) files of the VMAT plans using MATLAB software (MathWorks, Natick, MA, USA) (26).

Patient-specific QA for delivery accuracy. The dose distributions of the 10 CMP and KBP for validation were measured using ArcCHECK (SunNuclear, Melbourne, FL, USA). The delivery accuracy was evaluated by the difference of dose distributions between the plan and measurement using γ pass rate. The criteria were 3%/3 mm and 2%/2 mm (28) with a threshold of 10%.

Statistical analysis. The Wilcoxon signed rank test was used to compare the dose-volume parameters, plan complexity parameters, and γ pass rate between CMP and KBP. All statistical analyses were performed using R ver. 3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria), and $p<0.05$ was considered statistically significant. Pearson's correlation of $r<0.4$ was considered as weak, r of 0.4-0.7 as moderate, and $r>0.7$ as strong (5).

Results

KBP validation. Significant differences in dose-volume parameters of PTV (mean±SD) (CMP *vs*. KBP) were observed for $D_{2\%}$ (79.21±1.79 *vs*. 77.73±0.75, $p=0.009$) and $D_{50\%}$ (72.91±0.38 *vs*. 72.63±0.25, $p=0.04$). HI and CI_{95} were comparable between CMP and KBP. Significant differences in dose-volume parameters of OARs (CMP *vs*. KBP) were observed for D_{max} of the brainstem (52.66±4.94 *vs*. 47.82±2.08, $p=0.02$) and D_{median} (31.45±10.39 *vs*. 17.72±1.28, $p=0.002$) and D_{mean} (33.26±8.89 *vs*. 21.87±0.92, $p=0.003$) of the ipsilateral parotid. The D_{max} of the spinal cord and the D_{median} and D_{mean} of the contralateral parotid were comparable between KBP and CMP. The plan quality of KBP VMAT was superior or comparable to that of CMP.

Plan complexity metrics. Table I shows comparisons of the plan complexity parameters of MFA, MAD, CAS, CLS, SAS (thresholds of MLC separation: 2, 5, 10, and 20 mm), LT, MCSv, and MU between CMP and KBP. Significant differences in plan complexity parameters (CMP *vs*. KBP) were observed for MAD (15.82 mm *vs*. 18.90 mm, $p=0.04$), SAS_{5mm} (0.14 *vs*. 0.11, $p=0.02$), SAS_{10mm} (0.24 *vs*. 0.19, $p=0.01$), SAS_{20mm} (0.41 *vs*. 0.34, $p=0.02$), and MU (578.68 *vs*. 505.04, $p=0.02$). KBP generated more efficient MLC travel than CMP, as the mean LT values of CMP and KBP were 597.57 mm and 557.40 mm, respectively. Figure 1 shows the plan complexity parameters that correlated with MU in either KBP or CMP. The MFA and MAD correlated strongly with MU, and CLS correlated moderately with MU in CMP and KBP. On the other hand, the correlations of

Table I. *Plan complexity in the clinical manual plan (CMP) and knowledge-based plan (KBP).*

	CMP			KBP			*p*-Value
	Mean±SD	Max	Min	Mean±SD	Max	Min	
MFA (cm^2)	63.75±15.81	96.52	49.77	75.75±14.88	105.08	60.75	0.06
MAD (mm)	15.82±3.15	21.60	12.72	18.90±2.98	24.45	15.99	0.04
CAS	0.37±0.15	0.68	0.25	0.34±0.13	0.60	0.21	0.44
CLS	0.03±0.01	0.06	0.01	0.03±0.02	0.07	0.01	0.63
SAS_{2mm}	0.10±0.02	0.12	0.06	0.08±0.02	0.13	0.05	0.05
SAS_{5mm}	0.14±0.03	0.18	0.08	0.11±0.02	0.16	0.07	0.02
SAS_{10mm}	0.24±0.05	0.29	0.14	0.19±0.04	0.25	0.13	0.01
SAS_{20mm}	0.41±0.07	0.48	0.28	0.34±0.04	0.40	0.26	0.02
LT (mm)	597.57±34.25	652.63	538.70	557.40±42.66	626.06	512.37	0.06
MCSv	0.28±0.03	0.32	0.25	0.30±0.01	0.31	0.28	0.13
MU	578.68±64.52	666.10	452.58	505.04±47.51	577.15	412.17	0.02

MFA: Mean field area; MAD: mean asymmetry distance; CAS: cross-axis score; CLS: closed leaf score; SAS: small aperture score (threshold of MLC separation: 2, 5, 10, and 20 mm); LT: leaf travel; MCSv: modulation complexity score for VMAT; MU: monitor units.

Table II. *γ pass rates in clinical manual plan (CMP) and knowledge-based plan (KBP).*

	CMP			KBP			*p*-Value
	Mean±SD	Max	Min	Mean±SD	Max	Min	
2%/2 mm (%)	91.3±3.5	95.2	84.4	93.3±2.0	96.7	90.7	0.137
3%/3 mm (%)	98.8±0.7	99.8	97.9	99.2±0.5	99.9	98.4	0.288

SAS_{20mm} and MCSv with MU were weak for KBP but strong for CMP.

Patient-specific QA for delivery accuracy. Table II shows the γ pass rate of each criterion for CMP and KBP. No significant difference in γ pass rate was observed between CMP and KBP: 98.8% and 99.2%, respectively, for the 3%/3 mm criterion, and 91.3% and 93.3% for the 2%/2 mm criterion. For the 2%/2 mm criterion, γ pass rates >90% were observed for all cases (10/10) with KBP; however, only for 7 cases (7/10) with CMP.

In additional analysis, the transitions of the AAV, LSV, and MU values for each gantry angle were also evaluated for the three cases in which the γ pass rate was <90% under the 2%/2 mm criterion with CMP. Figure 2 shows an example of these cases. The LSV transitions shown in Figure 2B are almost equal between CMP and KBP. In contrast, for the AAV transition, less complex MLC movement was obtained in the KBP in many sequences compared with that in the CMP (Figure 2A). This resulted in simpler MLC modulation with KBP than with CMP. Additionally, the MU transition in KBP was stable, and lower values compared with that in CMP (Figure 2C).

Discussion

In this study, we clarified the plan complexity of VMAT plans for OPC generated by KBP with a single optimization, and evaluated their delivery accuracy using γ analysis. According to the dose-volume parameters, the KBPs were superior to the CMPs with regard to the sparing of OARs and provided comparable homogeneity and conformity for the target, whereas the KBPs were less plan complexity than the CMPs. The delivery accuracy of KBP was also no problem compared with that of CMP.

Compared with CMP, the plan complexity of KBP had the characteristics of larger MLC aperture size from high MFA and low SAS, low leaf travel distance, and low modulation due to high MCSv, although the MLC position in KBP was asymmetry compared with that in CMP, as shown in Table I. It was reported that for prostate cancer case, the MU of KBP were higher or comparable to those of CMP (4, 5, 29) because of the complicated MLC motion, such as more closed or smaller MLC apertures in KBP (5). In contrast, large MLC aperture values were observed when KBP was used for OPC in this study. Thus, the plan complexity may be different for each KBP model, and it should be validated as part of the

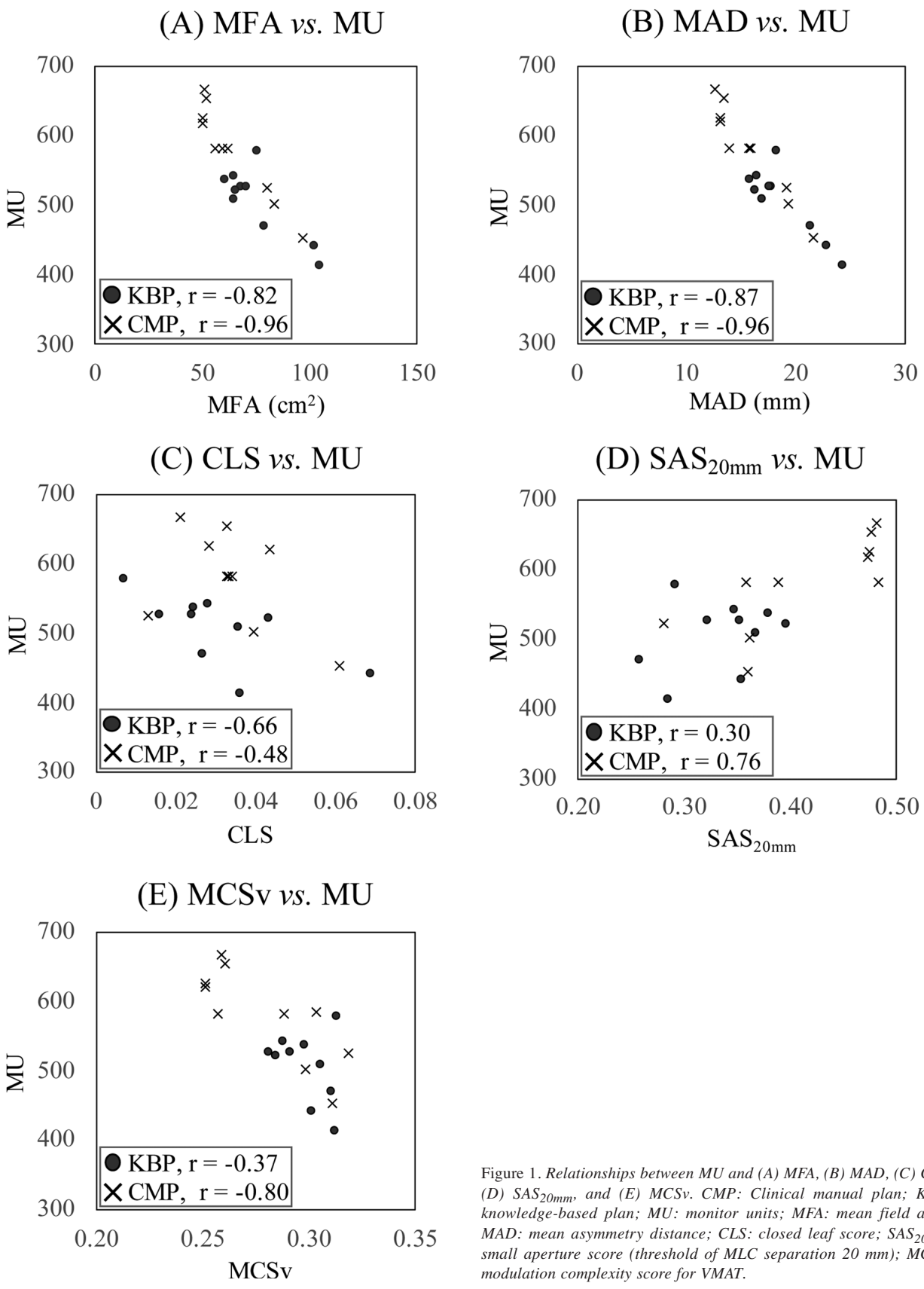

Figure 1. *Relationships between MU and (A) MFA, (B) MAD, (C) CLS, (D) SAS_{20mm}, and (E) MCSv. CMP: Clinical manual plan; KBP: knowledge-based plan; MU: monitor units; MFA: mean field area; MAD: mean asymmetry distance; CLS: closed leaf score; SAS_{20mm}: small aperture score (threshold of MLC separation 20 mm); MCSv: modulation complexity score for VMAT.*

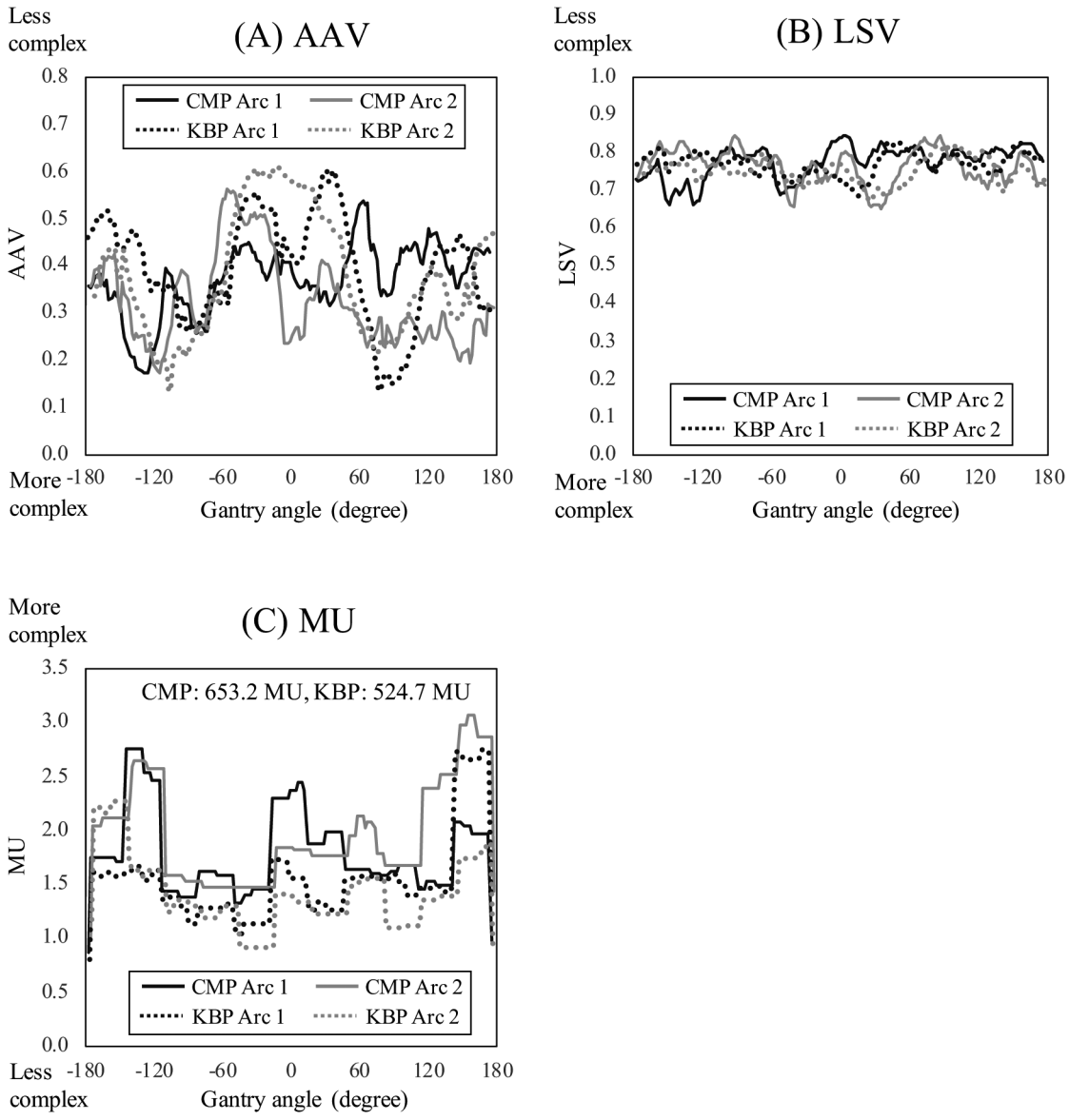

Figure 2. *Example case showing the transitions of (A) AAV, (B) LSV, and (C) MU for each gantry angle. This case had a γ pass rate of < 90% with the 2%/2 mm criterion for CMP. CMP: Clinical manual plan; KBP: knowledge-based plan; AAV: aperture area variability; LSV: leaf sequence variability; MU: monitor units.*

patient specific QA (19). MU negatively correlated with MFA and MAD strongly, although they did not correlate with MCSv in KBP (Figure 1). The MU depended on the average field size rather than MCSv, as suggested by Agnew *et al*. (18).

Patient-specific QA of KBP VMAT also needs to be performed to check the delivery accuracy of the dose calculations and clinically relevant errors in radiation delivery because of the simultaneous variations in gantry speed, dose rate, and MLC aperture (5, 27, 28, 30). Some CMPs resulted in a γ pass rate of < 90% for the 2%/2 mm criterion, whereas all KBP cases exceeded 90%. This was because the KBP for OPC generated more efficient MLC transitions and simpler MLC motions, such as large size and low variability of the MLC aperture and short MLC travel, as shown in Table I and Figure 2. The short LT of KBP allowed efficient movement between control points, as was also shown for prostate cancer cases (5), resulting in low speed and acceleration, which may improve the accuracy of MLC positioning (31). Thus, we suggested that KBP VMAT with a single optimization can be safely used for OPC in clinical practice.

In the future, KBP models are likely to be shared among institutions, and we expect that more advanced big data models based on multi-institutional clinical plans will be developed (32). The creation of multiple dummy structures to aid the manual optimization process, such as those representing overlapping regions between the target and OARs (16) and external ring structures based on the target, can cause large variations in plan quality and plan complexity at each institution, and may also result in increases in the MU value (33). With our KBP model (12), such dummy structures were not configured, and the parotid was distinguished not as ipsi- and contra-lateral structures, but just as right and left structures. Delineation of structures (target and OARs) and dose distributions of all clinical plans registered in the model were also confirmed by two expert radiation oncologists to standardize the plan quality (12). Thus, this KBP model could mitigate the complexity of MLC motion, and reduce the intra-center variability. If our KBP model is shared with other institutions, the beam delivery might be safer than that of other more complicated KBP modeling methods (*e.g.*, those including many dummy structures and/or tight distinction of structures), while providing high plan quality.

Conclusion

Our KBP model generated the VMAT plans for OPC with simple and efficient MLC motion, such as large MLC aperture size, low leaf travel distance, and low modulation, with a single optimization compared to the CMP because of no dummy structures and tight distinction of structures. The delivery accuracy for the KBP was also no problem compared with that for the CMP. The VMAT plans generated by this KBP model for OPC could be clinically applied.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

KO, HM, and MT designed the study. KM, MO, TU, HD and KI provided the study patients. MT, KK, and YU provided analysis tools. MT, KM and MO performed the measurements. KO, MT and KK analyzed the data. KO, HM, MT, and YN prepared the manuscript. All Authors collaborated on writing the manuscript, read and approved the final manuscript.

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