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REVIEW

Emerging radiotherapy technologies and trends in nasopharyngeal cancer

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Abstract

Technology has always driven advances in radiotherapy treatment. In this review, we describe the main technological advances in radiotherapy over the past decades for the treatment of nasopharyngeal cancer (NPC) and highlight some of the pressing issues and challenges that remain. We aim to identify emerging trends in radiation medicine. These include advances in personalized medicine and advanced imaging modalities, standardization of planning and delineation, assessment of treatment response and adaptive re-planning, impact of particle therapy, and role of artificial intelligence or automation in clinical care. In conclusion, we expect significant improvement in the therapeutic ratio of radiotherapy treatment for NPC over the next decade.

KEYWORDS

adaptive planning, artificial intelligence, nasopharyngeal cancer, particle therapy, personalized medicine, radiotherapy

1 | BACKGROUND

The 5-year overall survival rate of patients with nasopharyngeal cancer (NPC) has improved from about 17%-35% in the 1970s [1] to higher than 80% in contemporary series [2]. This remarkable progress has been made possible by numerous developments in medicine over the past half a century, including improved imaging, better systemic therapy options, salvage treatment, supportive care, pattern of care coordination, and advances in radiation therapy.

Technological advances have greatly impacted the field of medicine, including radiation oncology. NPC has always been technically challenging to be treated with irradiation. It typically arises in a relatively inaccessible location not easily amenable to surgery, but is also surrounded by radiosensitive critical organs. Improvements made so far in imaging, dose calculation, and radiation delivery have significantly improved cure rates and reduced adverse

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; AI, artificial intelligence; AJCC, American Joint Committee on Cancer; BEV, beam's eye view; BNCT, boron neutron capture therapy; CNN, convolutional neural network; CT, computed tomography; CTV, clinical target volume; DSC, dice similarity coefficient; EBV, Epstein-Barr virus; FDG, fluorodeoxyglucose; HEAD, Human Capital & Education for Asian Development; IMCT, intensity modulated carbon ion therapy; IMPT, intensity modulated proton therapy; IMRT, intensity modulated radiotherapy; MR, magnetic resonance; MRI, magnetic resonance imaging; MU, monitor unit; NCCN, National Comprehensive Cancer Network; NPC, nasopharyngeal cancer; NTCP, normal tissue complication probability; OAR, organs at risk; PET-CT, positron emission tomography-computed tomography; QoL, Quality of Life; QUANTEC, Quantitative Analysis of Normal Tissue Effects in the Clinic; RP, RapidPlan™; RTOG, Radiation Therapy Oncology Group; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; SUV, standardized uptake value; TLG, total lesional glycolysis; UICC, Union for International Cancer Control; VMAT, volumetric modulated arc therapy

events for NPC patients. Nevertheless, challenges remain. These include poor local control for large tumors [3], a relatively high rate of distant metastases [4], poor results of salvage reirradiation strategies [5], relatively high rate of late adverse events for long-term survivors [6], and lack of access to quality radiotherapy globally [7].

Here, we look at recent developments and trends in radiotherapy that can continue to improve the therapeutic ratio of treatment for NPC.

2 | PHOTON RADIOTHERAPY OF NPC

The photon radiotherapy of NPC has gone through several milestones in the past few decades, with improving radiation dose distribution.

2.1 | Two-dimensional (2D) conventional radiotherapy

In the 1950s, 2D conventional radiotherapy was the main approach for treating NPC, which depended heavily on clinical examination, bony landmark, and anatomy. The first breakthrough came in mid-1960s through the advent of megavoltage radiotherapy. A 5-year overall survival rate of 17%-35% was reported in various centers worldwide [1], and Professor Ho from Hong Kong reported the highest survival rate [8].However, the main difficulty was the sparing of the normal organs in the beam paths.

2.2 | Three-dimensional (3D) conformal radiotherapy

In contrast to 2D conventional radiotherapy, cross-sectional computed tomography (CT) images are used to reconstruct volumetric data set in 3DCRT. Increased number of beams is used and the field outlines closely conform to the beam's eye view (BEV) of the target volume. Conventional beam modifiers, such as wedge or compensating filters, are used to improve beam conformality. Forward planning is used, when the dosimetrist places beams with parameters in the planning system to generate a plan. It would be particularly challenging when the tumor is very near the organs at risk.

2.3 | Intensity-modulated radiotherapy (IMRT)

Grégoire and Ng [9] outlined a very useful series of key developments in IMRT since 1982 for head and neck cancer. IMRT was a significant breakthrough of 3D conformal radiotherapy, as the dose can be painted to the target volumes and organs at risk (OARs), through inverse planning and strict immobilization devices [3, 10]. Higher conformal dose can be given to gross tumor, thereby improving local control, while lowering the dose to the OAR. Fang *et al*. [11] reported statistically and clinically significant improved global quality of life (QoL), fatigue, taste/smell, dry mouth, and feeling ill at three months after completion of IMRT, compared to 3D conformal radiotherapy. There are some concerns about the low dose splash outside the target volumes, but no excessive incidences of second malignancy have been reported thus far.

2.4 | Volumetric arc therapy, tomotherapy, and stereotactic treatment

Volumetric arc therapy and tomotherapy are arc-based approaches (either helical or linear accelerator-based IMRT), which help to reduce treatment times. Lee *et al*. [12] have shown that RapidArc achieves significantly less total monitor unit (MU), less dose to the eye and normal tissues, and less treatment times (increased efficiency to 3.2 minutes per patient) compared to IMRT and tomotherapy. Stereotactic radiosurgery (SRS) or radiotherapy (SRT) uses many precisely focused beams to treat small targets in and outside of the brain, through linear accelerator or gamma knife technology. It can be used as a treatment component of residual or recurrent NPC, although most studies are small and only a few larger series show local control benefits [13, 14].

With the increased therapeutic ratio, there was also improvement in cancer outcome. Spanning from 2011 to 2018, several modern series have reported about 90% 5-year loco-regional control rate and about 80% 5-year overall survival rate [10, 15].

3 | CURRENT LIMITATIONS

Despite the improvement in cancer outcome, the following limitations still exist.

3.1 | One dose for all cases with different Tumor (T) or Nodal (N) stages and volumes

It has been common practice in many cancer centers to give same radical dose to gross primary tumor (any T stage) and nodal diseases (any N stage) with or without chemotherapy [3, 10]. Colevas et al. [16] reported on the updates to National Comprehensive Cancer Network (NCCN) guidelines (version 1.2018) for head and neck cancers. This is the largest consensus network incorporating

experiences from worldwide centers. Similar guidelines on radiotherapy were recommended. The question remains as to whether higher radical dose should be given to those with larger tumor volume.

3.2 | Inadequate local control for extensive T3/4 tumor

T4 classification in NPC staging has always been heterogeneous, including various subsites, such as intracranial extension, cranial nerve involvement, hypopharynx, orbit, parotid gland and/or extensive soft tissue infiltration beyond the lateral surface of lateral pterygoid based on the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 8th edition, TNM staging system. Pan *et al.* [17] reported 82%, 76%, and 71% 5-years loco-regional failure-free, distant failure-free and overall survival rates, respectively, for stage IVA patients with magnetic resonance imaging (MRI) staging and IMRT treatment, using the proposed 8th edition. Ng *et al.* [18] also reported unsatisfactory local control for extensive T3-4 diseases, especially if the underdosed (< 66.5 Gy) primary gross tumor volume was more than 3.4 cc. In Au's series, the 8-year actuarial local failure-free survival rate was 71.6%, significantly lower than that for T1-3 ($P < 0.001$) [10]. The main reason is likely to be the difficulty to deliver 70 Gy to the large tumor without exceeding the tolerance dose of the surrounding OARs.

3.3 | Severe late adverse events

Lee *et al.* [2] reported a large series of 1593 patients with 444 patients treated with IMRT and follow up duration of 4.3 years. There was a significantly increased rate of adverse events after using IMRT at 5 years, e.g. 1.8% of any grade of neurological events, 0.5% soft tissue/bone necrosis (grade $\geq$ 3), but significantly worse hearing impairment (grade $\geq$ 3) of 17.2%. Kong *et al.* [19] reported on a large series of 184 previously irradiated patients undergoing second course of IMRT. About 53% of the patients had grade 3-4 late adverse events (6.8% mucosal necrosis, 12.8% headache, 11.9% cranial nerve palsy, 19.9% trismus, and 5.6% hearing deficit), and 24.9% died of massive bleeding due to mucosal necrosis (grade 5, 44 patients). Certainly, there is more room to reduce late adverse events.

3.4 | Adaptive planning is time-consuming and labor-intensive

Although there is value of interim re-planning during the IMRT course, Zhao *et al.* [20] reported a significantly higher 3-year local relapse-free rate for T3-4 patients after re-planning, whereas Yang *et al.* [21] reported an significantly increased QoL scales, reduced radiotherapy-related adverse events, 97.2% 2-year local regional control rate (versus 92.4% without re-planning, $P = 0.040$), but there was no benefit in 2-year overall survival.

4 | PROGNOSTICATION AND PERSONALIZED TREATMENT IN NPC

4.1 | Clinical factors

The current framework for management of NPC is dependent on the AJCC/UICC staging system [22]. The AJCC/UICC system stratifies patients into different stages, reflecting prognosis based on the anatomical structures involved by tumor. Adjuncts to the AJCC/UICC system may potentially improve outcome predictions and consequently tailor treatment. Pan *et al.* [23] developed a nomogram to refine prognostication for patients with non-metastatic NPC, incorporating clinical prognostic factors like age, primary tumor volume, and lactate dehydrogenase levels. These factors were found to be independent predictors for overall survival on multivariate analysis, and incorporating these into the nomogram improved prognostication when compared to using staging alone. Two studies, using different cut-off levels of Epstein-Barr virus (EBV) genome copies per mL, showed independently that EBV DNA can be incorporated into the existing staging system to further enhance outcome predictions [24, 25].

4.2 | EBV DNA

Apart from the initial assessment, post-treatment EBV DNA response may be useful for predicting outcome [26, 27]. A study monitoring serial EBV DNA concentrations at diagnosis, during treatment, and after treatment showed that post-treatment levels are more predictive of relapse than pre-treatment levels [28]. Detectable EBV DNA at week 4 of treatment portends higher risk for distant failure [29].

In centers where the standard of care involves concurrent chemoradiotherapy alone, the potential for treatment intensification with further adjuvant chemotherapy for patients with detectable EBV DNA is attractive. One prospective trial identified patients with detectable EBV DNA 6 to 8 weeks after curative-intent treatment of locally advanced NPC and randomized them to either observation or further adjuvant chemotherapy [30]. However, this approach did not result in improved outcomes for the group receiving intensified treatment. The authors hypothesized that the negative results may be due to

the long period between completion of radiotherapy and initiation of adjuvant chemotherapy (median of 91 days). Adjuvant chemotherapy typically started 4 weeks after completion of radiotherapy [31-33]. The challenge of initiating adjuvant chemotherapy early in the EBV DNA era may be due, at least in part, to the false positive and negative results with EBV DNA seen in the early post-radiotherapy period [28]. Better identification of patients most likely to benefit from treatment escalation may lie with improved understanding of EBV DNA clearance kinetics and bounce occurrence [34].

4.3 | Functional imaging

One study of locally advanced NPC patients performed pre-treatment and mid-treatment ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) [35]. The maximum standardized uptake value (SUV_{max}) and total lesional glycolysis (TLG) of the index node pre- and mid-treatment predicted for regional and distant failures, as well as overall survival. This presents a potential avenue for identifying patients who may benefit from treatment escalation. Indeed, combining PET/CT and EBV DNA to identify patients at high risk for failure may be an approach in the future [36]. Similarly, tumor volume and contrast enhanced, T1-weighted images-based uniformity on MRI may predict radioresistance following IMRT for NPC [37].

4.4 | Genetic profile for tumor control: chemosensitivity and radiosensitivity

Gene expression has been shown to associate with chemosensitivity and radiosensitivity in non-NPC tumors [38, 39]. In NPC, gene expression has been studied in the context of mechanisms of carcinogenesis [40] and likelihood of developing distant metastases [41]. Thus far, it has not been studied with a view to identifying resistance to treatment and subsequent escalation of treatment.

In summary, there is robust evidence that adjunctive tools can be added to AJCC/UICC-based staging in NPC to identify patients at higher risk of treatment failure. The most established among these is the use of EBV DNA. However, it has not been demonstrated in a prospective, randomized setting that escalating treatment in EBV-selected patients improves clinical outcome. Future progress in this area may come from a better understanding of EBV DNA kinetics, or combining it with clinical factors, imaging or genomic techniques.

5 | OPTIMIZATION OF RADIOTHERAPY PARAMETERS WITH CURRENT TECHNOLOGY

5.1 | Advances in clinician knowledge

Progress made in the fight against NPC in the past few decades can be attributed to improvement in knowledge of the disease and of technological advances culminating in the utilization of IMRT [2]. Challenges in building on this progress and further improving the therapeutic ratio using IMRT include managing rapid emergence of new data and variations in practice across different centers. Hence, there is a need to strengthen the clinicians' fundamental knowledge of using IMRT in this disease, and establishing common reference standards of practice, thus forming a firm platform from which further advances can be made. In particular, the following sections highlight issues surrounding the contouring of target volumes, dose prioritization, and acceptance criteria, as well as optimal dose fractionation and how clinicians can glean further knowledge on these.

5.2 | Contouring of tumor targets

A major challenge in IMRT for NPC is the avoidance of geographic miss as a consequence of using highly conformal dose distribution in an attempt to respect constraints imposed on OARs [42]. While there are various trial protocols that specify target delineation such as that of Radiation Therapy Oncology Group (RTOG) Study 0615 [43], there has been a lack of comparative studies on these protocols as well as NPC-specific consensus guidelines that a clinician can refer to. To this end, Lee *et al*. [44] reviewed the literature on the natural behavior of NPC as well as existing international guidelines and protocols concerning contouring of the clinical target volume (CTV). The guidelines were finalized by iterative voting and consensus, and made recommendations on CTV delineation for both the primary tumor and regional lymph nodes. Controversial areas and variations in practices were analyzed and explained. The issue of CTV delineation following induction chemotherapy, which is commonly employed for locoregionally advanced disease, was also explored. To date, this is the first comprehensive international delineation guideline for NPC, based on best clinical evidence and practices, thus providing a useful and practical reference for practicing clinicians. It also establishes a common ground for target volumes in IMRT from which comparison and progress can be measured.

5.3 | Dose prioritization and acceptance criteria

An issue that needs to be addressed concurrently with standardized target volume delineation is the standardization of dose prioritization for tumor targets and OARs, and the acceptance criteria for each. Through a similar process of extensive literature review, and subsequent iterations of majority voting by international experts on preliminary recommendations, Lee *et al.* [45] developed a guideline describing appropriate dose prioritization and constraints for IMRT in NPC. Briefly, the authors proposed 4 levels of dose prioritization, with the highest level of priority given to the brainstem, spinal cord, and optic chiasm, given the dire consequences potentially associated with damage to these OARs. Planning target volume was accorded a level 2 priority. The temporal lobe was given a level 2 priority considering its potential to cause significant morbidity and even death. In addition to recommendations on dose constraints and acceptance criteria, this guideline provides a comprehensive and globally applicable reference to help clinicians maneuver through the complex challenge of improving the therapeutic ratio in NPC.

5.4 | More data on OAR tolerances and optimal dose fractionation

Despite the recent availability of consensus guidelines pertaining to NPC, the rapid advancement of treatment for NPC necessitates constant review and update of available data. With regards to OAR tolerances, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) group has published a widely used set of recommendations on normal tissue dose-effect relationships, with specific reports for head and neck endpoints [46]. Since then, radiotherapy technology has further evolved, and data on patient-reported outcomes have emerged. Consequently, Brodin *et al.* [47] conducted a systematic review of studies since the QUANTEC reports with normal tissue complication probability (NTCP) dose-response models for head and neck endpoints. The authors used a previously published method of deriving a relevance score to critically compare the dose-response models across studies [48]. Where available, comparisons were made with QUANTEC reports for similar endpoints covered. In this way, the authors provided NTCP estimates for endpoints such as dysphagia, esophagitis, xerostomia, and oral mucositis, adding clinically relevant information to what is already known from the QUANTEC reports to practicing clinicians.

Similarly, more data is required to improve our knowledge on the optimal dose fractionation. Many centers utilizing IMRT make use of dose sculpting by employing greater than 2 Gy per fraction to the gross tumor. Such dose sculpting may result in increased rates of temporal lobe necrosis as reported by Bakst *et al.* [49] and Peng *et al.* [50] (12% and 13%, respectively). Yet other groups have reported conflicting data with low rates of temporal lobe necrosis [51-53]. More prospective studies are needed to elucidate the effect of dose-fractionation on clinical outcomes and the optimal dose-fractionation in NPC.

6 | NEW TECHNOLOGIES IN NPC

6.1 | Imaging technologies

6.1.1 | FDG PET/MRI

FDG PET/CT has been shown to be more accurate in staging nodal and distant metastases compared to other imaging modalities [54]. Furthermore, it plays an important role in radiation therapy planning, prognostication, assessment of post-treatment responses, and surveillance [55]. More recently, FDG PET/MRI has been shown to be a good alternative. Chan *et al.* [56] examined 113 NPC patients who underwent pre-treatment, simultaneous whole-body PET/MRI and PET/CT for primary tumor staging. They found that the addition of FDG uptake information in PET/MRI increased the accuracy for assessing the primary tumor extent. For nodal staging assessment, the sensitivity of PET/MRI (99.5%) was higher than head and neck MRI (94.2%) or PET/CT (90.9%). For distant metastases staging, the sensitivity was broadly similar across the three modalities. They concluded that simultaneous whole-body PET/MRI was more accurate than head and neck MRI and PET/CT, and may be useful as a complete staging modality.

6.1.2 | Novel radioisotope tracers

Zhang *et al.* [57] compared the diagnostic value of ^{18}F-NaF PET/CT and FDG PET/CT for detection of skull base invasion and osseous metastases in patients with NPC (27 patients with ^{18}F-NaF PET/CT compared to 17 with FDG PET/CT). They found that the use of ^{18}F-NaF PET/CT was better at assessing skull base invasion and detected more osseous metastases than ^{18}F-FDG PET/CT.

6.2 | Simulation

Emami *et al.* [58] compared CT and MRI target volume delineation for treatment of NPC with IMRT. They found that CT/MRI co-registration improved accuracy of target volume delineation in NPC patients, and when

compared to 3D conformal radiotherapy, IMRT planning resulted in significantly improved coverage of composite CT/MRI targets and sparing of critical OARs. With time, increased utilization of MRI for radiotherapy has led to the implementation of MRI simulators for radiotherapy planning and influenced the development of MRI-guided treatment systems [59]. Paulson *et al.* [60] developed a comprehensive MRI simulation methodology for external beam radiation therapy planning.

6.3 | Knowledge-based planning

The use of IMRT in NPC allows a highly conformal dose distribution which improves treatment outcomes. However, the quality of the plan and planning time varies between planners and institutions. RapidPlan™ (RP) is a knowledge-based algorithm that utilizes constraints for the optimization and production of high-quality IMRT plans. In a study conducted by Chang *et al.* [61], they compared the IMRT plans for NPC patients with and without the use of RP. Target volume dose coverage and conformity were similar for both, and no difference was found in the maximum dose to the optic chiasm and brainstem. Planning time was significantly shorter for RP plans compared to manual plans (64 minutes versus 295 minutes, $P < 0.001$). The use of RP is able to significantly improve planning efficiency and produce good quality IMRT plans for NPC patients. Miguel-Chumacero *et al.* [62] found that the combination of multi-criteria optimization-based trade-off exploration and RP during the optimization of volumetric modulated arc therapy (VMAT) plans was also able to enhance the quality of the plan the most by significantly improving OAR sparing while maintaining comparable target dose coverage.

6.4 | Treatment delivery

6.4.1 | Magnetic resonance (MR)-linear accelerator

MR-guided radiotherapy systems provide superior soft tissue contrast imaging during treatment which increases the targeting precision. Currently, two hybrid MR-linear accelerator systems for MR-guided radiotherapy are available commercially. Tijssen *et al.* [63] published a comprehensive commissioning protocol for the installation of such machines. Adaptive planning for NPC patients has been shown to significantly reduce the dose to the ipsilateral parotid gland [64]. Chuter *et al.* [65] showed that it was feasible for an MR-linear accelerator to utilize current off-line strategies for adaptive planning for head and neck cancers.

6.4.2 | Proton therapy

Proton therapy offers a dosimetric advantage over IMRT in the management of head and neck cancers including NPC. IMPT is a highly sophisticated form of proton therapy that is promising for reducing treatment-related adverse events and potential dose escalation while respecting normal tissue dose constraints. However, not without limitations, IMPT is highly sensitive to radiologic density changes due to setup errors or anatomical changes during or in between fractions. Advancements with on-board image guidance resources, robust optimization algorithms, and standardization of patient-specific quality assurance programs and CT verification protocols will aid in establishing IMPT as a standard of care for head and neck cancers [66].

The University of Texas MD Anderson Cancer Center published their experience of using IMPT for NPC [67]. They found excellent 2-year locoregional control and overall survival rates of 100% and 89%, respectively, for a cohort of 10 patients treated with platinum-based concurrent chemoradiation using IMPT. The most common acute grade 3 adverse event was dermatitis, and one patient suffered from acute grade 3 mucositis. No chronic grade 3 or higher adverse events were seen. A dosimetric comparison study between treatment and theoretical IMRT plans suggested potential dosimetric benefits with IMPT as significant differences in OAR doses favored IMPT in 13 out of 15 patients. Furthermore, a 2:1 case-matched prospective analysis comparing these data with 20 IMRT NPC patients found significantly lower rates of gastrostomy tube insertion with IMPT (20% versus 65%, $P = 0.02$). This finding supports the preferential use of IMPT for these anatomically challenging cancers [68].

6.4.3 | Heavy ion therapy

Heavy ions such as carbon offer further advantages over proton therapy. Their increased mass has limited lateral scattering resulting in sharp lateral dose deposition edges, this allows greater sparing of organs surrounding the tumour [69].

Hu *et al.* [70] reviewed 75 patients with recurrent NPC who underwent reirradiation with intensity-modulated carbon ion therapy (IMCT) protocol. The median follow-up was 15.4 months (range, 2.6-29.7 months), and the 1-year overall survival, disease-specific survival, progression-free survival, local recurrence-free survival, regional recurrence-free survival, and distant metastasis-free survival rates were 98.1%, 98.1%, 82.2%, 86.6%, 97.9%, and 96.2%, respectively. No grade 2 or higher acute adverse event was noted and late severe (grade

3 or 4) adverse events were uncommon, but included mucosal necrosis (9.3%), xerostomia (1.3%), and temporal lobe necrosis (1.3%). Kong *et al.* [71] compared the efficacy and adverse events of 14 recurrent NPC patients undergoing reirradiation with IMCT with those treated with IMRT. Their findings were similar to Hu's study where no patient treated with IMCT developed grade 2 or higher acute adverse events but 29.8% of patients treated with IMRT experienced life-threatening mucosal hemorrhage/necrosis. Response rates and overall survival were similar between the two groups.

6.4.4 | Boron neutron capture therapy (BNCT)

BNCT is based on the nuclear reaction that occurs when boron is irradiated with neutrons. The reaction produces heavy particles which are a highly lethal form of radiation that selectively damages tumor cells, while sparing surrounding healthy cells [72].

Suzuki *et al.* [73] reviewed the outcomes and adverse events of 62 patients with unresectable advanced or recurrent head and neck cancers who underwent boron neutron capture therapy. The overall response rate at 6 months after treatment was 58%. The 1- and 2-year overall survival rates were 43.1% and 24.2%, respectively. The major acute grade 3 or 4 adverse events were hyperamylasemia (38.6%), fatigue (6.5%), mucositis/stomatitis (9.7%), and pain (9.7%). Three patients died of treatment-related adverse events. Further studies are required to determine the clinical benefit and utility of BNCT.

6.5 | Advanced computing technologies

In the last decade, we have seen that digitalization, automation, and artificial intelligence (AI) have significant impact in transforming healthcare. Of note, we have seen emerging data on the use of AI in NPC contouring [74] and head and neck cancer radiotherapy planning [75]. The utility of AI in NPC is primarily using prior data to augment decision making. This has been focused on the areas of image recognition for cancer diagnosis, auto segmentation, and radiation dose prediction. Applying AI to NPC may have two key benefits. Firstly, AI has the potential to integrate and process a huge amount of data in the radiation planning and streamline the planning and delivery of radiotherapy, thereby saving time and resources. Secondly, AI can reduce the variation in contouring of both tumor and OAR, enhancing reproducibility of contours.

Tumor diagnosis using neural networks has already surpassed clinicians in more than one clinical trial, for other tumors like skin [76], breast [77], lymph nodes [78] or lung cancers [79]. To make this happen, one needs to build convolutional neural networks (CNN), identify the features of the image to be extracted, and finally identify the tumor using deep learning algorithms. Li *et al.* [80] developed an endoscopic image-based deep learning model that had 88% accuracy. This was achieved using 28,966 images from 7951 subjects over 8 years to form the test set for an endoscopic image-based NPC detection model. The performance of this model was then prospectively tested against expert oncologist evaluations where the oncologists were outperformed by 7.5%.

Another area of great promise lies in auto-segmentation. Two different AI methodologies are commonly employed, CNN [81, 82] and atlas-based auto-segmentation [83-85], in a bid to improve the accuracy of contouring. Lin *et al.* [74] applied a 3D convolutional neural network to 818 MRI data sets to develop an AI contouring tool that can automate the primary gross tumor volume in NPC. The AI tool successfully improved the accuracy in contouring with radiation oncologists having a higher median Dice similarity coefficient (DSC) after assistance by the AI contouring tool. AI assistance also reduced intra-observer variations by 36.4% and inter-observer variations by 54.5%. The contouring time was also reduced by 39.4%. This is promising in the field of auto-segmentation and goes beyond the traditional confines of OAR auto-segmentation.

AI also begins to have an impact in radiotherapy planning in NPC. Kearney *et al.* [75] summarized the three main types of dose prediction techniques for IMRT in head and neck cancer as atlas-based, fully connected neural networks and convolutional neural networks. Of these, CNN has been the most widely used technique generally. Specifically, dilated CNN is particularly useful in predicting dose in NPC where the anatomy maybe mobile. The barriers to dilated CNN are that they are fundamentally complex programs and require special hardware.

In summary, the key challenge in using AI has been the input of data, as the output of AI can only be as good as the data put in. Hence, not only large quantities of study sets are required, these data also have to be authentic and of high quality in order to produce clinically useful AI algorithms. There is great promise in AI algorithms in NPC, but more trials are needed to have reproducible results in clinical use.

7 | CONCLUSIONS AND PERSPECTIVES

This article summarizes the historical context, and discusses current and future technologies which will likely impact patients with NPC both present and future. Current technologies include functional imaging with

FDG-PET and serial quantification of EBV DNA levels. These techniques can improve prognostication beyond anatomical TNM staging, and may help guide treatment intensification for higher risk patients. Current radiation treatment can be optimized by standardizing contouring and treatment planning parameters and refining organ-at-risk tolerance doses.

In the near future, improved imaging, e.g. hybrid FDG PET/MRI scanners and novel isotopes can improve disease localization. Improved onboard imaging with MRI as seen on MRI-linacs can also improve treatment accuracy. Early data on the use of particle therapy, including protons, heavy ions and neutrons have shown positive results for newly diagnosed NPC as well as locally recurrent disease. Advanced computing technologies, such as artificial intelligence, can also improve, standardize and streamline many of the radiation therapy processes. We expect that these innovations are likely to improve the cure rate of NPC, whilst minimizing acute and long term toxicity for our patients.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the conceptualization, writing and approval of the manuscript.

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