



Nasopharyngeal cancer: the impact of guidelines and teaching on radiation target volume delineation

Francesco Dionisi¹ · Alessia Di Rito² · Angelo Errico² · Giuseppe Iaccarino³ · Alessia Farneti¹ · Pasqualina D'Urso¹ · Alessia Nardangeli¹ · Santa Bambace² · Ida D'Onofrio⁴ · Elisa D'Angelo⁵ · Francesca De Felice⁶ · Giuseppe Fanetti⁷ · Liliana Belgioia^{8,9} · Daniela Alterio¹⁰ · Ester Orlandi¹¹ · Anna Merlotti¹² · Daniela Musio¹³ · Giuseppe Sanguineti¹

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Abstract

Target volume delineation in the radiation treatment of nasopharyngeal cancer is challenging due to several reasons such as the complex anatomy of the site, the need for the elective coverage of definite anatomical regions, the curative intent of treatment and the rarity of the disease, especially in non-endemic areas. We aimed to analyze the impact of educational interactive teaching courses on target volume delineation accuracy between Italian radiation oncology centers. Only one contour dataset per center was admitted. The educational course consisted in three parts: (1) The completely anonymized image dataset of a T4N1 nasopharyngeal cancer patient was shared between centers before the course with the request of target volume and organs at risk delineation; (2) the course was held online with dedicated multidisciplinary sessions on nasopharyngeal anatomy, nasopharyngeal cancer pattern of diffusion and on the description and explanation of international contouring guidelines. At the end of the course, the participating centers were asked to resubmit the contours with appropriate corrections; (3) the pre- and post-course contours were analyzed and quantitatively and qualitatively compared with the benchmark contours delineated by the panel of experts. The analysis of the 19 pre- and post-contours submitted by the participating centers revealed a significant improvement in the Dice similarity index in all the clinical target volumes (CTV1, CTV2 and CTV3) passing from 0.67, 0.51 and 0.48 to 0.69, 0.65 and 0.52, respectively. The organs at risk delineation was also improved. The qualitative analysis consisted in the evaluation of the inclusion of the proper anatomical regions in the target volumes; it was conducted following internationally validated guidelines of contouring for nasopharyngeal radiation treatment. All the sites were properly included in target volume delineation by >50% of the centers after correction. A significant improvement was registered for the skull base, the sphenoid sinus and the nodal levels. These results demonstrated the important role that educational courses with interactive sessions could have in such a challenging task as target volume delineation in modern radiation oncology.

Keywords Nasopharyngeal cancer · Target volume delineation · Contouring guidelines · Educational course

Introduction

Radiotherapy (RT) represents the mainstay curative treatment of nasopharyngeal carcinoma (NPC), a rare cancer in non-endemic countries with an estimated number of around 5000 new cases in Europe in 2020 and an age-standardized incidence rate of 0.44 per 100.000 [1]. In Italy, less than 700 new cases of NPC were estimated in 2020 [2].

In the context of RT, the use of Intensity Modulated Radiation Therapy (IMRT) is considered the standard of care for NPC treatment in light of the evidence coming from randomized clinical trials (RCT) of a reduction in acute and late toxicities for head and neck (HN) cancer compared with 3D conformal RT (3, 4).

The steep dose gradients that can be produced with the use of IMRT between target volumes (TV) and healthy tissues underline the primary importance that target delineation assumes in the era of modern RT in order to maintain adequate level of tumor control without excessive toxicity to organs at risk (OARs) thus limiting the burden of radio-induced complications which affect long-term survivors [5].

✉ Francesco Dionisi
francescodionisi2@gmail.com

Extended author information available on the last page of the article

The challenges in HN volume delineation are outlined by some recent publications in the field of RT quality assurance which reported that OARs and TV delineation represent the most considerable source of protocol deviations [6] and that such deviations could impact on tumor control [7]. Regarding NPC, the complex anatomy of the tumor site, the NPC high propensity to nodal diffusion along with the rarity of cases in non-endemic countries represent additional issues for adequate TV delineation. It has been reported that the use of guidelines and teaching could reduce inter-observer variability (IOV) in the field of RT volumes delineation [8].

On behalf of the Italian association for Radiotherapy and Clinical Oncology (AIRO), in this paper, we report that the results of the NPC TV delineation courses held by the Italian Association of Radiotherapy and Clinical Oncology (AIRO) in 2021 in order to analyze the impact of didactic lessons on the correct definition of TV in NPC in a large group of participants.

Materials and methods

Benchmark contour

The benchmark contour was delineated after consensus by radiation oncologists with prolonged experience in HN treatments (DM, FD, FDF, ADR, ED, GF, AM and LB) on behalf of the AIRO HN working group. The panel of experts agreed to adopt the international guidelines for NPC target volume delineation by Lee et al. [9], and multiple, online consensus meetings were held to define the benchmark contour. The Gross Tumor volume (GTV) and three risk clinical target volumes (CTV) were delineated: a high-risk primary tumor and node volume (CTV1, requiring full therapeutic dose), an intermediate risk primary and nodal volume (CTV2, requiring prophylactic dose) and a low-risk nodal volume (CTV3, requiring prophylactic dose) (Fig. 1). The CTV1 consisted of a 5 mm expansion of GTV (both GTV T and GTV N) in order to cover microscopic tumor extension as suggested by the above mentioned guidelines. The delineation of the left lacrimal gland, the left optic nerve and of the optic chiasm was also required.

Image dataset

The diagnostic images (fiber optic endoscopy, magnetic resonance MR, computer tomography CT and positron emission tomography PET) of a 60-year-old man affected by cT4 (VI cranial nerve invasion) N1 (according to the Tumor–Node–Metastasis cancer staging system, VIII edition) non-keratinizing NPC were selected as image dataset, completely anonymized, and shared with the participating centers. The patient gave written informed consent for the

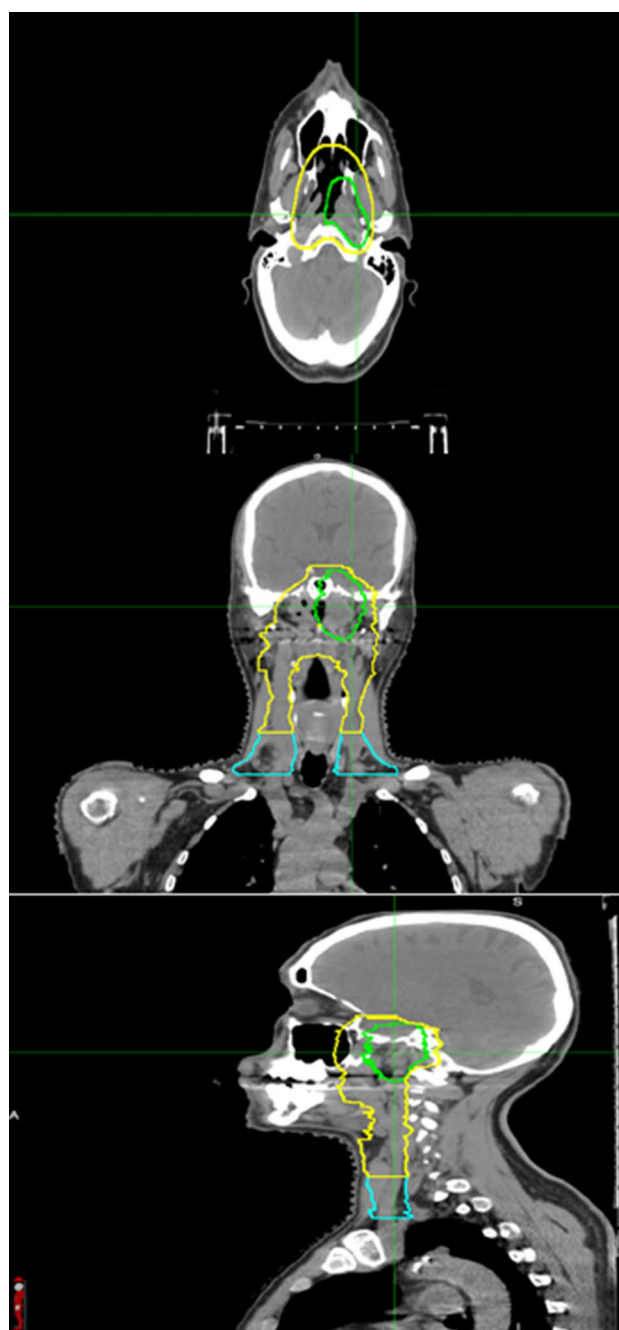


Fig. 1 Benchmark target volume contour, CTV1 (green), CTV2 (yellow) and CTV3 (cyan)

study. The study was notified to and approved by the Institutional Review Board of the IRCCS Regina Elena Cancer Institute, protocol 15,202 n.1792/22.

Delineation course

One month before the meeting, the participating centers were provided with the completely anonymized clinical

history and images of the selected case along with the request to delineate TV and selected OARs (i.e., optic nerve, chiasm and lacrimal gland) based upon the clinical experience of their center without predefined instructions to follow specific NPC guidelines. A maximum of five participants per center were admitted with the request of submitting only one shared contour dataset in order to detect the centers' experience in this setting. Two daily sessions, a week apart, were provided for each edition. Day one was dedicated to teaching lessons of several aspects of NPC (epidemiology, imaging and treatment options) including a detailed lecture about NPC delineation guidelines [9]. Moreover, at the end of day one and before contours resubmissions, the pre-course contours were reviewed and the operators were informed by the panel of the main lacking points of their contours. Then, the participants had one week to edit their original contours according to the teaching points of the day. Day two was dedicated to analyze and discuss original and post-day one contours of all participating centers.

Quantitative analysis of IOV in TV delineation

The comparison between the delineation of a particular structure before (A) and after (B) the training was evaluated using MIM® Software Inc, Cleveland, Ohio, USA, version 7. The comparison was made between the contours delineated by the participating centers and the benchmark contour using the specific tool in MIM®. Two similarity indices were analyzed: the Dice Similarity Coefficient (DSC) and the Jaccard Index (JI). The DSC is a measure of the overlap of the two structures and is calculated as follows: $2 \cdot (A \cap B) / (|A| + |B|)$. Therefore, the measure evaluates the ratio between the intersection of the two structures ($A \cap B$) and the total area of them both ($|A| + |B|$), such that total agreement provides a value of one, and no agreement provides a value zero. The JI is the percent overlap of the two structures and is calculated as follows: $(A \cap B) / (A \cup B)$ the ratio between the intersection ($A \cap B$) and the union ($A \cup B$). The JI can be directly calculated from DSC. According to its definition, the JI value is always lower than DSC. Moreover, the distance agreement between the two structures was evaluated with the Hausdorff distance (HD) and the Mean Distance to Agreement (MDA). The distance from a point a on the structure A to the other structure B is measured as the shortest distance between a and all the points b of the structure B by the following formula: $d(a, B) = \min_{(b \in B)} d(a, b)$ where d is Euclidean distance between points a and b . The HD is defined as the maximum distance between the structures A and B by the following formula: $HD(A, B) = \max [\max_{(a \in A)} d(a, B), \max_{(b \in B)} d(b, A)]$, i.e., the maximum value between the maximum distance between the points a from structure B and the maximum distance between the points b from structure A. The MDA implemented in MIM is the

average Hausdorff distance where the maximum variations are replaced by the average variations.

Qualitative analysis of IOV in TV delineation

A qualitative, clinical analysis of participants' TV contours (before and after meeting) regarding the inclusion of the proper regions at risk in the specific case was also performed by the above mentioned panel of experts.

Statistical analysis

The Wilcoxon matched-pairs signed rank test was used to compare quantitative variations in TV delineation between pre- and post-meeting contours. The Mc Nemar test was used to assess the clinical, qualitative variations between pre- and post-meeting delineations. $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using MedCalc® V 13.3.

Results

The first edition of the course was held in June, 2021. The initial maximum number of participating centers (=15) was increased due to the high participation request. A total of 67 participants representing 22 Radiation oncology centers from 11 out of the 20 Italian regions were admitted to the course and submitted the requested pre-course contours before day one of the course. The post-course contours were submitted by 19 centers and analyzed on day two.

Quantitative analysis of IOV in TV delineation (Pre- and post-course delineation)

The results of the quantitative analysis of pre- and post-course contours are illustrated in Table 1. Mean pre-course DSC values for GTV, CTV1, CTV2 and CTV3 for the 22 centers were 0.60, 0.67, 0.51 and 0.48, respectively. Mean post-course DSC values (calculated for the 19 centers which resubmitted the modified contours) for GTV, CTV1, CTV2 and CTV3 significantly increased to 0.62, 0.69, 0.65 and 0.52, respectively ($P = 0.07, 0.049, 0.002$ and 0.013 , respectively). A significant improvement was also registered for almost all post-course contours for JI and MDA indexes (Table 1). Mean HD was significantly improved for CTV2. Mean pre-course/post-course DSC values for the requested OARs (the optic chiasm, the left optic nerve and the left lacrimal gland) were 0.35/0.42 ($P = 0.09$), 0.54/0.54 ($P = 0.32$) and 0.50/0.52 ($P = 0.25$), respectively, with a slight and non-significant improvement between pre- and post-course contouring. In order to underline the importance of proper OAR contouring, the plan actually delivered to the

Table 1 Quantitative analysis of pre- and post-course TV delineation

| Index volumes | m DSC (SD) | | P | m HD (SD) | | P | Pre-course | | P | m JI (SD) post-course | | P | Pre-course | | P | m MDA (SD) Post-course | |
|---------------|-------------|-------------|-------|-------------|-------------|-------|-------------|-------------|-------|-----------------------|-------------|-------|------------|-------------|-------|------------------------|-------|
| | Pre-course | Post-course | | Pre-course | Post-course | | Pre-course | Post-course | | Pre-course | Post-course | | Pre-course | Post-course | | | |
| GTV | 0.60 | 0.62 | 0.007 | 15.53 | 14.25 | 0.007 | 0.44 | 0.45 | 0.125 | 2.79 | 2.68 | 0.02 | 2.79 | 2.68 | 0.02 | 2.68 | 0.02 |
| CTV1 | 0.67 (0.14) | 0.69 (0.12) | 0.049 | 22.6 (22.2) | 17 (8.4) | 0.13 | 0.51 (0.14) | 0.54 (0.13) | 0.049 | 5.1 (7.8) | 3.4 (1.63) | 0.058 | 5.1 (7.8) | 3.4 (1.63) | 0.058 | 3.4 (1.63) | 0.058 |
| CTV2 | 0.51 (0.24) | 0.65 (0.18) | 0.002 | 71.4 (43.8) | 39 (34.7) | 0.049 | 0.38 (0.2) | 0.5 (0.16) | 0.001 | 16.9 (18) | 7.6 (14.8) | 0.021 | 16.9 (18) | 7.6 (14.8) | 0.021 | 7.6 (14.8) | 0.021 |
| CTV3 | 0.48 (0.28) | 0.51 (0.25) | 0.013 | 70 (53) | 77 (62) | 0.76 | 0.36 (0.23) | 0.38 (0.22) | 0.013 | 18 (21) | 18.1 (19) | 0.013 | 18 (21) | 18.1 (19) | 0.013 | 18.1 (19) | 0.013 |

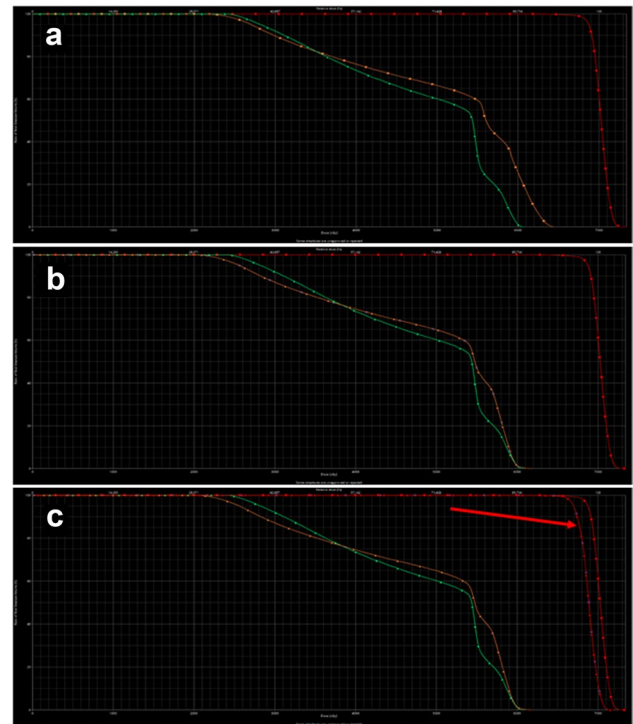


Fig. 2 **a** dose received by the benchmark (*green line*) and the C14 optic nerve (*orange line*), **b** dose re-optimized in order to achieve safe sparing of the C14 optic nerve and **c** consequent (*red arrow*) loss of coverage of the target volume (*red line*)

patient was re-optimized using one of the submitted optic nerve as new OAR: Fig. 2 shows the unavoidable loss of coverage of the CTV due to the need to spare the new OAR.

Qualitative analysis of IOV in TV delineation (Pre- and post-course delineation)

The results of the TV delineation and the inclusion of the proper anatomic sites before and after the course are presented in Table 2. In the pre-course submitted volumes, the main critical anatomic sites in terms of delineation resulted the sphenoid sinus, the posterior part of the maxillary sinuses and the nodal levels, which were properly included in the TV by $\leq 50\%$ of the participating centers (41, 41 and 50%, respectively). A proper GTV delineation was submitted by 12 out of the 22 centers (55%). The best results in the pre-course delineation were registered for the CTV1 and the clivus, which were properly included by 82 and 73% of the participating centers, respectively. The analysis of post-course submitted volumes revealed a considerable improvement in the delineation of all the anatomic sites. All the sites were properly included in TV delineation by $> 50\%$ of the 19 centers which resubmitted the TV after the course. The best performance was registered by the CTV1, which was properly delineated

Table 2 Qualitative analysis of pre- and post-course TV delineation

| TV centers | High-risk primary tumor and node volume | | | | | | | | | | | | | | | |
|------------|---|--|--|-----|-------------|--|--|-----|------------------------------|--|--|--|-------------|--|--|-----|
| | GTV delineation | | | | | | | | CTV 1 = GTV (T and N) + 5 mm | | | | | | | |
| | Pre-course | | | | Post-course | | | | Pre-course | | | | Post-course | | | |
| C1 | | | | | | | | NS | X | | | | | | | NS |
| C2 | | | | X | | | | X | X | | | | | | | X |
| C3 | | | | X | | | | X | X | | | | | | | X |
| C4 | | | | X | | | | X | X | | | | | | | X |
| C5 | | | | X | | | | X | X | | | | | | | X |
| C6 | | | | | | | | X | | | | | | | | X |
| C7 | | | | | | | | X | X | | | | | | | X |
| C8 | | | | X | | | | X | X | | | | | | | X |
| C9 | | | | X | | | | X | X | | | | | | | X |
| C10 | | | | X | | | | X | X | | | | | | | X |
| C11 | | | | | | | | X | X | | | | | | | X |
| C12 | | | | | | | | X | X | | | | | | | X |
| C13 | | | | X | | | | X | X | | | | | | | X |
| C14 | | | | X | | | | X | X | | | | | | | X |
| C15 | | | | X | | | | X | X | | | | | | | X |
| C16 | | | | X | | | | X | X | | | | | | | X |
| C17 | | | | | | | | X | | | | | | | | X |
| C18 | | | | | | | | NS | | | | | | | | NS |
| 19 | | | | | | | | X | X | | | | | | | X |
| C20 | | | | | | | | X | | | | | | | | |
| C21 | | | | | | | | | X | | | | | | | X |
| C22 | | | | X | | | | NS | X | | | | | | | NS |
| Total | | | | 55% | | | | 89% | 82% | | | | | | | 95% |

| TV centers | Intermediate risk primary and nodal volume (CTV2) | | | | | | | | | | | | | | | |
|------------|---|-------------|------------|-------------|---------------------------------------|-------------|----------------|-------------|-------------------------------|-------------|------------|-------------|----------------------|-------------|-------------------------------------|-------------|
| | Cavernous sinus | | Skull base | | 5 mm posterior wall maxillary sinuses | | Sphenoid sinus | | Nasal cavity (posterior part) | | Clivus | | Parapharyngeal space | | Nodal level RP, II-III-Va bilateral | |
| | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course |
| C1 | X | NS | | NS | | NS | | NS | | NS | | NS | | NS | | NS |
| C2 | | X | | X | | | | | | X | | X | | X | | X |
| C3 | | | | | | X | | | | X | | | | X | | X |
| C4 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| C5 | X | X | X | X | X | X | | | X | X | X | X | X | X | X | X |
| C6 | X | X | X | X | | | | X | | X | X | X | | | | X |
| C7 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| C8 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| C9 | | | | X | | | | | | | | | | | | |
| C10 | | | | X | | X | | | X | X | X | X | X | X | | X |
| C11 | | | | X | X | X | | X | X | X | X | X | X | X | | X |
| C12 | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| C13 | X | X | X | X | X | X | | X | X | X | X | X | X | X | | |
| C14 | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| C15 | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| C16 | X | X | X | X | X | X | X | X | X | X | X | X | | | X | X |
| C17 | | | X | X | | X | | X | | X | X | X | X | X | | X |
| C18 | X | NS | X | NS | X | NS | X | NS | X | NS | X | NS | X | NS | X | NS |
| C19 | | X | | | | | | X | | X | | X | | X | | X |
| C20 | | X | | | | | | X | | | X | X | X | X | | |
| C21 | | | | X | | | | | | | | | | | | X |
| C22 | X | NS | X | NS | X | NS | X | NS | X | NS | X | NS | X | NS | X | NS |

Table 2 (continued)

| TV centers | Intermediate risk primary and nodal volume (CTV2) | | | | | | | | | | | | | | | | |
|------------|---|-------------|------------|-------------|---------------------------------------|-------------|----------------|-------------|-------------------------------|-------------|------------|-------------|----------------------|-------------|-------------------------------------|-------------|-----|
| | Cavernous sinus | | Skull base | | 5 mm posterior wall maxillary sinuses | | Sphenoid sinus | | Nasal cavity (posterior part) | | Clivus | | Parapharyngeal space | | Nodal level RP, II-III-Va bilateral | | |
| | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | Pre-course | Post-course | |
| TOTAL | 50% | 63% | 68% | 84% | 50% | 58% | 41% | 68% | 55% | 79% | 73% | 84% | 64% | 89% | 41% | 84% | |
| TV centers | Low-risk nodal volume (CTV3) | | | | | | | | | | | | | | | | |
| | Level IV bilateral | | | | | | | | | | | | | | | | |
| | Pre-course | | | | | | | | | | | | | | | Post-course | |
| C1 | | | | | | | | X | | | | | | | | | NS |
| C2 | | | | | | | | X | | | | | | | | | X |
| C3 | | | | | | | | | | | | | | | | | X |
| C4 | | | | | | | | | | | | | | | | | X |
| C5 | | | | | | | | X | | | | | | | | | X |
| C6 | | | | | | | | X | | | | | | | | | X |
| C7 | | | | | | | | X | | | | | | | | | X |
| C8 | | | | | | | | X | | | | | | | | | X |
| C9 | | | | | | | | X | | | | | | | | | X |
| C10 | | | | | | | | | | | | | | | | | X |
| C11 | | | | | | | | X | | | | | | | | | X |
| C12 | | | | | | | | | | | | | | | | | |
| C13 | | | | | | | | | | | | | | | | | |
| C14 | | | | | | | | | | | | | | | | | X |
| C15 | | | | | | | | X | | | | | | | | | X |
| C16 | | | | | | | | X | | | | | | | | | X |
| C17 | | | | | | | | | | | | | | | | | X |
| C18 | | | | | | | | X | | | | | | | | | NS |
| C19 | | | | | | | | X | | | | | | | | | X |
| C20 | | | | | | | | X | | | | | | | | | X |
| C21 | | | | | | | | X | | | | | | | | | X |
| C22 | | | | | | | | | | | | | | | | | NS |
| TOTAL | | | | | | | | 64% | | | | | | | | | 89% |

Abbreviations NS: not submitted, the X defines the proper target volume delineation, bold percentages represent regions with a statistically significant improvement after course

by 95% of the centers after the course. GTV delineation significantly improved: it was properly performed by 17 out of the 19 centers (89%). The delineation of the skull base also improved, passing from 68 to 84% between pre- and post-course contours. A statistically significant improvement in the pre- and post-course delineations was registered also for the sphenoid sinus and the nodal levels, which were properly included by 58% and 84% of the participating centers after the course, respectively, compared with 41% of both sites registered in the pre-course volumes.

Discussion

Volume delineation represents one of the major critical tasks in radiation oncology: the process of TV and OARs delineation could introduce a systematic error [10] which, in the era of steep dose gradients achievable with IMRT or, more recently, intensity modulated proton therapy (IMPT) [11], could have an impact on the quality of treatment planning and consequently on tumor control and late toxicity. Indeed, a recent quality assurance (QA) analysis of 767 patients included in the RTOG 0522 study revealed that deviation from per-protocol contouring of both TV and OARs had a statistically significant impact on local control

[4]. The case of NPC is even more challenging from a radiation oncology's perspective for several reasons: (1) being the cure rates NPC high with radical dose RT which represents the cornerstone of curative treatments, the impact of TV delineation errors could be devastating, (2) the complex anatomy of nasopharynx along with the NPC diffusion pattern [12] hamper the delineation process and increase the risk of errors, (3) the therapeutic window between cure and toxicity is narrow due to the often close vicinity between TV and OARs, thus making the delineation process crucial for patients' long-term outcome [13], and (4) moreover, in non-endemic areas such as Italy, NPC is considered a rare disease, thus negatively affecting the possibility of acquiring the required clinical training and experience that is mandatory for treatment.

Efforts in educational activities and feedback intervention have been recently put in place within a prospective study of the International Atomic Energy Agency aimed to improve the overall quality of the RT plans and finally the outcome for NPC patients managed in low-income and middle-income countries [14].

In this context, it has been demonstrated that teaching could reduce IOV in TV delineation [15, 16].

These findings are confirmed by the results of the present paper, which analyzed the effects of a comprehensive, theoretical and practical, multidisciplinary, online educational course on NPC contouring. The strengths of the course were numerous: (1) the multidisciplinary approach allowed the insertion of a dedicated radiological session regarding nasopharyngeal anatomy and cancer diffusion pattern, (2) the decision to fix a maximum number of participants allowed a deeper and detailed analysis of pre- and post-course contouring, (3) the provision and explanation of international NPC contouring guidelines during the course aimed to establish standard contouring protocols in order to reduce IOV [17], and (4) the configuration of the course with timely separated sessions (pre-course contouring-phase/live session phase/post-course contour editing phase and live session phase dedicated to pre- and post-contouring analysis) allowed adequate time for pre- and post-course delineation and consequently permitted a reliable analysis of the course findings. Moreover, considering that the quantitative score of mathematical indices such as DSC and JI could not always reflect the clinical validity of the improvements registered after delineation courses, we performed a qualitative, clinical analysis of the pre- and post-course contours which reinforced the finding that the method of the online course and teaching provided satisfying results in the challenging scenario of NPC volume delineation.

Going into details of these findings, the GTV delineation showed a significant improvement between pre- and post-course contouring. These results have several explanations:

in the specific case, a macroscopic enhancement of V3 along with neoplastic tissue through the intrapetrous tract of the left carotid artery and cavernous sinus was reported but adequately included in the delineation by a low (55%) percentage of the participating centers. The clinical tip (the patient presented diplopia) could help in understanding the cancer invasion pattern. MR is the most accurate imaging for the definition of the primary tumor GTV, demonstrating the base-of-skull invasion, the intracranial extension with nerves involvement and the invasion of the prevertebral fascia [18]. During the course, the images of the case were reviewed in a dedicated radiological session. Moreover, the use of guidelines for cranial nerve contouring was suggested [19]. As already mentioned, these interventions led to a significant improvement in GTV delineation (from 55 to 89%) in the post-course resubmitted contours. A recent analysis by the Mount Vernon cancer center demonstrated the positive impact of peer-reviews with dedicated radiologists on HN contouring: Major changes were recommended for 30 patients (41%) [20]. In NPC, the GTV volume has been found to be a prognostic factor both in endemic and non-endemic regions [21, 22]. Moreover, an adequate GTV coverage is essential for treatment outcome: As demonstrated by Ng et al., the dosimetric under-coverage of GTV (> 3.4 cm receiving less than 66.5 Gy) negatively impacts local control, disease-free and overall survival [23]. Similarly, Iacovelli et al. recently reported that dosimetric parameters such as V95, V100, D99 and Dmean relative to GTV significantly impacted LC [24].

In the context of GTV delineation in NPC, the application of modern technology such as artificial intelligence (AI) has been tested: In a recent paper by Lin et al. [25], Deep Learning (DL, a specific subtype of AI that uses artificial neural networks) was used to retrospectively generate GTV contours for 203 patients affected by NPC. The AI-generated contours were compared with the volumes delineated by human experts: A high level of concordance was observed with a median DSC of 0.79. Nevertheless, a human revision was still required for a maximum of 20% of volumes in the majority of patients, especially in advanced T category. In T3-T4 stages, a revision of > 20–40% of volumes was required in 11.2% of contours. Interestingly, a low level of accuracy of the automate contours was detected at the skull base, confirming the complexity of defining intracranial infiltration boundaries for T4 NPC. The results of this study confirmed the potential impact of AI tools in assisting (without replacing) human TV delineation.

The delineation of CTV1 demonstrated a good level of concordance in both pre- and post-course contours. This is presumably due to the adoption in the guideline of the rule of the "5 mm margin" from GTV to create CTV1; this recommendation is preferred over the option of including

the whole nasopharynx in the radical dose region because it would spare large volume of mucosa unnecessary high dose. Moreover, target delineation variability among centers could be reduced [26]. The concept of the “5 mm margin” was already adopted by the international guidelines of the delineation of the primary CTV in HN (not nasopharyngeal) cancer [27], which were already illustrated in previous AIRO educational courses [28], and this could explain, in the present analysis, its good adoption in the pre-course delineation.

The CTV 2 (T and N) encompasses anatomical sites at risk for cancer spread: Its proper delineation requires a detailed knowledge of HN anatomy and the literature regarding NPC loco-regional extension in order to define areas at major risk for involvement [29]. The comprehension of sites at risk for tumor invasion represented a key-point of the course: The significant improvement registered both in the quantitative and qualitative analysis established the good results of the course in improving TV delineation and reduce IOV. However, albeit a general improvement in the delineation of all regions at risk, some anatomical sites, such as the cavernous sinus and the posterior wall of the maxillary sinus, were still not correctly included in the TV. The cavernous sinus is at risk for invasion in T3-T4 cranial NPC with a global percentage of invasion of around 18% in the series of Li et al. [21]. Its location that is cranially to the nasopharynx, laterally to the pituitary fossa and close to the apex of the orbit could explain the difficulty of some centers (around 30%) in including this cranial site in the TV.

Another region that was still missed by around 30% of the participating centers in the post-course contours was the posterior part of the maxillary sinuses. This region is usually required to cover in order to ensure the inclusion in the TV of the pterygopalatine fossae bilaterally, which represent access gates to skull base foramina, cranial nerve and intracranial invasion [9].

Another considerable result of the teaching course was the significant improvement observed in the delineation of the prophylactic nodal CTV2 which proper coverage is essential for the oncological outcome. As a matter of fact, the high propensity of neck involvement is a well-known characteristic of NPC [30]: The study of Lee et al. regarding 5037 patients affected by NPC showed a significant reduction (from 40 to 11%) in the risk of nodal relapse with the use of prophylactic neck irradiation [31]. Moreover, despite the successful treatment of nodal recurrence, the risk of distant metastasis remained higher (21% vs 6%) in patients not receiving prophylactic nodal irradiation.

During the course, the delineation of the optic structures close to the target and of the left lacrimal gland was also required: The low values of DSC observed especially for the optic structures are consistent with other studies which pointed out the issue of adequate OAR contouring in HN treatment [6, 32]. Moreover, we confirmed the results of

other recent studies which showed the significant dosimetric impact of the IOV in OAR contouring in NPC planning [33, 34]. The small and non-significant improvement which was observed between pre- and post-course OARs volumes could be attributed to the time (one week) allowed to resubmit the corrected contours: presumably in the time consuming task of re-contouring submission, priority was given to the target volumes.

In this context, automated OAR contouring with the use of DL has been recently implemented as a fast alternative to manual contouring with the aim of reducing the delineation time and its variability. In the work of van Rooij et al., which evaluated DL performance in HN OAR contouring compared with manual delineation, DL-based segmentation was scored “sufficient” for planning purposes; the procedure was fast (<10 s per patient) and was judged useful for online adaptive planning procedures. Another recent work by the University of Groningen compared DL contouring with atlas-based and manual contouring for HN OAR and reported similar results [35]. Despite DL contouring outperformed atlas-based delineation and was in some cases confused with manual contours, manual delineation still outperformed both DL and atlas-based contouring.

In conclusion, the results of our study showed that the online multidisciplinary AIRO Educational course with didactic teaching and practical contouring session is a valid method to acquire knowledge and reduce IOV in NPC volumes’ delineation process. In an era of pandemic, a biannual scheduling of such online courses with the aim to standardize the volumes’ delineation of such a rare disease between RT centers is warranted.

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Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical standards The study was conducted according to the guidelines of the Declaration of Helsinki. All the patient data were completely anonymized: The patient gave written informed consent for the study. The study was notified to and approved by the Institutional Review Board of the IRCCS Regina Elena Cancer Institute, protocol 15202 n.1792/22.

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Authors and Affiliations

Francesco Dionisi¹  · Alessia Di Rito² · Angelo Errico² · Giuseppe Iaccarino³ · Alessia Farneti¹ · Pasqualina D'Urso¹ · Alessia Nardangeli¹ · Santa Bambace² · Ida D'Onofrio⁴ · Elisa D'Angelo⁵ · Francesca De Felice⁶ · Giuseppe Fanetti⁷ · Liliana Belgioia^{8,9} · Daniela Alterio¹⁰ · Ester Orlandi¹¹ · Anna Merlotti¹² · Daniela Musio¹³ · Giuseppe Sanguineti¹

¹ Department of Radiation Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy

² Radiation Oncology Unit, Hospital “Mons. A.R. Dimiccoli”, Barletta, Italy

³ Laboratory of Medical Physics and Expert Systems, IRCCS Regina Elena National Cancer Institute, Rome, Italy

⁴ Unit of Radiation Oncology, Ospedale del Mare, Naples, Italy

⁵ Department of Radiation Oncology, University Hospital of Modena, Modena, Italy

⁶ Department of Radiotherapy, Policlinico Umberto I, “Sapienza” University of Rome, Rome, Italy

⁷ Division of Radiotherapy, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy

⁸ Department of Radiation Oncology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

⁹ Department of Health Science (DISSAL), University of Genoa, Genoa, Italy

¹⁰ Division of Radiation Oncology, European Institute of Oncology (IEO), IRCCS, Milan, Italy

¹¹ Radiation Oncology, Clinical Department, National Center for Oncological Hadrontherapy (CNAO), Pavia, Italy

¹² Department of Radiation Oncology, S. Croce and Carle Teaching Hospital, Cuneo, Italy

¹³ Department of Radiotherapy, Azienda Ospedaliera San Giovanni Addolorata, Rome, Italy