Evaluation of deep learning-based multiparametric MRI oropharyngeal primary tumor auto-segmentation and investigation of input channel effects: Results from a prospective imaging registry

Kareem A. Wahid a, Sara Ahmed a, Renjie He a, Lisanne V. van Dijk a, Jonas Teuwen b, Brigid A. McDonald a, Vivian Salama a, Abdallah S.R. Mohamed a, Travis Salzillo a, Cem Dede a, Nicolette Taku a, Stephen Y. Lai c, Clifton D. Fuller a, Mohamed A. Naser a, *.

a Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX USA
b Department of Medical Imaging, Radboud University Medical Centre, Nijmegen, The Netherlands
c Department of Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, TX USA

A B S T R A C T

Background/Purpose: Oropharyngeal cancer (OPC) primary gross tumor volume (GTVp) segmentation is crucial for radiotherapy. Multiparametric MRI (mpMRI) is increasingly used for OPC adaptive radiotherapy but relies on manual segmentation. Therefore, we constructed mpMRI deep learning (DL) OPC GTVp auto-segmentation models and determined the impact of input channels on segmentation performance.

Materials/Methods: GTVp ground truth segmentations were manually generated for 30 OPC patients from a clinical trial. We evaluated five mpMRI input channels (T2, T1, ADC, Ktrans, Ve). 3D Residual U-net models were developed and assessed using leave-one-out cross-validation. A baseline T2 model was compared to mpMRI models (T2 + T1, T2 + ADC, T2 + Ktrans, T2 + Ve, all five channels (ALL)) primarily using the Dice similarity coefficient (DSC). False-negative DSC (FND), false-positive DSC, sensitivity, positive predictive value, surface DSC, Hausdorff distance (HD), 95% HD, and mean surface distance were also assessed. For the best model, ground truth and DL-generated segmentations were compared through a blinded Turing test using three physician observers.

Results: Models yielded mean DSCs from 0.71 ± 0.12 (ALL) to 0.73 ± 0.12 (T2 + T1). Compared to the T2 model, performance was significantly improved for FND, sensitivity, surface DSC, HD, and 95% HD for the T2 + T1 model (p < 0.05) and for FND for the T2 + Ve and ALL models (p < 0.05). No model demonstrated significant correlations between tumor size and DSC (p > 0.05). Most models demonstrated significant correlations between tumor size and HD or Surface DSC (p < 0.05), except those that included ADC or Ve as input channels (p > 0.05). On average, there were no significant differences between ground truth and DL-generated segmentations for all observers (p > 0.05).

Conclusion: DL using mpMRI provides reasonably accurate segmentations of OPC GTVp that may be comparable to ground truth segmentations generated by clinical experts. Incorporating additional mpMRI channels may increase the performance of FND, sensitivity, surface DSC, HD, and 95% HD, and improve model robustness to tumor size.

1. Introduction

Oropharyngeal cancer (OPC), a type of head and neck squamous cell carcinoma (HNSCC), is among the most common malignancies globally [1]. Treatment for OPC often includes radiotherapy because of its high cure rate [2]. Segmentation (also termed contouring) of the primary gross tumor volume (GTVp) on radiologic imaging is necessary for the OPC radiotherapy workflow. The GTVp, with a clinical and planning safety margin, acts as a target volume to deliver the radiotherapy dose. Consequently, inadequate GTVp definition may cause under-dosage of the tumor or over-dosage of surrounding normal tissues [3,4]. However, the current clinical standard is manual segmentation by physician experts, which is labor-intensive and subject to high inter-observer variation [5-7]. Therefore, an auto-segmentation tool would be a promising alternative to the current manual standard in OPC radiotherapy workflows.

Deep learning (DL) has found wide success in auto-segmentation [8,9], with many HNSCC auto-segmentation studies applying DL to CT imaging [10-12]. Although CT is the most commonly used imaging modality in OPC radiotherapy planning, MRI has been increasingly recognized as essential for tumor segmentation because of its exceptional soft-tissue contrast [13,14]. Additionally, the emergence of MR-Linac technology, an image-guided adaptive radiotherapy approach [15], has further incentivized the incorporation of MRI in OPC...
radiotherapy planning. Importantly, we recently demonstrated the utility of DL for HNSCC organ-at-risk auto-segmentation using MRI, with improvements in performance, execution time, and dosimetric differences compared to other auto-segmentation methods [16]. While several DL tumor auto-segmentation studies for nasopharyngeal cancer using MRI have been published [17–26], to our knowledge, only one study has been published for OPC [27]. Since HNSCC tumors at different anatomical sites have distinct anatomic boundaries and characteristics [28,29], it is crucial that tumor segmentation models are developed for each site accordingly. Thus, there exists an unmet need for OPC DL tumor segmentation tools using MRI.

Multiparametric MRI (mpMRI) incorporates multiple sequence acquisitions that highlight anatomical and functional information in tumors. For example, dynamic contrast-enhanced (DCE) MRI and diffusion-weighted imaging (DWI) can quantify tumor perfusion and diffusion patterns, respectively, and may affect OPC treatment guidance [30,31]. Recent studies of PET/CT HNSCC DL auto-segmentation [11,21,32–37] have demonstrated increased segmentation performance when combining functional and anatomical modalities. However, investigations that combine anatomical with functional MRI in HNSCC to achieve acceptable DL auto-segmentation performance are lacking [38,39].

In this pilot study, we evaluated the effects of anatomical and functional mpMRI inputs on OPC GTVp segmentation performance. Using open-source DL frameworks with standardized clinical trial data, we trained and evaluated DL models based on variable mpMRI input channels. We then compared the models qualitatively and quantitatively to determine which channel combinations led to the best segmentation results. Finally, we characterized the clinical acceptability of the best-performing model using physician expert observers.

2. Methods

Imaging data

We acquired pre-radiotherapy T2-weighted (T2), contrast-enhanced T1-weighted Dixon fat-suppressed (T1), DCE, and DWI MRI sequences in Digital Imaging and Communications in Medicine (DICOM) format for 124 HNSCC patients from a prospective clinical trial investigating longitudinal mpMRI (NCT03145077). Images were collected from August 2018-August 2019 under a HIPAA-compliant protocol (PA16-0302) approved by The University of Texas MD Anderson Cancer Center’s institutional review board. All patients provided study-specific informed consent. We curated 30 OPC patient data sets with a visible GTVp based on the complete availability of T2, T1, DCE, and DWI image sets (Appendix C, Fig. C1). Demographic characteristics of the patients are shown in Appendix C Table C1. Imaging was performed on a Siemens Aera scanner with a magnetic field strength of 1.5 T and standardized acquisition parameters (Appendix C Table C2). All patients were immobilized with a thermoplastic mask. Apparent diffusion coefficient (ADC) parametric maps were derived from DWI sequences through a proprietary Siemens algorithm (Munich, Germany) using a mono-exponential model. The Tofts model was used to generate parametric maps from DCE sequences for the volume transfer constant (Ktrans) and the extravascular extracellular volume fraction (Ve) [40] (additional details can be found in Appendix A). GTVp ground truth structures were manually segmented in the DICOM-RT Structure format by a physician observer (radiologist with > 5 years of expertise in HNSCC) in Velocity AI v.3.0.1 (Atlanta, GA, USA). GTVp ground truth structures were segmented on the T2 MRI with all other co-registered images made available to the observer during the segmentation process. An example of the mpMRI images used in this study and overlaying GTVp segmentation for one patient is shown in Fig. 1A.

Image processing

To ensure adequate MRI comparability between patients [41], we performed intensity standardization for all images. Anatomical sequences (T2, T1) were standardized using a Z-score (mean = 0, standard deviation = 1), while functional parametric maps (ADC, Ktrans, Ve) were truncated to the 10th and 90th percentile for all patients to remove potential outliers and rescaled to [-1, 1] as per a previous study [38]. All
images were cropped to the smallest field of view (Ktrans, Ve) and resampled to the T2 resolution. An example of the image processing workflow is shown in Fig. 1 B.

Segmentation model architecture and implementation

A DL convolutional neural network based on the 3D Residual U-net architecture [42,43] was implemented in the Medical Open Network for Artificial Intelligence (MONAI) software package [44] (Fig. 1 C). The GTVp mask was used as the ground truth target to train the segmentation model. The MRI images acted as variable-channel inputs to the models. We investigated the following channel combinations as separate models: T2, T2 + T1, T2 + ADC, T2 + Ktrans, T2 + Ve, and all five input channels (ALL). The T2 model acted as a baseline of comparison for all other models. We implemented an Adam optimizer with a Sørensen-Dice similarity coefficient (DSC) loss function. The models were trained for 700 iterations with a learning rate of $2 \times 10^{-4}$ for the first 550 iterations and $1 \times 10^{-4}$ for the remaining 150 iterations based on empirical observations in previous studies [35]. We implemented data augmentation to mitigate overfitting, which included random horizontal flips of 50 % and random affine transformations with an axial rotation range of 12 degrees and a scale range of 10 %. Additional details on the DL architecture and implementation are found in Appendix A.

Model evaluation

Model performance was primarily assessed using DSC. We also implemented additional spatial similarity metrics, including Hausdorff.
Fig. 3. 2D axial slice representations of ground truth segmentations (red dotted outline) and predicted segmentations (yellow dotted outline) for high- (green), medium- (blue), and low- (orange) performance cases. Slices for each case are shown in rows superiorly to inferiorly (top, middle, and bottom). Models are shown in columns. The DSC scores for corresponding models are shown in the top left corners. The high-performance case corresponds to a left tonsillar T4 tumor. The medium-performance case corresponds to a left base of tongue T4 tumor. The low-performance case corresponds to a right base of tongue T4 tumor. T2 = T2-weighted MRI, T1 = T1-weighted MRI, ADC = apparent diffusion coefficient, Ktrans = volume transfer constant, Ve = extravascular extracellular volume fraction, ALL = all five input channels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
distance (HD), false-negative DSC (FND), false-positive DSC (FPD), sensitivity, positive predictive value (PPV), surface DSC, 95% HD, and mean surface distance (MSD). For surface DSC, a tolerance of 3.0 mm was selected as suitable from previous inter-observer variability studies on T2 MRI of OPC GTVp [45]. Surface distance metrics were calculated using the surface-distance Python package [46], while all other metrics were calculated in Elekta ADMIRE v.2.9 (Stockholm, Sweden). Each model was trained and evaluated using leave-one-out cross-validation (LOOCV) (Fig. 1D).

Clinical evaluation

For our best-performing model, we assigned three physician expert observers (radiologist from 2.1 > 1-year post-segmenting, two radiation oncologists) to evaluate the ground truth and corresponding DL-generated segmentations using subjective scoring criteria based on a 4-point Likert scale. The score categories were: 1 = requires corrections, large errors; 2 = requires corrections, minor errors; 3 = clinically acceptable, errors not clinically significant; 4 = clinically acceptable, highly accurate. Additionally, we asked observers to predict the source of the segmentations as either human (ground truth) or DL-generated through a modified Turing test [47]. Ground truth and DL-generated segmentations for all 30 patients were anonymized and randomly presented to experts for clinical evaluation. Experts were blinded to the segmentation source.

Statistical analysis

After performing a Shapiro-Wilk test, we found that our data were not normally distributed (p < 0.05); therefore, we utilized nonparametric statistical tests. We used one-sided Wilcoxon signed-rank tests (alternative hypothesis of greater than for DSC, sensitivity, surface DSC, and PPV; alternative hypothesis of less than for HD, FND, FPD, 95% HD, and MSD) to evaluate differences between our baseline T2 model and models with additional channels. Given the utilization of a small number of a priori planned comparisons and exploratory nature of this work, corrections for multiple hypotheses were not considered. We used Mann-Whitney U tests to detect differences in model performance based on tumor subsite (base of tongue vs tonsil). Additionally, to assess correlations of tumor size with model performance, we calculated Pearson correlation coefficients with corresponding p-values of ground truth against DSC, HD, and surface DSC for every model. Finally, to assess the clinical evaluation of ground truth against DL-generated segmentations, for each observer we implemented a two-sided Wilcoxon signed-rank test for scores and a McNemar test for source predictions. For all statistical analyses, p-values < 0.05 were considered significant. Analyses were performed in Python v.3.7.9. Code notebooks can be found at GitHub (https://github.com/kwahid/mpMRI_OP_C_GTVP_segmentation).

3. Results

Model performance

T2 + T1 was the best performing model overall with the best mean scores in DSC, HD, sensitivity, surface DSC, and 95% HD, while ALL had the worst performing model overall with the worst mean scores in DSC, FPD, and PPV (Fig. 2). To further quantify the impact of specific channel combinations in comparison to the baseline T2 model, significance testing was performed between different channel combinations and the baseline model. Of the significant relationships, T2 + T1 had better performance (p < 0.05) than the baseline T2 model for HD, FND, sensitivity, surface DSC, and 95% HD while T2 + Ve and ALL had better performance (p < 0.05) than the baseline T2 model for FND. These combined results suggest the T2 + T1 model to be the optimal combination for this segmentation task and was further analyzed in the Clinical

![Fig. 4. Dependence of tumor size on the Dice Similarity Coefficient (DSC) (A), Hausdorff Distance (HD) (B), and surface DSC (C), for various input channel models. T2 = T2-weighted MRI, T1 = T1-weighted MRI, ADC = apparent diffusion coefficient, Ktrans = volume transfer constant, Ve = extravascular extracellular volume fraction, ALL = all five input channels.]
Table 1

Clinical evaluation and Turing test results for three physician expert observers. Each observer was asked to score blinded ground truth (GT) or deep learning (DL)-generated segmentations on a 4-point Likert scale (1 = requires corrections, large errors; 2 = requires corrections, minor errors; 3 = clinically acceptable, errors not clinically significant; 4 = clinically acceptable, highly accurate) and asked to identify the source of the segmentation (GT or DL). DL-generated segmentations corresponded to the best DL model tested (T2-weighted + T1-weighted).  

| Observer                  | Score | GT (#) | DL (#) | p-value \(^1\) | Source | GT (#) | DL (#) | p-value \(^2\) |
|---------------------------|-------|--------|--------|----------------|--------|--------|--------|----------------|
| Observer 1 (Radiologist)  | 1     | 3      | 6      | 0.13           | GT     | 16     | 10     | 0.18          |
|                           | 2     | 7      | 11     |                |        |        |        |                |
|                           | 3     | 7      | 4      |                |        |        |        |                |
|                           | 4     | 13     | 9      |                |        |        |        |                |
| Observer 2 (Radiation Oncologist) | 1 | 3 | 6 | 0.44 | GT | 14 | 14 | 1.00 |
|                           | 2     | 10     | 4      |                |        |        |        |                |
|                           | 3     | 16     | 13     |                |        |        |        |                |
|                           | 4     | 1      | 7      |                |        |        |        |                |
| Observer 3 (Radiation Oncologist) | 1 | 1 | 3 | 0.98 | GT | 9 | 12 | 0.61 |
|                           | 2     | 8      | 6      |                |        |        |        |                |
|                           | 3     | 11     | 10     |                |        |        |        |                |
|                           | 4     | 10     | 11     |                |        |        |        |                |

\(^1\) Two-sided Wilcoxon signed rank tests were used for score comparisons.  \(^2\) McNemar tests were used for source prediction comparisons.

performance case, the T2 model demonstrates a DSC of 0.71, with the incorporation of additional channels leading to DSC scores of 0.72–0.78. For the low-performance case, the T2 model demonstrated a DSC of 0.37 and many spuriously predicted voxels in the posterior region of the head, with the incorporation of additional channels reducing the number of spurious voxels and leading to DSC scores of 0.52–0.61. These results indicate improved performance in select cases when incorporating additional input channels. Additional in-depth analysis of this low performance case, a second low performance case, and an HPV-negative tumor case are explored in Appendix B.

Size dependence of models

To determine the impact of tumor size on model performance, we investigated correlations comparing tumor size to representative metrics of volumetric and surface overlap, i.e., DSC, HD, and surface DSC (Fig. 4). The range of values for tumor size were 1.74–45.19 cc. Every model showed non-significant positive correlations for DSC (\(p > 0.05\)) and significant positive correlations for HD (\(p < 0.005\), except for T2 + Ve (\(r = 0.33, p = 0.079\)) and ALL (\(r = 0.06, p = 0.76\)). Every model also showed significant negative correlations for surface DSC (\(p < 0.05\), except for T2 + ADC (\(r = -0.34, p = 0.07\)), T2 + Ve (\(r = -0.30, p = 0.11\)), and ALL (\(r = -0.30, p = 0.1\)).

3.3. Clinical Evaluation: The mean segmentation quality evaluation scores for ground truth vs DL-generated segmentations for the selected model (T2 + T1) were 3.0 vs 2.5, 2.5 vs 2.7, and 3.0 vs 3.0 for observers 1, 2, and 3, respectively. Significance testing revealed no observer could differentiate between the scores (\(p > 0.05\)) or source (\(p > 0.05\)) of the ground truth segmentations compared to the DL-generated segmentations (Table 1). Sub-analysis of clinical evaluation results for select cases can be found in Appendix B.

4. Discussion

In this pilot study, we determined the impact of mpMRI input channel combinations (T2, T2 + T1, T2 + ADC, T2 + Ktrans, T2 + Ve, ALL) on DL model segmentation performance. Recent work has suggested that the average agreement between physicians measured in DSC for OPC tumor segmentation is exceptionally low [45]. Notably, compared to previous fully-automated primary tumor segmentation studies of HNSCC patients, we achieved promising average DSC performance (Table 2). While it is difficult to directly compare DSCs between studies due to different datasets and model training, our models seemingly improve upon the only other fully-automated OPC tumor segmentation study to our knowledge, which exclusively investigated anatomical MRI [27].

The best average DSC performance was achieved by the T2 + T1 model (DSC = 0.73), which was higher than the baseline T2 model (DSC = 0.72) but not statistically significant. Moreover, average DSC decreased when combining all input channels (DSC = 0.71), though non-significantly. However, a previous similar study by Bielak et al. investigating HNSCC tumors with segmentations derived from T2 MRI demonstrated an increased DSC after the inclusion of all available mpMRI channels [38], which is in direct opposition to our results. Importantly, the authors used a smaller number of patients (\(n = 18\)) than our study and implemented repeat imaging at different time-points, which could confound their results. Additionally, their results may be more relevant for a specific HNSCC tumor site, but no analysis was performed to verify this. Notably, auto-segmentation studies in prostate cancer have also reported conflicting results on the additive effects of additional mpMRI input channels for DSC when using ground truth annotations derived from T2 MRI [48–50]. Therefore, further investigations are likely needed to verify if a significant positive DSC effect exists for mpMRI input channel combinations in OPC tumor auto-segmentation.

While most auto-segmentation studies have focused on DSC as an evaluation metric, it has been argued that other metrics should also be taken into consideration, depending on the use-case of the auto-segmentation tool [51,52]. Therefore, to increase the robustness of our analysis, we have included complimentary metrics (HD, FND, FPD, sensitivity, PPV, surface DSC, 95% HD, and MSD) to evaluate our models. Like DSC, most metrics show high performance across various models, with some models demonstrating significantly better values than the baseline T2 model. Interestingly, we demonstrated that in certain edge cases (low-performance example), the inclusion of additional channels could circumvent spurious voxel predictions derived from the baseline T2 model (a possible byproduct of model overfitting), which may increase model robustness (see further discussion in Appendix B, Case 2). These results indicate that the additional channels may contain underlying additive information to improve performance for aspects other than traditional DSC-based evaluation. Notably, the specific anatomic subsite of the tumor (base of tongue or tonsil) had no significant effect on performance for any models for any evaluation metric, indicating that the models were robust to the spatial location of the OPC. Moreover, while the majority of the cases in our study cohort were HPV-positive, our best model (T2 + T1) was minimally affected in the evaluation of an HPV-negative case, though other models were negatively affected (Appendix B, Case 1). Generally, cases that were not well-represented in model training, i.e., irregular tumor presentations, led to suboptimal auto-segmentation performance (Appendix B, Cases 2 and 3).

Previous studies [17,38] have suggested small tumors may be more difficult for DL models to segment, which would hinder the incorporation of models into radiotherapy workflows. Importantly, there were no
significant correlations between tumor size and DSC for any of our models. However, it should be noted that surface distance metrics, such as the HD and surface DSC, demonstrate some size dependence, with larger and smaller tumors being easier for our models to segment, respectively. Interestingly, the surface distance metrics do not demonstrate a significant size dependence for some models that utilize additional channels, particularly those that correspond to functional parametric maps. Therefore, the inclusion of additional channels may strengthen the robustness of models to tumor size for surface distance metric performance, but further confirmatory work is needed.

The acceptability of segmentations used in a radiotherapy workflow is ultimately determined by physician judgment, with physician rating scales considered the gold standard for clinically relevant segmentation quality [52]. While subjective evaluation through rating scales is common in auto-segmentation studies, the established variability of OPC tumor segmentation between observers [45] highlights the difficulty in the interpretation of multi-observer segmentation quality analysis. Therefore, we implemented a comparative approach for each observer to determine if significant clinical differences were present between the ground truth segmentations and the corresponding segmentations of the best DL model (T2 + T1). We demonstrated that experts were on average unable to determine differences between the ground truth and the DL-generated segmentations or identify the source of the segmentations. Of note, the radiologist who provided the original ground truth segmentations was the closest among the observers to correctly discriminating the segmentation sources but was still unable to achieve statistical significance. Additionally, for the radiation oncologist observers the mean clinical acceptability score of the DL-generated segmentations was equal to or higher than the ground truth segmentations, which may indicate a slight preference towards DL-generated OPC tumor segmentations for radiotherapy end users. Importantly, while these results are encouraging, they should not be conflated with a necessarily positive indication for the desired endpoint of radiation therapy planning, which would require further dosimetric studies [52]. Moreover, we demonstrate several DL segmentation failure cases confirmed by clinical evaluation (Appendix B, Cases 2 and 3), so further work is needed to ensure the generation clinically useful segmentations using these approaches.

One limitation of our study is the use of a small cohort of predominately HPV-positive tumors with standardized acquisition parameters, thus the generalizability of the tested models as well as their robustness to different patient groups and acquisition settings may be restricted. However, we have taken steps to optimally utilize our data by implementing a LOOCV approach and investigating various evaluation metrics. Moreover, we plan to include additional prospectively acquired data for model training and use external heterogenous validation sets in future studies to increase model generalizability. Another limitation of our study is that we have constrained our analysis of input image channels based on those that were investigated in previous literature [38]. However, mpMRI input channels can be further investigated through additional quantitative parametric maps (e.g., extended Tofts model [53], advanced DWI fitting models [54], etc.). Moreover, additional data sources such as CT and PET could also be integrated into existing models to determine their impact on auto-segmentation performance. Additionally, we have limited our analysis to primary tumor volumes, so the utility of mpMRI DL for metastatic cervical lymph node tumor volume segmentation in OPC remains unknown. We plan to include additional input channels and incorporate lymph node segmentation in future analyses. A final limitation of our study is the lack of overlap image registration. Our images were acquired from a standardized clinical trial with patient immobilization; therefore, implicit co-registration was deemed adequate for tumor overlap. However, small amounts of motion artifacts may cause the segmentation mask to overlap improperly on mpMRI image channels, impacting auto-segmentation quality. Furthermore, though no geometric distortion was observed on any parametric maps, distortions were not explicitly quantified. Future studies should investigate the role of additional OPC-specific registration algorithms and geometric distortion correction in combination with mpMRI DL auto-segmentation algorithms.

5. Conclusions

In summary, using mpMRI inputs, we built OPC primary tumor DL auto-segmentation models that demonstrated reasonable performance across multiple evaluation metrics. While most channels did not significantly impact model performance as long as the T2 MRI was
included, we find that adding T1 MRI significantly improved HD, FND, sensitivity, surface DSC, and 95% HD and adding Ve or using all input channels simultaneously significantly improved FND. Additionally, certain favorable aspects of model construction, including decreased spurious voxel predictions and robustness to tumor size when considering surface distance metric performance, are apparent for models that leverage additional input channels. Finally, blinded physician experts could not differentiate ground truth from DL-generated segmentations (on average), demonstrating our model shows promise in a Turing test scenario, but should be further investigated in dosimetric impact studies. Our results should be verified in large independent external datasets. Moreover, future studies should investigate if the incorporation of additional images germane to the radiation oncology workflow, such as CT and PET, can further improve model performance. Overall, our pilot study is an important step towards fully automated MR-guided OPC radiotherapy workflows.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Ms. Ann Sutton from the Editing Services Group at The University of Texas MD Anderson Cancer Center Research Medical Library for editing this article. This work was supported by the National Institutes of Health (NIH) through a Cancer Center Support Grant (P30-CA016672-44). K.A. Wahid and T. Salzillo are supported by training fellowships from The University of Texas Health Science Center at Houston for Clinical and Translational Sciences TL1 Program (TL1-TR003169). K.A. Wahid is also supported by the American Legion Auxiliary Fellowship in Cancer Research and a NIDCR F31 fellowship (1F31 DE031502-01). S. Ahmed and M.A. Naser are supported by an NIH National Institute of Dental and Craniofacial Research (NIDCR) Award (R01 DE028290-01). R. He, A.S.R. Mohamed, and S.Y. Lai are supported by a NIH NIDCR Award (R01 DE025248). L.V. van Dijk receives funding and salary support from the Dutch organization NWO ZonMw during the period of study execution via the Rubicon Individual career development grant. B.A. McDonald receives research support from an NIH NIDCR Award (F31DE029093) and the Dr. John J. Kopchick Fellowship through the University of Texas MD Anderson UTHealth Graduate School of Biomedical Sciences. C.D. Fuller received funding from an NIH NIDCR Award (1R01 DE025248-01/R56 DE025248) and Academic-Industrial Partnership Award (R01 DE028290); the National Science Foundation (NSF), Division of Mathematical Sciences, Joint NIH/NSF Initiative on Quantitative Approaches to Biomedical Big Data (QuBBD) Grant (NSF 1557679); the NIH Big Data to Knowledge (BD2K) Program of the National Cancer Institute (NCI) Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science Award (1R01 CA241825); the NCI Early Phase Clinical Trials in Imaging and Image-Guided Interventions Program (1R01 CA218148); the NIH/NCI Cancer Center Support Grant (CCSG) Pilot Research Program Award from the UT MD Anderson CCSG Radiation Oncology and Cancer Imaging Program (P30 CA016672); the NIH/NCI Head and Neck Specialized Programs of Research Excellence (SPORE) Developmental Research Program Award (P50 CA097007); and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) Research Education Program (R25 EB025797). He has received direct industry grant support, speaking honoraria, and travel funding from Elekta AB.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.10.003.

References

[1] Brzy F, Forlaj Y, Soejoetiantara I, Siegel RL, Laera JA. Global cancer statistics 2018. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[2] De Felice F, Tombolini V, Valentinii V, de Vincentiis M, Mezi S, Brugnoli E, et al. Advances in the Management of HPV-Related Oropharyngeal Cancer. J Oncol 2019;2019:9713726.
[3] Njeh CF. Tumor delineation: The weakest link in the search for accuracy in radiotherapy. J Med Phys 2006;33:136–40.
[4] Njeh CF, Dong L, Ortan CG. Point/Counterpoint. IGRT has limited clinical value due to lack of accurate tumor delineation. Med Phys 2013;40:040601.
[5] Vorwerk H, Zink K, Schiller R, Budach V, Böhrner D, Kampfer S, et al. Protection of quality and innovation in radiation oncology: The prospective multicenter trial. German Society of Radiation Oncology (DEGRO–QUIBO study). Strahlenther Onkol 2014;190:433–43. https://doi.org/10.1007/s00066-014-0634-0.
[6] Seganid B, Petric P. Uncertainties in target volume delineation in radiotherapy—are they relevant and what can we do about them? Radiol Oncol 2016;50:254–62.
[7] Rauch C, Steenbakkers R, van Herk M. Target definition in prostate, head, and neck. Semin Radiat Oncol 2005;15:336–45.
[8] Guo Y, Liu Y, Georgiou T, Lew MS. A review of semantic segmentation using deep neural networks. Int J. Multimed. Inform. Retr. 2018;7:87–93.
[9] García-García A, Ortiz-Escalona O, Sopera S, Villena-Martínez V, García-Rodriguez J. A review on Deep Learning Techniques Applied to Semantic Segmentation. ArXiv [CsCV] 2017.
[10] Maleki F, Le WT, Sananmattan T, Kadowe S, Forghani R. Machine Learning Applications for Head and Neck Imaging. Neuroimaging Clin N Am 2020;30:517–29.
[11] Lo Faso EA, Gambino O, Pireno R. Head-neck Cancer Delineation. NATO Adv Sci Inst Ser E Appl Sci 2011;12:2721.
[12] Koasim M, Lednam J, Romera-Paredes B, Menders R, Moinuddin S, de Souza D, et al. Rapid advances in auto-segmentation of organs at risk and target volumes in head and neck cancer. Radiother Oncol 2019;135:130–40.
[13] Zima AJ, Wenslovski JR, Ibrahim M, Lantig AAD, Lantig J, Mukherji SK. Magnetic resonance imaging of oropharyngeal cancer. Top Magn Reson Imaging 2007;18:237–42.
[14] Lewis-Jones H, Colley S, Gibson D. Imaging in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016;130:528–31.
[15] McDonald BA, Vedam S, Yang J, Wang J, Castillo P, Lee B, et al. Initial feasibility and clinical implementation of daily MR-guided adaptive head and neck cancer radiation therapy on a 1.5T MR-linac system: Prospective R-IDEAL 2a/2b systematic clinical evaluation of technical innovation. Int J Radiat Oncol Biol Phys 2019;109:1609–18.
[16] McDonald BA, Cardenas C, O’Connell N, Ahmed S, Naser MA, Wahid KA, et al. Investigation of Autosegmentation Techniques on T2-Weighted MRI for Off-line Dose Reconstruction in MR-linac: Adapt to Position Workflow for Head and Neck Cancers. medRxiv 2021. https://doi.org/10.1101/2021.09.30.21264372.
[17] Lin L, Dou Q, Jin Y-M, Zhou Q-G, Tang Y-Q, Chen W-L, et al. Deep Learning for Automated Contouring of Primary Tumor Volumes by MRI for Nasopharyngeal Carcinoma. Radiology 2019;291:87–96.
[18] Ye Y, Cai Z, Huang B, He Y, Zeng P, Zou G, et al. Fully-Automated Segmentation of Nasopharyngeal Carcinoma on Dual-Sequence MRI Using Convolutional Neural Networks. Front Oncol 2020;10:166.
[19] Ma Z, Wu X, Song Q, Luo Y, Wang Y, Zhou J. Automated nasopharyngeal carcinoma segmentation in magnetic resonance images by combination of convolutional neural networks and graph cut. Exp Ther Med 2016;18:2511–21.
[20] Li Q, Xu J, Chen Z, Liu D, Feng S-T, Law M, et al. Tumor Segmentation in Contrast-Enhanced Magnetic Resonance Imaging for Nasopharyngeal Carcinoma: Deep Learning with Convolutional Neural Networks. Biomed Res Int 2018;2018:9128527.
[21] Chen H, Qi Y, Yin L, Yi T, Liu X, Li X, et al. MPNet: A multi-modality MRI fusion network for segmentation of nasopharyngeal carcinoma. Neurocomputing 2020;394:27–40.
[22] He Y, Yu X, Liu C, Zhang J, Hu K, Zhu HC. A 3D Dual Path U-Net of Cancer Segmentation Based on MLI. In: 2018 IEEE 3rd International Conference on Image, Vision and Computing (ICIVC). 2018. p. 268–72.
[23] Ke L, Deng Y, Xia W, Qiang M, Chen X, Liu K, et al. Development of a self-constrained 3D DenseNet model in automatic detection and segmentation of nasopharyngeal carcinoma using magnetic resonance images. Oral Oncol 2020;110:104862. https://doi.org/10.1016/j.joraloncol.2020.104862.
[24] Wang Y, Yu C, Hu G, Luo Y, Ma Z, He K, et al. Automatic tumor segmentation with deep convolutional neural networks for radiotherapy applications. Neural Processes Letters 2018;48:1323–34.
[25] Ma Z, Zhou S, Wu X, Zhang H, Yan W, Sun S, et al. Nasopharyngeal carcinoma segmentation based on enhanced convolutional neural networks using multi-modal metric learning. Phys Med Biol 2019;64:025005.
[26] Huang J-B, Zhou E, Li H, Liu L, Cai H, Ou Y. Achieving Accurate Segmentation of Nasopharyngeal Carcinoma in MR Images Through Recurrent Attention. Medical Image Computing and Computer Assisted Intervention – MICCAI 2019, Springer International Publishing: 2019. p. 494–502.
[27] Rodrigues Outeiral R, Bo S, Al-Mangani A, Jenser B, Simões R, van der Heide U. Oropharyngeal primary tumor segmentation for radiotherapy planning on magnetic resonance imaging using deep learning. Phys Imaging Radiat Oncol 2021;1:9:39–44.
[28] Shiga K, Ogawa T, Katagiri K, Yoshida F, Tateda M, Matsura K, et al. Differences between oral cancer and cancers of the pharynx and larynx on a molecular level. Oncol Lett 2012;3:238–43.
[29] Rothenberg SM, Ellisen LW. The molecular pathogenesis of head and neck squamous cell carcinoma. J Clin Invest 2012;122:1951–7.

[30] van der Heide UA, Hosoe CG, Groenendaal G, Beets-Tan RGH, Lambin PF. Functional MRI for radiotherapy dose painting. Magn Reson Imaging 2012;30:1216–23.

[31] Salzillo T, Taku N, Wahid K, McDonald B, Wang J, van Dijk I, et al. Advances in imaging for HPV-related oropharyngeal cancer: Applications to radiation oncology. Semin Radiat Oncol 2021.

[32] Andrearczyk V, Oreiller V, Vallières M, Castelli J, Elbalawani H, Jreige M, et al. Automatic segmentation of head and neck tumors and nodal metastases in PET-CT scans. In: Arbel T, Ayed IB, de Brujine M, Descoteaux M, Lombarhert H, Pal C, editors. Proceedings of the Third Conference on Medical Imaging with Deep Learning, vol. 121, Montreal, QC, Canada: PMLR; 2020, p. 33–43.

[33] Moir YM, Groenendaal AR, Moodie N, Tomic O, Isdahl U, Dale I, et al. Deep learning for automatic tumour segmentation in PET/CT images of patients with head and neck cancer. ArXiv [Eess/LV] 2019.

[34] Huang B, Chen Z, Wu P-M, Ye Y, Feng S-T, Wong C-YO, et al. Fully Automated Delineation of Gross Tumor Volume for Head and Neck Cancer on PET-CT Using Deep Learning: A Dual-Center Study. Contrast Media Mol Imaging 2018;2018:8923028.

[35] Naser MA, van Dijk LV, He R, Wahid KA, Fuller CD. Tumor Segmentation in Patients with Head and Neck Cancers Using Deep Learning Based-on Multi-modality PET/CT Images. Head and Neck Tumor Segmentation, Springer International Publishing; 2021, p. 85–98.

[36] Iantsen A, Visvikis D, Hatt M. Squeeze-and-Excitation Normalization for Automatic Delineation of Head and Neck Primary Tumors in Combined PET and CT Images. Head and Neck Tumor Segmentation, Springer International Publishing; 2021, p. 37–43.

[37] Ren J, Erikson JG, Nijamp J, Korreman SS. Comparing different CT, PET and MRI multi-modality image combinations for deep learning based head and neck tumour segmentation. Acta Oncol 2021;1–8.

[38] Bielak L, Wiedemann N, Berlin A, Nicolay NH, Gunashekar DD, Hagele I, et al. Convolutional neural networks for head and neck tumor segmentation on 7-channel multiparametric MRI: a leave-one-out analysis. Radiat Oncol 2020;15:181.

[39] Bielak L, Wiedemann N, Nicolay NH, Lottner T, Fischer J, Bunea H, et al. Automatic Tumor Segmentation With a Convolutional Neural Network in Multiparametric MRI: Influence of Distortion Correction. Tomography 2019:5–29.

[40] Gaddikeri S, Gaddikeri RS, Tailor T, Anzai Y. Dynamic Contrast-Enhanced MR Imaging in Head and Neck Cancer: Techniques and Clinical Applications. AJNR Am J Neuroradiol 2016;37:588–95.

[41] Wahid KA, He R, McDonald BA, Anderson BM, Salzillo T, Mulder S, et al. MRI Intensity Standardization Evaluation Design for Head and Neck Quantitative Imaging Applications. MedRxiv 2021.

[42] Ronneberger O, Fischer P, Brox T. U-Net: Convolutional Networks for Biomedical Image Segmentation. Medical Image Computing and Computer-Assisted Intervention – MICCAI 2015, Springer International Publishing; 2015, p. 234–41.

[43] Naser MA, Deon MJ. Brain tumor segmentation and grading of lower-grade glioma using deep learning in MRI images. Comput Biol Med 2020;121:103758.

[44] Ma N, Li W, Brown R, Wang Y, Gorman B, Behrooz A, et al. Project-MONAI/MONAI: 0.5.0. 2021. https://doi.org/10.5281/zenodo.4679866.

[45] Blende S, Mohamed ARR, Al-Mamgani A, Newbold K, Karam I, Robbins JR, et al. Large interobserver variation in the international MR-LINAC oropharyngeal carcinoma delineation study. Int J Radiat Oncol Biol Phys 2017;99:E539–40.

[46] Nikolov S, Blackwell S, Zversnich A, Mendes R, Livne M, De Fauw J, et al. Deep learning to achieve clinically applicable segmentation of head and neck anatomy for radiotherapy. ArXiv [GeCV] 2018.

[47] Gooding MJ, Smith AJ, Tariq M, Aljabar P, Peressutti D, van der Steen J, et al. Comparative evaluation of autocontouring in clinical practice: A practical method using the Turing test. Med Phys 2018;45:5105–15.

[48] Nai Y-H, Teo BW, Tan NL, Chua KYW, Wong CK, O’Doherty S, et al. Evaluation of Multimodal Algorithms for the Segmentation of Multiparametric MRI Prostate Images. Comput Math Methods Med 2020;2020:8861035.

[49] Zhao X, Xie P, Wang M, Li W, Pickhardt PJ, Xia W, et al. Deep learning-based fully automated detection and segmentation of lymph nodes on multiparametric-mri for rectal cancer: A multicentre study. ElsioMedicine 2020;56:102780.

[50] Pellicer-Valero OJ, Marenco Jimenez JL, Gonzalez-Perex V, Ramirez-Borja JL, Garcia IM, Benito MB, et al. Deep Learning for fully automatic detection, segmentation, and Gleason Grade estimation of prostate cancer in multiparametric Magnetic Resonance Images. ArXiv [PhysicsMed-Pd] 2021.

[51] Taha AA, Hanbury A. Metrics for evaluating 3D medical image segmentation: analysis, selection, and tool. BMC Med Imaging 2015;15:29.

[52] Sherer MV, Lin D, Elgundis S, Duke S, Tan L-T, Caccioc J, et al. Metrics to evaluate the performance of auto-segmentation for radiation treatment planning: A critical review. Radiother Oncol 2021;160:185–91.

[53] Bourbon SP, Buckley DL. On the scope and interpretation of the TPFs models for DCE-MRI. Magn Reson Med 2011;66:735–45.

[54] Fujimura N, Sakashita T, Homma A, Shinizu Y, Yoshida A, Harada T, et al. Advanced diffusion models in head and neck squamous cell carcinoma patients: Goodness of fit, relationships among diffusion parameters and comparison with dynamic contrast-enhanced perfusion. Magn Reson Imaging 2017;36:16–23.