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Systematic Review

Artificial intelligence-supported applications in head and neck cancer radiotherapy treatment planning and dose optimisation

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Introduction: The aim of this review is to describe how various AI-supported applications are used in head and neck cancer radiotherapy treatment planning, and the impact on dose management in regards to target volume and nearby organs at risk (OARs).

Methods: Literature searches were conducted in databases and publisher portals Pubmed, Science Direct, CINAHL, Ovid, and ProQuest to peer reviewed studies published between 2015 and 2021.

Results: Out of 464 potential ones, ten articles covering the topic were selected. The benefit of using deep learning-based methods to automatically segment OARs is that it makes the process more efficient producing clinically acceptable OAR doses. In some cases automated treatment planning systems can outperform traditional systems in dose prediction.

Conclusions: Based on the selected articles, in general AI-based systems produced time savings. Also, AI-based solutions perform at the same level or better than traditional planning systems considering auto-segmentation, treatment planning and dose prediction. However, their clinical implementation into routine standard of care should be carefully validated

Implications to practice: AI has a primary benefit in reducing treatment planning time and improving plan quality allowing dose reduction to the OARs thereby enhancing patients' quality of life. It has a secondary benefit of reducing radiation therapists' time spent annotating thereby saving their time for e.g. patient encounters.

Introduction

Globally, head and neck cancer (HNC) represents the sixth most common type of cancer and in 2020, nearly a million new cases were reported.[1,2] HNC comprises a diverse group of malignant tumors that develop in the region of the upper aerodigestive tract i.e. lips, oral cavity, salivary glands, larynx, nasal cavity, paranasal sinuses and pharynx.[3] Treatment of HNC requires a multimodality approach and depends on several factors.[4,5] Along with surgery and chemotherapy, radiotherapy is one of the most efficient and frequently used treatments either as a sole treatment method or combined with other options.[4,6,7] It is estimated that around 50% of all cancer patients are treated with radiation therapy.[8]

Although radiotherapy is an integral part of HNC cancer treatment, it is often a challenging process and requires multidisciplinary approach.[9] HNC radiotherapy requires high level of radiation delivered to a relatively small, irregular-shaped and precisely targeted area.[10] In addition, this particular area is an anatomically complex structure containing a large number of organs at risk (OARs). Any damage to these organs as a result of unintentional irradiation may lead to many acute and late side effects such as xerostomia and dysphagia.[11] These adverse effects can have a negative impact on a patient's overall quality of life. However,

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advanced radiotherapy techniques have improved tumor targeting while sparing adjacent healthy tissue, reduced toxicities and therefore improved the clinical outcomes of many patients. Technologies like image-guided radiation therapy (IGRT) and intensity modulated radiation therapy (IMRT) have improved both target precision and accuracy. In particular, for tumors located near critical structures, the deep step gradient dose of IMRT allows a higher rate of tumor control compared to 2D and 3D RT techniques, without increasing the toxicity profile.[10]

Radiotherapy treatment for HNC is often delivered by a linear accelerator. The total dose is fractionated over time so that normal tissue can recover while tumor cells which are more sensitive to radiation, will be destroyed. Radiation therapy steps can be altered depending on the disease site, but in general, the following steps are included: immobilization, radiological imaging (i.e., simulation), treatment planning including target volume and nearby structures contouring and dose optimisation, plan verification (QA) and dose delivery.[12]

The fields of medical imaging and radiation oncology have advanced in the last few decades. The improvement in radiotherapy treatment planning and delivery accuracy can be attributed to the increase in details of collected data of tumors and their surrounding structures.[12] In addition, new high-precision radiotherapy techniques such as intensity modulated radiotherapy (IMRT) are currently widely used for head and neck cancer patients and they have improved the overall accuracy of the treatment. In IMRT technology, multiple precisely shaped fields conform the dose to the target volumes by means of beamlets in with varying intensities.[13] These sharp dose gradients achieved through the use of VMAT improve dose conformality and enable the administration of high radiation doses to the target area while reducing the dose received by surrounding OARs.[9] In addition, for advanced treatment delivery techniques including both Volumetric modulated arc therapy (VMAT) and IMRT, higher conformal dose distributions with improved target volume coverage and sparing of normal tissues can be achieved when compared with the older three-dimensional (3D) conformal radiotherapy techniques. Moreover, the treatment time for VMAT is usually shorter than in IMRT.[14,15] Treatment planning is a crucial step in the radiotherapy workflow. HNC radiotherapy IMRT-treatment planning is based on inverse treatment planning where predefined dose constraints are determined before the calculations of beam intensities.[16] This demands multiprofessional collaboration with a high level of clinical expertise to maximize the therapeutic ratio.[17] In addition, it is often a tedious and time consuming task where several iterations are performed to achieve an optimal radiation dose and distribution to the target volume.[17]

Radiotherapy and AI-based applications

With the proliferation of development works in artificial intelligence, varying medical fields have seen and benefited from its impact. Radiomics means the extraction of mineable data from medical images and it has been applied within oncology to improve diagnosis, prognosis, and clinical decision support in order to deliver personalized medicine. The radiomics workflow is multidisciplinary, including e.g radiologists and data and imaging scientists. It is a sequential process comprising tumor segmentation, image preprocessing, feature extraction, model development, and validation.[18] In radiotherapy, AI-based solutions have already been implemented in clinical practice to some extent in different stages of radiotherapy workflow (e.g. in target volume and OARs segmentation, treatment planning, radiotherapy delivery and treatment response assessment).[19,20]

In particular, machine learning (ML) and its different fields have been under extensive research. As part of this, deep learning (DL) development has focused around target volume and organs at risk (OAR) delineation. Manual contouring of target volumes and OARs is widely utilized and persists at present even though it is time consuming and highly variable due to planner experience and skills.[21]

One solution to reduce the plan quality variations is to automate or semi-automate the planning process by using knowledge-based planning solutions (Varian's RapidPlan software is one such commercial vendor). Studies have shown that these solutions significantly speed up the treatment planning process of HNC patients.[22–24] Even though AI-based solutions are now used in clinical settings, there are still significant challenges with them. For example, the training process of AI is usually time consuming and the training results are not robust for certain applications. Additionally, the ethical and juridical aspects of AI are still relatively unknown. Despite the challenges, there are still untapped possibilities with AI usage within the field of radiotherapy and it can be predicted that in the future it will revolutionize cancer treatment and be a significant part of radiotherapy.[18,19] However, more clear and consistent information is needed about the potentials of AI-based solutions in treatment planning of HNC radiation therapy.

The aim of this review is to describe how AI-supported applications are used in the HNC radiotherapy treatment planning, and what kind of impact they can have on the dose management of the target volume and nearby OARs.

The following search questions were set:

1. How can artificial intelligence be used in HNC treatment planning?
2. What are the possibilities of using AI in dose optimization during the HNC treatment planning process?

Methods

Database search

Literature searches were conducted in five databases and publisher portals: Pubmed, Science Direct, CINAHL, Ovid, and ProQuest. The following keywords with different combinations were used, and they were adapted for each database: “artificial intelligence OR machine learning OR deep learning AND radiotherapy OR radiation therapy AND radiation dose AND head and neck cancer OR HNC”. The keywords “organs-at-risk” and “OAR” closely related to the topic were omitted from the final search as they were found to limit search results in excess and therefore potential studies might have been excluded from the review. Additional manual search from the reference lists of the final studies that were included in the review was undertaken to uncover all appropriate data on the topic.

The PICO or PICo model that stands for Population, Intervention, Context, Outcome is recommended to use as a guide to formulate a clear and meaningful research question as well as to help define inclusion and exclusion criteria in the search process.[25] These mnemonics regarding the search questions of this review are presented in Table 1.

Inclusion/exclusion criteria

Inclusion and exclusion criteria were defined according to the PICO -strategy. Articles were included if they addressed any aspect of artificial intelligence in relation to dose management in the head and neck cancer radiotherapy treatment planning. The search was limited to peer reviewed studies that were published between 2015 and 2021. Since the topic is rapidly evolving, only the studies that were published in the recent years were considered as relevant. In

Table 1
The PiCOs in research questions 1 and 2.

The PICo for question 1	The PICO for question 2
***P**opulation: head and neck cancer patients*	***P**opulation: head and neck cancer patients*
***I**ntervention: artificial intelligence*	***I**ntervention: artificial intelligence*
***Co**ntext: radiotherapy treatment planning*	***C**ontext: radiotherapy treatment planning*
	***O**utcomes: dose optimization*

addition, other types of evidence besides original research studies might not have been useful considering the objectives of this review. Only the articles written in the English language were included in this review.

Study selection

The selection of articles was conducted in three phases. In the first screening stage the selection (n = 464) was done based on the title level and any potential duplicates were removed. In the second stage, articles (n = 68) were read on the abstract level and relevant studies corresponding to the topic were chosen for the next phase. A total of 27 articles were read at full text level on the third phase. After full text evaluation 12 articles were selected. Furthermore, after data extraction additional two articles were excluded due to their irrelevance to the topic. Thus, ten articles were finally included for this scoping review. The manual search was then performed from the reference lists of the included articles but studies that met the inclusion criteria were not found.Two reviewers independently undertook the study selection process for filtering the articles. Any disagreement between reviewers after every screening phase was solved in consensus through discussion. The search process is presented in the PRISMA -flowchart in Fig. 1.

Data extraction

The final ten articles that met the inclusion criteria were documented in a data extraction form. They were tabulated according to the AI technique used in the study to make the results easier to interpret.The following data of each study was collected: author(s), year of publication, country where study performed, objective of the study, dataset, used AI -technology, methods and primary results. Articles were divided into three categories based on the topics they covered: deep learning/machine learning based segmentation and delineation, knowledge based planning/applications and DL/ML-based applications for dose prediction (Table 2).

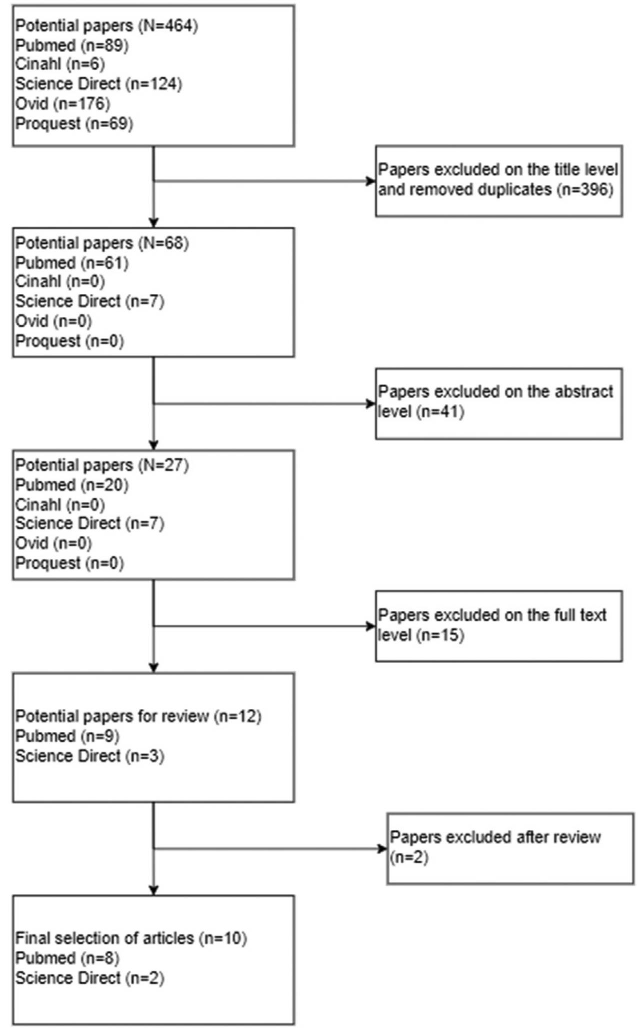

Figure 1. PRISMA-diagram illustrating the search process.

Results

Auto-segmentation

Auto-segmentation means any system that uses some form of AI to automatically segment, contour or delineate the target area or OARs.[26] The benefit of using auto-segmentation, such as a deep learning-based method to automatically segment OARs, is that it makes the process more efficient producing clinically acceptable OAR doses.[27] Chen et al.[28] used deep learning-based semantic segmentation to contour OARs called WBNet, which consists of three different deep learning models, with UA-net being used specifically for the HNC area. It was discovered that the WBNet outperformed three other commercially available auto-segmentation models in 21 out of 28 head and neck OARs.[28] In the study performed by Alliotta et al.[29] the proposed auto-delineation (AD) workflow reduced the number of OARs requiring manual delineation or review by 33% across ten HNC patients and up to 63% for individual patients without affecting any clinically relevant OAR doses. In the study by Thor et al.[30] auto-segmentation of HNC radiation therapy was combined with automated treatment planning to study the possibility of introducing new masticatory OARs. The study found out that automated treatment planning could efficiently incorporate new structures from DL auto-segmentation. However, the study also found that the systematic dose differences in the six OARs between using manual segmentation and using DL segmentation were small.

Automated treatment planning

Automated treatment planning, on the other hand means, any technology that uses some form of AI to automatically provide a treatment plan with the intent to make the planning process more efficient and at least on the same level as manual treatment plans when looking at dose levels.[31] McIntosh et al.[32] showed that in some cases, their method outperformed the clinical plan in dose prediction. In their study automated plans achieved an average of 0.6% higher dose for target coverage, and 2.4% lower dose at the organs at risk levels evaluated compared with clinical. There was no statistically significant difference in high-dose conformity between

Table 2
Summary of selected articles categorized into three different methods *.

Reference and country	Objective of the study	Dataset	Technology used	Methods	Main results
Chen et al.[28] China/USA	To develop a DL-based automatic segmentation system (WBNet) that can precisely delineate all vital OARs in the entire body.	755 CT scans HNC (320 cases) Thorax (110 cases) Abdomen (200 cases) Pelvis (125 cases) Training (505 cases) Test set (250 cases)	Auto-segmentation Deep Learning-based	Development and validation of WBNet using the training set and test set. Evaluation of the delineation quality for each OAR were calculated with Dice similarity coefficient (DSC) and 95th-percentile Hausdorff distance (95% HD). Performance of WBNet was compared with three AS algorithms (ABAS, AnatomyNet, nnU-Net)	WBNet outperformed the three AS-algorithms it was compared to. It reduced the delineation time significantly and performed well in treatment planning with clinically acceptable dose differences in treatment plans.
van Rooij et al.[27] Netherlands	To study a DL-based auto-delineation of numerous OARs in HNC radiotherapy treatment planning and to investigate geometric and dosimetric impact.	DICOM files (157 cases) Training set (142) Test set (15)	Auto-segmentation Deep learning-based	Deep learning (DL) model was trained using a training set of 142 manual delineation (MD) cases. Test set of 15 was used to test the quality of the DL model and it was compared to original MD of these 15 cases.	The performance of the DL model produced dose differences that were clinically acceptable when compared to manual delineation.
Aliotta et al.[29] USA	To develop an approach that automatically identifies and contours low priority OARs before HNC treatment planning.	HNC (10 cases)	Auto-segmentation Knowledge-based	OARs were delineated using an AD. OARs that had estimated clinically tolerated low doses were excluded from manual delineation (MD)/review. The AD plans were compared to MD OARs.	AD could identify 67 out of 201 OARs as low priority. The AD plans when comparing to MD plans were at a clinically acceptable level.
Thor et al.[30] USA	To investigate DL auto-segmentation of masticatory structure OARs combined with automated treatment planning in HNC.	Training set (48 cases) Test set (10 cases)	Auto-segmentation and Deep learning-based	Three rounds of plan optimization was done (Echo0,Echo1 and Echo2). DL replaced a set of six manually segmented OARs that were optimized with Echo1. Two scenarios were compared with clinical dose volume criteria. Echo0 vs Echo1 and Echo1 vs Echo2.	Automated treatment planning could efficiently incorporate new structures from DL auto-segmentation. Between the DL segmentation and manual segmentation only small systematic dose differences were found in the six OARs. Echo1 provided better normal tissue sparing
McIntosh et al.[32] Canada	To create a fully automated HNC treatment planning pipeline using voxel-based dose prediction and dose mimicking.	Training set (54 cases) Test set (12 cases)	*Automated treatment planning* (dose prediction, dose mimicking) Knowledge-based/ Machine learning	For all patients a treatment plan was created using Pinnacle treatment planning system.	Preliminary results showed that automated methods can produce dose distributions that are comparable to manual treatment planning methods.
Babier et al.[33] Canada	To develop an automated knowledge-based treatment planning workflow by combining two KBP prediction methods with an inverse optimization.	Oropharyngeal cancer (217 cases)	*Automated treatment planning* Knowledge-based	Two KBP methods were created, bagging query (BQ) method and generalized principal component analysis based (gPCA) method, to predict target dose volume histograms and feasible OARs. The predictions resulting from these KBPs were compared to clinical DVHs that were put through an IO pipeline creating clinical inverse optimized plans (CIO).	When comparing the two methods to clinical DVHs the BQ method predicted a lesser dose while the gPCA method predicted a dose that was more inline with the clinical plan. While looking at the clinical criteria performance, the most similar was the CIO following that the gPCAˆprime and after that the BQ method.
Cornell et al.[34] USA	To evaluate automated knowledge-based treatment plans to human-driven plans by comparing dosimetric quality and plan variability across multiple disease sites.	Prostate (41 cases) Prostatie fossa (32 cases) Lung SBRT (36 cases) HNC (36 cases)	*Automated treatment planning* Knowledge-based	Human generated plans and KBP generated plans were put through blind selection process using non inferiority framework testing. The target and OAR metrics from the selected plans were then compared together.	Across all disease sites the KBP plans were noninferior and in HN the plans were superior compared to human-driven planning. The KBP also in prostate, prostatic fossa and HN sites showed greater OAR sparing but lesser target homogeneity compared to the human-driven plans.

(*continued on next page*)

Table 2 (*continued*)

Reference and country	Objective of the study	Dataset	Technology used	Methods	Main results
Cilla et al.[35] Italy	To perform an extensive plan quality and OARs sparing evaluation of the Pinnacle automated treatment planning system in HNC treatments.	Oropharynx/hypopharynx/ Oral cavity (15 cases)	*Automated treatment planning* Knowledge-based	Manually generated plans and automated plans were compared together using DVHs and blind clinical evaluation. Two aspects of these plans were compared planning time and dose accuracy.	Automated plans generated less irritation to healthy tissue and significantly reduced the dose to different OARs like the spinal cord. Overall the automated plans created a better plan quality compared to manually generated plans.
Sher et al.[38] USA	To evaluate the benefits of AI -based decision support tool (DST) in dose prediction of the HNC treatment planning workflow.	Training set (276 cases) Test set of (50 cases)	**Dose prediction** AI/Machine learning-based	A physician created a custom OAR directive for the 50 patient test set. After this the DST estimated the doses for each OAR (Ai directive). The results were compared together. The same physician formed a hybrid directive using the AD.	Overall the highest reduction to dose objectives came from the hybrid directive following the Ai directive and then the physician directive.
Miki et al.[37] Japan/Netherlands	To develop and evaluate two independent dose distribution prediction methods in the HNC treatment planning.	Oropharynx/hypopharynx tumor (81 cases) Test set (10 cases)	**Dose prediction and distribution** Deep learning-based	Dose distribution was done using a modified filtered back projection (mFBP) and a hierarchically densely connected U-net (HD-Unet).	Significant differences were observed when comparing the two dose prediction methods to clinical plans.

automated and clinical plans as measured by the conformation number.[32] It is also possible that different methods produce predictions or plans that have much better OAR sparing while being too complex when compared to clinical plans and thus being overly optimistic.[33] One such example is through using knowledge based planning system bagging query (BQ), where more OAR sparing could be achieved, but the predictions tend to be too overly complex for them to be feasibly implemented in clinical settings. However, generalized principal component analysis-based (gPCA) approach can produce more clinically inline predictions that are not as complex and overly optimistic and more like clinical dose-volume histograms (DVH).[33]

Cornell et al.[34] found out in their blind review study that when comparing knowledge-based planning (KBP) to human planning, physicians chose the KBP two-thirds of the time over human planning. The KBP also produced lower doses to critical OARs like larynx and pharynx. The human-made plans, on the other hand, were found to produce lower doses to the spinal cord and reduced target volume hotspots.

Cilla et al.[35] found in their study that in dosimetric evaluation of Elekta VersaHD linac, an automated treatment planning method produced better results when compared to manually generated volumetric modulated arc therapy (VMAT) plans. It increased dose conformity and reduced integral dose by 6–10%. Moreover, overall planning time was reduced significantly. In the blinded evaluation, the oncologists considered the automated plans to be better or on par with manual plans in more than 80% of the cases.

Dose prediction

Dose prediction is anything that uses some form of AI to automatically predict the doses to OARs or the target area in a manner that helps to optimize the dose or make the radiotherapy process more efficient.[36] The same or superior plan quality can be produced using two different dose prediction methods in dose distribution HD-Unet and mFBP in volumetric modulated arc therapy (VMAT). The benefits of using these methods can distinctly be seen in planning efficiency since the predicted doses do not need trial and error like the clinical prediction plans do.[36]

Sher et al.[38] described a hybrid model that combined the use of AI and human made OAR directive that they called augmented intelligence. In their study the use of AI only, manual and hybrid OAR directive were compared. The hybrid model produced the best overall results in dose objective reductions and provided significantly lower (at least 3 Gy less) dose prediction in up to 39% of the cases.

Discussion

Based on the results of the studies included in this review, it can be seen that artificial intelligence utilization in head and neck radiotherapy treatment planning might be useful in some cases. Many developed AI algorithms have been aimed to facilitate laborious HNC inverse treatment planning. In particular, auto segmentation, dose prediction, automated treatment planning, supporting clinical decision and modeling results have been under investigations,[17,20] with results showing that AI-based treatment planning can outperform manual plans in dose prediction.[32] Based on the articles inspected in this review, and from the point of view of dose optimization, there seems to be a clinical need for feasible AI-based auto segmentation and automatic treatment planning. However, at the moment human intervention is still required for most AI solutions and due to their infancy they still require significant time to setup and to teach the systems and check the results.

Regarding the utilization of auto segmentation using deep learning, the results showed that utilizing auto delineation of OARs reduced the variability between plans which sometimes may be a problem when different structures are delineated manually. Also, the number of OARs requiring manual delineation or review were reduced.[29] Automated treatment planning could efficiently incorporate new structures from DL auto-segmentation.[30] In the studies of this review, auto-segmentation performed well enough to be implemented in clinical practices.[27,28] However, there can be variations between different knowledge based planning systems e.g. between bagging query (BQ) method and generalized principal component analysis based (gPCA).[3] Optimal auto-segmentation means that the dose will be given only to tumour volumes which would result in reduced amounts of side-effects for the patient. This is very important for maintaining the quality of life of HNC patients.

Articles of this review[34,35,38] reported that knowledge based planning systems generally exhibited improved performance in OAR sparing compared to manually generated treatment plans. Still, there can be significant differences between dose prediction systems.[37] For HNC patients, lower doses to the OAR means lesser side-effects and improved patient quality of life outcome.[39] After all, with cancer treatment being a field of personalized medicine, regardless of the actual treatment encounter with the patient, the human actor role will still remain essential even with the usage of auto-segmentation in the treatment process.

Limitations

This scoping review included articles with language restriction (English) from five online databases and publisher databases and therefore, may not have included all relevant articles, thus potentially resulting in selection bias. The actual reviewers' limited experience on the scoping review method may also have caused bias. However, the reviewers were closely supervised and advised by other authors having wide experience on the method. Following the scoping review framework, assessment of scientific quality of articles or risk of bias of the evidence was not performed, therefore limiting implications for clinical practice[40,41]

Conclusions

Use of AI in head and neck cancer radiotherapy treatment planning and dose optimisation has been studied to a lesser extent. While the results are diverse, they still generally point at the fact that AI-based solutions perform at similar levels or even better when compared to traditional planning systems considering auto-segmentation, treatment planning or dose prediction. However, their clinical feasibility still needs to be developed. AI has a primary benefit in reducing treatment planning time and improving plan quality allowing dose reduction to the OARs thereby enhancing patients' quality of life. It has a secondary benefit of reducing radiation therapists' physical and cognitive load thus allowing them to have more bandwidth for other activities, e.g. patient encounters.

Conflict of interest statement

None

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