

# Knowledge-Based Planning for Intensity-Modulated Proton Therapy for Patients with Locally Advanced Esophageal Cancer

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## Abstract

**Purpose:** To introduce a knowledge-based planning (KBP) framework for intensity-modulated proton therapy (IMPT) that generates patient-specific dose-volume histogram (DVH) objectives using a database of geometric and dosimetric data from previously treated esophageal cancer patients. **Methods:** The framework employs overlap-volume histogram (OVH) to quantify spatial relationship between organs at risk (OARs) and targets. For a new patient, OVH is calculated from DICOM CT and RT-structure and compared with those in a reference database to derive individualized DVH objectives for IMPT optimization. The reference database contains pre-calculated OVHs and DVH data for targets and OARs from previously clinically delivered plans. Eighteen patients with locally advanced esophageal cancer treated with IMPT were retrospectively analyzed. KBPs were created using a leave-one-out approach: DVH objectives for each KBP were generated from the remaining 17 patients and applied in the RayStation TPS for IMPT optimization. KBPs were compared with clinical plans (CPs: clinically delivered plans, manually created by planners) in target coverage and OAR sparing. **Results:** KBPs achieved comparable dosimetric quality to CPs in target coverage. OAR sparing was generally similar, with a significantly reduced spinal canal dose in KBPs. **Conclusions:** This study demonstrates the feasibility of an OVH-driven KBP framework for IMPT in esophageal cancer. By leveraging geometric-dosimetric correlations from prior patients, the method enables the automatic generation of individualized planning objectives, achieving plan quality comparable

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to clinical standards.

## Keywords

Knowledge-Based Planning, IMPT, Esophageal, Overlap-Volume Histogram

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## 1. Introduction

The incidence of esophageal adenocarcinoma has been increasing over recent decades [1]-[5]. For patients with locally advanced disease, tri-modality therapy—comprising chemotherapy, radiotherapy, and surgical resection—remains the standard of care. Conventional radiotherapy, which employs megavoltage photon beams delivered using three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), or volumetric modulated arc therapy (VMAT), represents the established standard approach in radiotherapy [6].

In the last decade, proton beam therapy (PBT) has emerged as an alternative radiation modality [7]. The defining physical property of proton beams—the Bragg peak—enables precise dose deposition with no exit dose, thereby improving sparing of healthy tissues distal to the target volume. This characteristic represents the principal dosimetric advantage of protons over photons [8]. Comparative studies of PBT versus IMRT/VMAT for esophageal cancer have consistently demonstrated significant reductions in radiation exposure to the heart and lungs [8]-[13]. These findings underscore the potential of PBT to improve treatment outcomes for tumors located near critical organs-at-risk (OARs), including the lungs, heart, kidneys, bowel, stomach, and spinal canal.

As with IMRT, intensity-modulated proton therapy (IMPT) planning relies on an iterative, trial-and-error optimization process that can be time-consuming and subject to inter-planner variability. Enhancing planning efficiency and ensuring consistent plan quality therefore remain major challenges in IMPT.

Knowledge-based planning (KBP) is a data-driven methodology originally developed for IMRT to improve planning efficiency and plan quality consistency [14]-[19]. One KBP strategy developed by our group is the overlap-volume histogram (OVH)-driven KBP method, whose feasibility and effectiveness have been demonstrated across multiple anatomical sites [15]-[19]. Several commercial implementations of KBP are now clinically available [20]-[22].

The present study extends the OVH-driven KBP approach to IMPT for esophageal cancer. Its primary objectives are:

- To apply the OVH-KBP methodology, originally developed for IMRT, to IMPT in a cohort of esophageal cancer patients; and
- To evaluate whether the KBP-guided IMPT plans are comparable in quality to manually created clinical plans (CPs) while improving planning efficiency. Here, CPs refer to IMPT plans manually generated by planners and clinically

delivered to patients.

As a side note, planning and optimization time for KBP generation was not recorded in this study, as these metrics have been reported in our previous publications [15] [19].

## 2. Methods and Materials

### 2.1. Knowledge-Based Planning (KBP) Model

A well-established data-driven auto-planning methodology, originally developed for IMRT [15]-[19], was adapted for IMPT planning. The central premise is that patients with similar anatomical configurations of targets and OARs should achieve similar dose-volume histograms (DVHs) in inverse planning. At the core of this approach is the overlap-volume histogram (OVH), a one-dimensional function  $v = \text{OVH}(r)$  that characterizes the spatial relationship between an OAR and a target. The OVH quantifies the fractional volume  $v$  of an OAR (normalized by the total OAR volume) that lies within a distance  $r$  from the target surface.

It is hypothesized that  $v = \text{OVH}(r)$  directly correlates with the OAR's cumulative DVH  $v' = \text{DVH}(D)$ , where  $v'$  represents the fractional volume of the OAR (normalized by the total OAR volume) receiving dose  $D$  or higher. Assuming that OVH and DVH curves share the same fractional volume axis  $v$  (or  $v'$ ), a point-to-point mapping between OVH distance  $r$  and DVH dose  $D$  can be established for a specific OAR-and-target pair [19]. A database of OVH and DVH data from the previously delivered clinical plans is then to establish the statistical correlation between distance and dose. By comparing OVH of new patients to the established correlation between distance and dose in the database, the OAR's DVH objectives of new patients are derived and utilized in planning. The details of our OVH-KBP approach can be found in publications [15]-[19].

### 2.2. Patient Characteristics

DICOM sets of computed tomography (CT), RT-structure, and RT-dose from 18 patients previously treated with IMPT (age:  $71.3 \pm 12.9$  years, Male/Female: 11/7, tumors located in the middle to lower third of the esophagus) in our institution are selected for this study. Thirteen patients presented with advanced adenocarcinoma (T3N1M0 or T3N2M0), five patients with squamous cell carcinoma, and one patient with T4 neuroendocrine carcinoma.

The gross tumor volume (GTV) was delineated based on initial staging PET/CT, endoscopy findings, and planning CT according to institutional and consensus-based guidelines on free-breathing CT [13]. The GTV encompassed the entire esophageal wall involved by disease, as well as any PET/CT-avid or enlarged lymph nodes. The clinical target volume (CTV) included peri-esophageal lymph nodes (corresponding to a 3 - 4 cm superior-inferior expansion from the GTV and a 1.0 - 1.5 cm radial expansion), as well as other at-risk regional lymph nodes at the discretion of radiation oncologist. The lungs, heart, liver, kidneys, stomach,

bowels, and spinal canal were contoured as OARs.

Dose prescriptions were 41.4 Gy (RBE: relative biological effectiveness) in 23 daily fractions ( $n = 4$ ) or 45 Gy (RBE) in 25 daily fractions ( $n = 14$ ), per institutional practice. Patients were simulated using 4D-CT, and target and OARs were contoured on average CT. Abdominal compression was routinely applied for target motion greater than 5 mm. Planning dose-volume objectives for target volumes were: mean dose of 41.4 Gy (RBE) or 45 Gy (RBE) to the GTV and CTV respectively. Target coverage required a minimum of  $V_{98\%} \geq 98\%$  for both CTV and PTV. For all targets, the  $D_{1\%}$  was minimized as much as possible. Planning objectives for OARs were as follows:

- Lungs: mean dose  $\leq 32$  Gy,  $V_{20\text{Gy}} \leq 20\%$ ;
- Heart: mean dose  $\leq 10$  Gy,  $V_{30\text{Gy}} \leq 10\%$ ;
- Liver: mean dose  $\leq 15$  Gy;
- Kidneys: mean dose  $\leq 15$  Gy,  $V_{20\text{Gy}} \leq 32\%$ ;
- Other OARs: doses ( $D_{\text{mean}}$  or  $D_{1\%}$ ) were minimized as much as achievable without compromising target coverage.

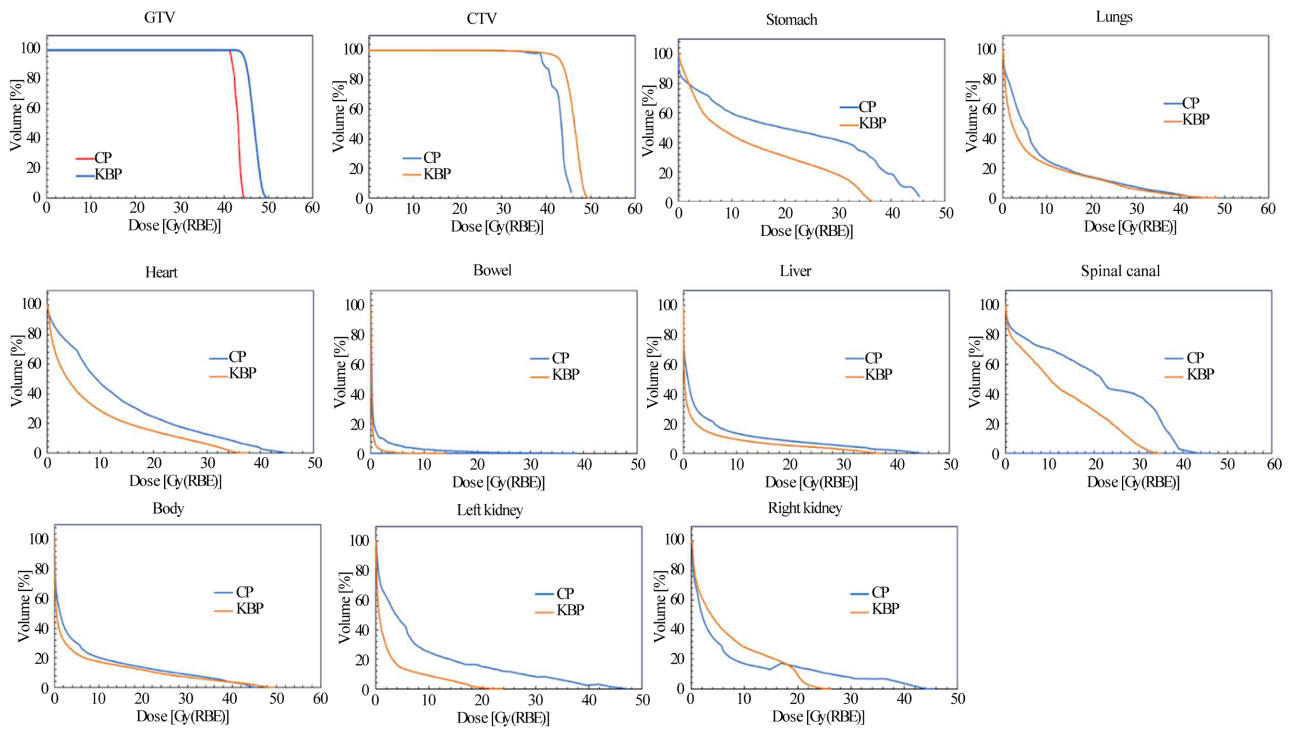
### 2.3. IMPT: KBPs and CPs Generation and Comparison Criteria

Eighteen patients with locally advanced esophageal cancer treated with IMPT were retrospectively analyzed. KBPs were created using a leave-one-out approach: DVH objectives for each KBP were generated from the remaining 17 patients and applied in the RayStation-RS-11A version (RaySearch Laboratories, Sweden) TPS for optimization. Therapeutic proton beams were delivered by a Mevion S250i system with pencil beam scanning (Mevion Medical Systems, Littleton, USA) [23] [24]. Dose distributions were optimized using the Monte Carlo engine with energy layer spacing set at 1 and spot spacing at 0.6. The actual physical spacing between layers and spots varied depending on beam energy: higher energies resulted in larger layer separation, while lower energies had smaller separation; smaller spot spacing increased spatial resolution. Multifield simultaneous spot optimization was used, with a constant RBE of 1.1 applied.

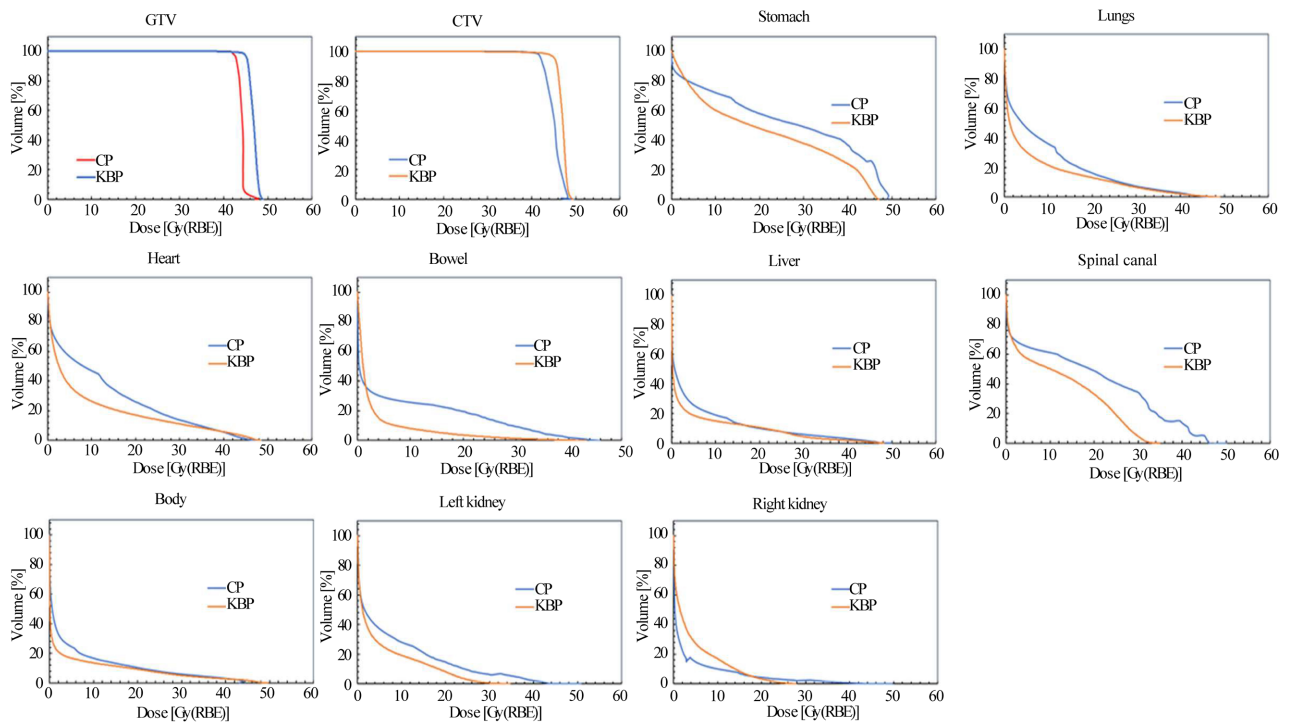
For KBPs, a class solution geometry was used with two posterior oblique fields at gantry angles of  $140^\circ$  and  $220^\circ$ . CPs had beam angles determined by individual planners, generally around  $140^\circ$  and  $220^\circ$ . In both KBPs and CPs, robust optimization was applied to the CTV to account for setup and range uncertainties, considering  $\pm 5$  mm shifts in the isocenter along the x, y, and z axes and  $\pm 3.5\%$  in beam range. Robust optimization ensures that plans meet clinical objectives under various uncertainty scenarios.

Dosimetric evaluation was performed using DVH metrics, including mean dose to targets and OARs;  $D_x$ : the dose covering x% of the OAR's volume;  $V_x$ : the volume receiving at least x Gy. All doses are reported in Gy (RBE). Metrics were expressed in relative (%) or absolute in cc ( $\text{cm}^3$ ). Statistical comparisons between CPs and KBPs were performed using Student's t-test, with significance defined as  $p < 0.05$ .

### 3. Results



**Figure 1.** Average achieved DVHs for the GTV, CTV and OARs for CTV prescription of 41.4 Gy (RBE). Data is shown for CPs (red line) and KBPs (blue line).



**Figure 2.** Average achieved DVHs for the GTV, CTV and OARs for CTV prescription of 45 Gy (RBE). Data is shown for CPs (red line) and KBPs (blue line).

**Figure 1** and **Figure 2** present the achieved average DVHs for the CPs and KBPs across target volumes and OARs for prescription levels 41.4 Gy and 45 Gy respectively. Quantitative dose-volume parameters extracted from individual patient DVHs are summarized in **Tables 1-4**, including mean values, clinical planning goals, and interpatient standard deviations.

**Table 1.** Summary of the planning objectives of the CTV prescription of 41.4 Gy (RBE).

	Objectives	CPs	KBPs	p
<b>GTV</b>				
Mean [Gy]	41.4	50.34 ± 4.46	45.61 ± 0.76	0.21
D <sub>1%</sub> [Gy]	Minimize	54 ± 3.92	47.43 ± 1	0.17
V <sub>98%</sub>	≥98%	100%	100%	0.17
<b>CTV</b>				
Mean [Gy]	41.4	49.05 ± 4.03	44.97 ± 0.18	0.29
D <sub>1%</sub> [Gy]	Minimize	51.78 ± 3.96	47.96 ± 0.09	0.18
V <sub>98%</sub>	≥98%	98.77 ± 2.19	96.18 ± 2.73	0.43
HI	Minimize	1.02 ± 0.12	1.19 ± 0.53	0.05

**Table 2.** Summary of the planning objectives of the CTV prescription of 45 Gy (RBE).

	Objectives	CPs	KBPs	p
<b>GTV</b>				
Mean [Gy]	45	53.16 ± 4.89	46.84 ± 0.69	<0.05
D <sub>1%</sub> [Gy]	Minimize	54.79 ± 5.05	48.5 ± 1.05	<0.05
V <sub>98%</sub>	≥98%	100	99.27 ± 1.81	0.17
<b>CTV</b>				
Mean [Gy]	45	51.76 ± 4.41	46.44 ± 1.1	<0.05
D <sub>1%</sub> [Gy]	Minimize	55.45 ± 5.53	48.37 ± 1.26	<0.05
HI	Minimize	1.04 ± 0.09	1.09 ± 0.02	0.75
V <sub>98%</sub>	≥98%	99.76 ± 0.29	97.76 ± 1.15	<0.05

**Table 3.** Summary of the average results for the OARs of the CTV prescription of 41.4 Gy (RBE).

	Objectives	CPs	KBPs	p
<b>Lungs</b>				
Mean [Gy]	≤12	8.07 ± 3.62	7.04 ± 4.72	0.63
V <sub>20Gy</sub> [%]	≤20	14.71 ± 7.88	14.18 ± 9.82	0.96
<b>Whole Heart</b>				
Mean [Gy]		13.36 ± 2.52	9.02 ± 6.22	0.06
V <sub>30Gy</sub>		15.76 ± 4.57	11.52 ± 8.45	0.31

## Continued

<b>Liver</b>				
Mean [Gy]	≤15	4.61 ± 1.98	3.35 ± 3.64	0.98
<b>Left kidney</b>				
Mean [Gy]	≤15	7.43 ± 5.31	3.2 ± 3.94	0.37
V <sub>20Gy</sub> [%]	≤32	14.59 ± 11.34	5.62 ± 8.51	0.60
<b>Right kidney</b>				
Mean [Gy]	≤15	4.67 ± 5.49	7.94 ± 8.66	0.78
V <sub>20Gy</sub> [%]	≤32	8.41 ± 12.83	16.41 ± 23.56	0.47
<b>Stomach</b>				
Mean [Gy]	Minimize	22.42 ± 10.66	14.81 ± 13.66	0.77
D <sub>1%</sub> [Gy]	Minimize	50.23 ± 4.36	35.03 ± 23.36	0.10
D <sub>1cc</sub> [Gy]	Minimize	50.45 ± 4.42	35.27 ± 23.51	0.10
<b>Bowels</b>				
Mean [Gy]	Minimize	2.31 ± 0.23	0.33 ± 0.42	0.50
D <sub>1%</sub> [Gy]	Minimize	28.84 ± 4.29	4.89 ± 7.2	0.75
D <sub>1cc</sub> [Gy]		36.15 ± 3.13	6.29 ± 8.7	0.49
<b>Spinal canal</b>				
D <sub>1%</sub> [Gy]	Minimize	39.97 ± 3.79	31.01 ± 8.79	0.02
D <sub>0.1cc</sub> [Gy]	Minimize	40.58 ± 4.01	32.52 ± 8.01	0.03

**Table 4.** Summary of the average results for the OARs of the CTV prescription of 45 Gy (RBE).

	<b>Objectives</b>	<b>CPs</b>	<b>KBPs</b>	<b>p</b>
<b>Lungs</b>				
Mean [Gy]	≤32	7 ± 1.94	7.08 ± 1.94	0.91
V <sub>20Gy</sub> [%]	≤20	12.91 ± 3.76	14.52 ± 4.19	0.32
<b>Whole Heart</b>				
Mean [Gy]	≤32	11.02 ± 4.23	9.36 ± 4.91	0.37
V <sub>30Gy</sub> [%]	≤10	13.17 ± 5.66	12.41 ± 7.47	0.78
<b>Liver</b>				
Mean [Gy]	≤15	3.94 ± 1.6	4.57 ± 3.03	0.58
<b>Left kidney</b>				
Mean [Gy]	≤15	4.51 ± 4.69	4.42 ± 5.04	0.97
V <sub>20Gy</sub> [%]	≤32	7.48 ± 10.81	10.58 ± 14.83	0.62
<b>Right kidney</b>				
Mean [Gy]	≤15	3.21 ± 3.2	5.66 ± 6.88	0.33
V <sub>20Gy</sub> [%]	≤32	5.87 ± 7.28	15.04 ± 18.57	0.18

## Continued

Stomach				
Mean [Gy]	Minimize	25.05 ± 13.69	20.3 ± 14.19	0.48
D <sub>1%</sub> [Gy]	Minimize	48.85 ± 5.95	41.07 ± 14.6	0.15
D <sub>1cc</sub> [Gy]	Minimize	48.7 ± 6.7	41.23 ± 14.72	0.18
Bowels				
Mean [Gy]	Minimize	4.95 ± 4.96	4.52 ± 8.22	0.91
D <sub>1%</sub> [Gy]	Minimize	34.86 ± 9.28	26.57 ± 15.8	0.26
D <sub>1cc</sub> [Gy]		43.1 ± 5.2	39.41 ± 10.08	0.41
Spinal canal				
D <sub>1%</sub> [Gy]	Minimize	40.61 ± 5.36	32.45 ± 7.4	0.00
D <sub>0.1cc</sub> [Gy]	Minimize	41.17 ± 5.32	33.67 ± 7.02	0.01

### 3.1. Prescription of 41.4 Gy (RBE)

As summarized in **Table 1**, no statistically significant differences were observed between CPs and KBPs in GTV and CTV coverage. Both plans achieved clinical target coverage objectives. **Table 3** lists the average achieved dosimetric results for OARs. No statistically significant differences were found between CPs and KBPs for the combined lungs, whole heart, liver, kidneys, stomach, or bowels. However, KBPs demonstrated statistically significant dose reductions to the spinal canal, with mean decreases of 8.9 Gy for D<sub>1%</sub> and 7.9 Gy for D<sub>0.1cc</sub> compared with those of CPs ( $p < 0.05$ ).

### 3.2. Prescription of 45 Gy (RBE)

Statistically significant differences were observed in the mean dose and D<sub>1%</sub> for both GTV and CTV, with higher values recorded in CPs (**Table 2**). Coverage remained high for both planning strategies, with V<sub>98%</sub> of the GTV equal to 100% for CPs and 99.27% for KBP, and V<sub>98%</sub> of the CTV equal to 99.76% for CP and 97.76% for KBP. No statistically significant differences were identified for OARs other than the spinal canal, where KBP plans again yielded significantly lower D<sub>1%</sub> and D<sub>0.1cc</sub> than CPs ( $p < 0.05$ ; **Table 4**).

## 4. Discussion

The aim of this study was to apply a KBP framework for IMPT in patients with locally advanced esophageal cancer. The framework generated feasible DVH objectives using a database containing geometric and dosimetric information from previously treated patients. The results demonstrate that the proposed KBP model can efficiently generate IMPT plans with plan quality comparable to that of clinically implemented, manually generated plans by human planners.

This work employed proton beams delivered by a Mevion S250i proton therapy system, which utilizes an energy modulation mechanism distinct from those of

other commercial systems [24]. The Mevion system produces proton energies through the binary insertion of polycarbonate plates of varying thicknesses into the beam path, whereas most other systems use magnetic dipoles or quadrupoles for energy selection. Consequently, the Mevion S250i generally produces larger spot sizes but achieves substantially shorter energy-switching times. To compensate for the dosimetric effects of larger spot sizes, a spot-size-trimming device, the Adaptive Aperture (AA), is employed to sharpen the beam penumbra. These unique beam characteristics directly influence the dose distribution and differentiate the Mevion system from other proton platforms. Therefore, the dosimetric outcomes reported here may not be directly transferrable to other proton therapy systems. Extending this KBP methodology to other systems would require the development of a clinical plan database specific to proton platforms of comparable beam design.

The database utilized in this study was relatively small and constructed from plans generated at a single institution, which inevitably introduces some limitations in terms of plan diversity and consistency. Expanding this database to include plans from multiple institutions—particularly those using the same proton therapy system (e.g., Mevion S250i utilized in this study)—would enhance model robustness and facilitate the generation of more consistent, high-quality plans across diverse clinical environments. Such an expanded dataset would also improve planning efficiency and reduce variability between planners.

Anatomical characteristics of the distal esophagus and adjacent structures influenced beam arrangement decisions, which typically consisted of right and left posterior oblique beams at approximately  $140^\circ$  and  $220^\circ$ . Previous investigations in liver treatment have indicated that minor variations in beam angles exert minimal influence on plan quality [14]. However, larger deviations from the modeled gantry angles could lead to suboptimal optimization outcomes because robust optimization is highly dependent on the geometric relationships between beam paths, targets, and OARs [25]. If different esophageal segments were considered, alternative beam configurations—such as anterior oblique arrangements—may be required. This further emphasizes the need for a larger and more diverse database encompassing the full range of anatomical and geometric scenarios encountered in clinical practice.

All treatment plans in this study were normalized to the mean dose to the CTV, although other institutions may adopt different normalization practices. One of the central aims of KBP is to standardize the planning process, thereby reducing variability introduced by individual planner preferences and experience. Expanding the database to encompass a broader range of target volumes and geometric relationships between targets and OARs will strengthen the KBP model's ability to produce consistent, high-quality plans across varying patient anatomies. Another limitation of this study stems from the wide variation in esophageal length among patients; in some cases, two isocenters and two fields per isocenter were required to achieve full target coverage, rather than a single isocenter with two

fields.

The favorable dosimetric outcomes demonstrated in this study, together with the strong performance of our KBP framework, underscore the value of our patient database as a foundational resource for institutions aiming to implement PBT for advanced esophageal cancer. Notably, the average spinal canal doses— $D_{0.1cc}$  and  $D_{1\%}$ —in the KBP-generated plans were approximately 8 Gy lower than those in the CPs, suggesting a meaningful reduction in the risk of radiation-induced myelopathy if KBP is integrated into IMPT planning. In addition, the KBP plans achieved significantly lower mean dose and  $D_{1\%}$  for both the GTV and CTV. A lower  $D_{1\%}$  indicates reduced hotspot regions within the targets, which can be advantageous when a more homogeneous dose distribution is desired. However, the broader applicability of our approach across institutions may be affected by contouring heterogeneity among physicians and institutions. Because the OVH—a key geometric descriptor in KBP—depends on the accuracy and consistency of contour delineations, variations in contouring practices could influence model performance. The next phase of this research will evaluate the KBP model using datasets from multiple institutions to assess the impact of contouring variability on plan quality and generalizability. This systematic investigation aims to elucidate the extent to which inter-institutional differences in contouring influence the efficacy of KBP models and to inform strategies for harmonizing contouring standards across centers.

## 5. Conclusion

This study demonstrates that the KBP methodology originally developed for IMRT can be effectively adapted to IMPT. By leveraging geometric and dosimetric data from previously delivered treatment plans, this approach enables an optimal balance between target coverage and OAR sparing. The KBP framework provides a reliable and consistent method for predicting clinically achievable DVH objectives prior to optimization, thereby facilitating the generation of high-quality treatment plans with minimal manual adjustment. These findings support the clinical feasibility of KBP-based IMPT planning and underscore its potential to enhance planning efficiency and standardization in proton therapy for esophageal cancer. As a next step, we aim to validate the proposed KBP-IMPT strategy across multiple institutions.

## Aurther Contributions

**Boran Zhou:** Performed OVH, DVH calculations, data analysis and presentation in figures and tables; writing of the original draft of manuscript. **Binbin Wu:** Provided software for OVH calculations, consultation on the methodology. **Markus Wells:** Compiled patient plans for library data construction. **Keith Unger:** Reviewed and edited the manuscript. **Dalong Pang:** Originated and supervised this research; advised on manuscript preparation and reviewed and edited the manuscript.

## Conflicts of Interest

The authors declare no conflicts of interest.

## References

- [1] Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J.W.W., Comber, H., et al. (2013) Cancer Incidence and Mortality Patterns in Europe: Estimates for 40 Countries in 2012. *European Journal of Cancer*, **49**, 1374-1403. <https://doi.org/10.1016/j.ejca.2012.12.027>
- [2] Castro, C., Bosetti, C., Malvezzi, M., Bertuccio, P., Levi, F., Negri, E., et al. (2014) Patterns and Trends in Esophageal Cancer Mortality and Incidence in Europe (1980-2011) and Predictions to 2015. *Annals of Oncology*, **25**, 283-290. <https://doi.org/10.1093/annonc/mdt486>
- [3] Obermannová, R., Alsina, M., Cervantes, A., Leong, T., Lordick, F., Nilsson, M., et al. (2022) Oesophageal Cancer: ESMO Clinical Practice Guideline for Diagnosis, Treatment and Follow-Up. *Annals of Oncology*, **33**, 992-1004. <https://doi.org/10.1016/j.annonc.2022.07.003>
- [4] Hoepfner, J., Lordick, F., Brunner, T., Glatz, T., Bronsert, P., Röthling, N., et al. (2016) ESOPEC: Prospective Randomized Controlled Multicenter Phase III Trial Comparing Perioperative Chemotherapy (FLOT Protocol) to Neoadjuvant Chemoradiation (CROSS Protocol) in Patients with Adenocarcinoma of the Esophagus (NCT02509286). *BMC Cancer*, **16**, Article No. 503. <https://doi.org/10.1186/s12885-016-2564-y>
- [5] Reynolds, J.V., Preston, S.R., O'Neill, B., Baeksgaard, L., Griffin, S.M., et al. (2017) ICORG 10-14: NEOadjuvant Trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study (Neo-AEGIS). *BMC Cancer*, **17**, Article No. 401.
- [6] Xu, D., Li, G., Li, H. and Jia, F. (2017) Comparison of IMRT versus 3D-CRT in the Treatment of Esophagus Cancer: A Systematic Review and Meta-Analysis. *Medicine*, **96**, e7685. <https://doi.org/10.1097/md.00000000000007685>
- [7] Xi, M. and Lin, S.H. (2017) Recent Advances in Intensity Modulated Radiotherapy and Proton Therapy for Esophageal Cancer. *Expert Review of Anticancer Therapy*, **17**, 635-646. <https://doi.org/10.1080/14737140.2017.1331130>
- [8] Hirano, Y., Onozawa, M., Hojo, H., Motegi, A., Zenda, S., Hotta, K., et al. (2018) Dosimetric Comparison between Proton Beam Therapy and Photon Radiation Therapy for Locally Advanced Esophageal Squamous Cell Carcinoma. *Radiation Oncology*, **13**, Article No. 23. <https://doi.org/10.1186/s13014-018-0966-5>
- [9] Warren, S., Partridge, M., Bolsi, A., Lomax, A.J., Hurt, C., Crosby, T., et al. (2016) An Analysis of Plan Robustness for Esophageal Tumors: Comparing Volumetric Modulated Arc Therapy Plans and Spot Scanning Proton Planning. *International Journal of Radiation Oncology, Biology, Physics*, **95**, 199-207. <https://doi.org/10.1016/j.ijrobp.2016.01.044>
- [10] Liu, C., Bhango, R.S., Sio, T.T., Yu, N.Y., Shan, J., Chiang, J.S., et al. (2019) Dosimetric Comparison of Distal Esophageal Carcinoma Plans for Patients Treated with Small-Spot Intensity-Modulated Proton versus Volumetric-Modulated Arc Therapies. *Journal of Applied Clinical Medical Physics*, **20**, 15-27. <https://doi.org/10.1002/acm2.12623>
- [11] Xi, M., Xu, C., Liao, Z., Chang, J.Y., Gomez, D.R., Jeter, M., et al. (2017) Comparative Outcomes after Definitive Chemoradiotherapy Using Proton Beam Therapy versus

- Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis. *International Journal of Radiation Oncology, Biology, Physics*, **99**, 667-676. <https://doi.org/10.1016/j.ijrobp.2017.06.2450>
- [12] Warren, S., Hurt, C.N., Crosby, T., Partridge, M. and Hawkins, M.A. (2017) Potential of Proton Therapy to Reduce Acute Hematologic Toxicity in Concurrent Chemoradiation Therapy for Esophageal Cancer. *International Journal of Radiation Oncology, Biology, Physics*, **99**, 729-737. <https://doi.org/10.1016/j.ijrobp.2017.07.025>
- [13] Wu, A.J., Bosch, W.R., Chang, D.T., Hong, T.S., Jabbour, S.K., Kleinberg, L.R., *et al.* (2015) Expert Consensus Contouring Guidelines for Intensity Modulated Radiation Therapy in Esophageal and Gastroesophageal Junction Cancer. *International Journal of Radiation Oncology, Biology, Physics*, **92**, 911-920. <https://doi.org/10.1016/j.ijrobp.2015.03.030>
- [14] Celik, E., Baues, C., Claus, K., Fogliata, A., Scorsetti, M., Marnitz, S., *et al.* (2021) Knowledge-Based Intensity-Modulated Proton Planning for Gastroesophageal Carcinoma. *Acta Oncologica*, **60**, 285-292. <https://doi.org/10.1080/0284186x.2020.1845396>
- [15] Wu, B., McNutt, T., Zahurak, M., Simari, P., Pang, D., Taylor, R., *et al.* (2012) Fully Automated Simultaneous Integrated Boosted-intensity Modulated Radiation Therapy Treatment Planning Is Feasible for Head-and-Neck Cancer: A Prospective Clinical Study. *International Journal of Radiation Oncology, Biology, Physics*, **84**, e647-e653. <https://doi.org/10.1016/j.ijrobp.2012.06.047>
- [16] Wu, B., Ricchetti, F., Sanguineti, G., Kazhdan, M., Simari, P., Chuang, M., *et al.* (2009) Patient Geometry-Driven Information Retrieval for IMRT Treatment Plan Quality Control. *Medical Physics*, **36**, 5497-5505. <https://doi.org/10.1118/1.3253464>
- [17] Wu, B., Ricchetti, F., Sanguineti, G., Kazhdan, M., Simari, P., Jacques, R., *et al.* (2011) Data-Driven Approach to Generating Achievable Dose-Volume Histogram Objectives in Intensity-Modulated Radiotherapy Planning. *International Journal of Radiation Oncology, Biology, Physics*, **79**, 1241-1247. <https://doi.org/10.1016/j.ijrobp.2010.05.026>
- [18] Wu, B., Pang, D., Simari, P., Taylor, R., Sanguineti, G. and McNutt, T. (2013) Using Overlap Volume Histogram and IMRT Plan Data to Guide and Automate VMAT Planning: A Head-and-Neck Case Study. *Medical Physics*, **40**, Article 021714. <https://doi.org/10.1118/1.4788671>
- [19] Wu, B., Pang, D., Lei, S., Gatti, J., Tong, M., McNutt, T., *et al.* (2014) Improved Robotic Stereotactic Body Radiation Therapy Plan Quality and Planning Efficacy for Organ-Confined Prostate Cancer Utilizing Overlap-Volume Histogram-Driven Planning Methodology. *Radiotherapy and Oncology*, **112**, 221-226. <https://doi.org/10.1016/j.radonc.2014.07.009>
- [20] Lin, S.H., Hobbs, B.P., Verma, V., Tidwell, R.S., Smith, G.L., Lei, X., *et al.* (2020) Randomized Phase IIB Trial of Proton Beam Therapy versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer. *Journal of Clinical Oncology*, **38**, 1569-1579. <https://doi.org/10.1200/jco.19.02503>
- [21] Hall, D.C., Trofimov, A.V., Winey, B.A., Liebsch, N.J. and Paganetti, H. (2017) Predicting Patient-Specific Dosimetric Benefits of Proton Therapy for Skull-Base Tumors Using a Geometric Knowledge-Based Method. *International Journal of Radiation Oncology, Biology, Physics*, **97**, 1087-1094. <https://doi.org/10.1016/j.ijrobp.2017.01.236>
- [22] Smulders, B., Stolarczyk, L., Seiersen, K., Nørrevang, O., Sommer Kristensen, B., Schut, D.A., *et al.* (2023) Prediction of Dose-Sparing by Protons Assessed by a

- Knowledge-Based Planning Tool in Radiotherapy of Brain Tumours. *Acta Oncologica*, **62**, 1541-1545. <https://doi.org/10.1080/0284186x.2023.2264482>
- [23] Forsthoefel, M.K., Ballew, E., Unger, K.R., Ahn, P.H., Rudra, S., Pang, D., *et al.* (2020) Early Experience of the First Single-Room Gantry Mounted Active Scanning Proton Therapy System at an Integrated Cancer Center. *Frontiers in Oncology*, **10**, Article 861. <https://doi.org/10.3389/fonc.2020.00861>
- [24] Kang, M. and Pang, D. (2020) Commissioning and Beam Characterization of the First Gantry-Mounted Accelerator Pencil Beam Scanning Proton System. *Medical Physics*, **47**, 3496-3510. <https://doi.org/10.1002/mp.13972>
- [25] Gutierrez, A., Rompokos, V., Li, K., Gillies, C., D'Souza, D., Solda, F., *et al.* (2019) The Impact of Proton LET/RBE Modeling and Robustness Analysis on Base-of-Skull and Pediatric Craniopharyngioma Proton Plans Relative to VMAT. *Acta Oncologica*, **58**, 1765-1774. <https://doi.org/10.1080/0284186x.2019.1653496>