International Guideline

International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma

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ABSTRACT

Purpose: Target delineation in nasopharyngeal carcinoma (NPC) often proves challenging because of the notoriously narrow therapeutic margin. High doses are needed to achieve optimal levels of tumour control, and dosimetric inadequacy remains one of the most important independent factors affecting treatment outcome.

Method: A review of the available literature addressing the natural behaviour of NPC and correlation between clinical and pathological aspects of the disease was conducted. Existing international guidelines as well as published protocols specified by clinical trials on contouring of clinical target volumes (CTV) were compared. This information was then summarized into a preliminary draft guideline which was then circulated to international experts in the field for exchange of opinions and subsequent voting on areas with the greatest controversies.

Results: Common areas of uncertainty and variation in practices among experts experienced in radiation therapy for NPC were elucidated. Iterative revisions were made based on extensive discussion and final voting on controversial areas by the expert panel, to formulate the recommendations on contouring of CTV based on optimal geometric expansion and anatomical editing for those structures with substantial risk of microscopic infiltration.

Conclusion: Through this comprehensive review of available evidence and best practices at major institutions, as well as interactive exchange of vast experience by international experts, this set of consensus guidelines has been developed to provide a practical reference for appropriate contouring to ensure optimal target coverage. However, the final decision on the treatment volumes should be based on full consideration of individual patients' factors and facilities of an individual centre (including the quality of imaging methods and the precision of treatment delivery).

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Introduction

Radiation therapy (RT) is the primary treatment modality for nasopharyngeal carcinoma (NPC). Target delineation in NPC often proves challenging because of the notoriously narrow therapeutic margin. High doses are needed to achieve optimal levels of tumour control, despite the apparent radio-sensitivity of the tumour in many patients. Even in the contemporary era of intensity-modulated radiotherapy (IMRT) with extensive use of concurrent chemotherapy, dosimetric inadequacy remains one of the most important independent factors affecting treatment outcome. A study by Ng et al. showed that the 5-year local failure-free rate dropped to 54% if more than 3 cc volume within the gross primary tumour was under-dosed to below 66.5 Gy, compared with 90% in patients with smaller under-dosed volumes ($p < 0.001$) [1].

With the anatomical proximity of critical organs-at-risk (OARs), the importance of appropriate contouring to attain optimal balance between the risk of tumour recurrence due to marginal miss and the risk of serious late damage cannot be over-emphasized. The first fundamental step is accurate delineation of the Gross Tumour Volume (GTV) for individual patients based on the best available investigation methods. With the well-known highly infiltrative behaviour of NPC, especially the common non-keratinizing subtype, the next critical step is proper delineation of the clinical target volume (CTV) to cover the sites at relatively high risk of microscopic involvement. However, there are marked variations in philosophy and practice among clinicians [2].

The Danish national guidelines for delineation of CTV for head and neck squamous cell carcinoma (2013) [3] proposed the concept of isocentric "5 + 5 mm" geometric expansion of the primary tumour Gross Tumour Volume (GTVp), with corrections for natural anatomic boundaries such as bone or air cavities [4]. The principle is to deliver the full therapeutic dose to the CTV1 that covers at least the GTV + 5 mm margin, and a lower (prophylactic or intermediate) dose to the CTV2 that covers CTV1 + an additional 5 mm rim of tissue. The use of these guidelines has led to much more homogeneous target volume delineation among centres, as noted in data collected by Hansen et al. [5]. However, as the editing was mainly proposed for natural boundaries only, it is expected that the Danish national guidelines result in the inclusion of more non-target tissues in the tumour CTV (CTVp) than should ideally be included. Further refinement has recently been initiated by Vincent Grégoire and Cai Grau, to comprehensively review the Danish national guidelines and to edit for each anatomic location within the larynx, hypopharynx, oropharynx and oral cavity; and specifically, for each T-category within the TNM staging classification by incorporating knowledge of anatomy and the patterns of spread of disease into the geometric CTV delineation concept [6].

The key objective of this proposed guideline is to develop recommendations on delineation of CTV specific to NPC that will provide clinicians with a practical reference on treatment principles, with a fundamental goal of providing a reference for appropriate contouring to ensure adequate tumour coverage. This document is based on consensus built by review of available evidence, comparison of published guidelines [2,7–9] and detailed consideration of opinions and successive rounds of consensus by international experts experienced in the treatment of NPC. This guideline represents the concerted efforts of key oncologists from Asia (China, Hong Kong, Korea, Singapore, Taiwan), Australia, North America (Canada, United States), Saudi Arabia and Europe (Belgium, Denmark, France, The Netherlands, Turkey, United Kingdom). The guideline should be applicable for all histological subtypes of NPC.

General description of the procedures for acquisition of planning CT and delineation of GTV

Acquisition of the planning CT

The patient should typically lie in the supine position on the flat table-top of the simulation CT scanner with the head and neck immobilized in a neutral neck position by a reproducible immobilization device, most commonly a 4–5 fixation point thermoplastic mask covering from skull vertex to shoulder [10].

Thin CT sections (preferably 2 mm thickness) should be acquired typically from vertex to 2 cm below the sternoclavicular joints. We suggest scanning from the vertex in order to include the entire brain, to facilitate dose calculations. As parts of the brain will receive an appreciable dose of radiation which can result in significant toxicity, this will enable future examination of any dose–effect relationships for different endpoints within the central nervous system (CNS) anatomical substructures.

CT acquisition should ideally be done with intravenous iodine contrast enhancement. In cases where intravenous contrast medium is contraindicated, such as allergies to contrast medium or renal insufficiency, all measures should be taken to ensure the availability of optimal image sets for planning, e.g. fusion with MRI ± FDG-PET images.

Delineation of the primary tumour GTV

Accurate delineation of the primary tumour GTV (GTVp) requires the synthesis of clinical and imaging data collected during the work-up procedure.

This includes:

- a detailed clinical examination of the anterior nasal space, nasopharynx, and oral cavity, with fiberoptic nasopharyngoscopy with a detailed description of the tumour extension and infiltration,
- a diagnostic contrast-enhanced MRI performed within 2–3 weeks of RT planning and fused with the planning CT. Ideally, the MRI should be acquired in the treatment position with the use of an MRI-compatible radiation therapy immobilization device,
- close collaboration with diagnostic radiologists sub-specializing in head and neck oncology, is highly encouraged for clarification of anatomy and disease extensions,
- additional information from PET/CT images may be useful, especially for advanced cases. PET volumes should preferably be reconstructed using user-independent segmentation algorithms [11]. Furthermore, window and contrast level adjustments can drastically alter the target volume, thus the PET/CT images may be helpful to identify small lymph node (LN) metastases that may have been missed on CT or MRI. However, PET/CT should serve only as a guide, as the lack of spatial resolution as well as the partial volume effect results in insufficient accuracy for target volume delineation.

Delineation of the primary tumour CTV

Patterns of spread

Nasopharyngeal carcinomas tend to arise from the fossa of Rosenmüller, spreading submucosally with early infiltration of the palatal muscles within the parapharyngeal space. Due to its highly infiltrative nature, it spreads easily through areas of lesser resistance within the pharyngobasilar fascia, and tends to infiltrate along neural pathways. Dubrulle et al. [12] described the routes of

tumour extension of NPC based on review of MRI imaging, noting that the routes of spread are often well defined.

The tumour tends to spread easily to the nasal fossa anteriorly, due to the lack of anatomical barriers. From there, the tumour may extend to the pterygopalatine fossa via the sphenopalatine foramen, and subsequently from there superiorly into the foramen rotundum along the maxillary nerve (V2) or through the inferior orbital fissure, then the orbital apex followed by the superior orbital fissure, both eventually resulting in possible intracranial invasion. Furthermore, the tumour can also spread through the foramen lacerum, even if it is contained by the pharyngobasilar fascia, via the fibrous cartilage closing the foramen lacerum, along which cavernous sinus and intracranial extension may occur. Laterally, spread to the parapharyngeal spaces can occur directly through the pharyngobasilar fascia or indirectly through the sinus of Morgagni, the fascia's point of weakness. From there, the tumour can spread to the infratemporal fossa, or extend perineurally along the mandibular nerve (V3) into the foramen ovale and upwards into the cavernous sinus. Posterolateral extension in larger tumours may eventually involve the jugular foramen and the hypoglossal canal, as well as the nerves passing through them.

Liang et al. [13] and Li et al. [14] further characterized the invasion patterns of NPC above, by dividing the anatomic sites of invasion of tumour into high, medium and low risk regions, summarized in Table 1. Liang et al. showed that the anatomic sites at the highest risk of tumour invasion were adjacent to the nasopharynx. When high-risk anatomic sites were involved, the adjacent sites at medium risk had high rates of tumour invasion (up to 55.2%); while conversely, when anatomic sites at high risk were not involved, the adjacent sites at medium risk had low rates of tumour invasion (mostly <10%). This led to the conclusion that local disease tends to spread stepwise from proximal sites to more distal sites. In addition, the authors observed that neural foramina and neural pathways served as privileged routes for infiltration of tumour.

These two principles of stepwise tumour progression and ease of tumour spread following neural pathways and foramina serves as the basis of our recommendations for the primary tumour CTV delineation.

Recommendations and consensus guidelines

In the following sections, we will present our proposed guidelines on CTV target volume delineation; addressing the high-risk primary tumour (full therapeutic dose) CTV (CTVp1), the intermediate risk (prophylactic dose) CTV (CTVp2), as well as the high risk nodal volumes (full therapeutic dose), defined as CTVn1 and the intermediate risk (prophylactic dose) nodal regions (CTVn2).

These guidelines were based on review of the available literature addressing the natural behaviour of nasopharyngeal carcinoma and correlation between clinical and pathological aspects of the disease. Existing international guidelines and published protocols specified for clinical trials were compared (Table 2). This information was then summarized into a preliminary draft guideline which was then circulated to international experts in the field. This draft guideline subsequently underwent iterative revisions based on exchange of comments, and voting on the areas with the greatest controversies by the expert panel. Based on these voting results, we thereby established this set of consensus guidelines based on majority views to serve as a practical reference. Nonetheless this is not intended to be a dogmatic instruction. Variations in practice do exist and further studies are needed on the areas of uncertainties. To enable readers to appreciate these controversial points, voting results are presented

Table 1
Tumour invasion into anatomic sites surrounding the nasopharynx.

Author	Liang et al. [13]	Li et al. [14]
Cohort	2003–2004	2003–2008
No of patients	943	2366
	Percent	Percent
High risk		
Parapharyngeal space	67.7	
Levator veli palatine muscle	65.5	
Prestyloid compartment	64.2	
Tensor veli palatine muscle	57.2	66.4
Poststyloid compartment	50.6	
Nasal cavity	47.8	51.7
Basis of sphenoid bone	44.3	46.7
Pterygoid process	46.3	44.9
Clivus	38.3	39.5
Petrous apex	38.7	39.4
Prevertebral muscle	38.5	37
Foramen lacerum	35.9	34.9
Medium risk		
Foramen ovale	23.2	23.5
Great wing of sphenoid bone	22.3	23.4
Oropharynx	19.8	21.5
Medial pterygoid muscle	19.9	19
Cavernous sinus	17.4	17.9
Pterygopalatine fossa	17.2	17.2
Sphenoidal sinus	17.3	15.8
Hypoglossal canal	10.2	10.8
Lateral pterygoid muscle	10.6	9.3
Foramen rotundum	9.2	
Ethmoid sinus	5.3	5.2
Jugular foramen	5.1	5.1
Low risk		
Orbit		3.9
Inferior orbital fissure	3.7	
Infratemporal fossa	2.9	3.1
Cervical vertebrae	3.3	2.3
Maxillary sinus	2.6	2.2
Cistern	2.1	
Temporal lobe	1.8	
Meninges	1.4	
Orbital apex	1.1	
Superior orbital fissure	0.6	
Hypopharynx	0.5	0.9
Frontal sinus	0.2	0.2

as percentage of agreement (with levels of agreement arbitrarily defined as: high (≥85% agreement), moderate (75–84%) and low (<75%)).

General principles for delineation of CTV

(I) Rationale for the concept of "5 + 5 mm expansion" margin from the GTV to delineate the CTV

It should be noted that data specific for NPC are lacking because surgery is not a primary treatment modality. The current recommendations are based on extrapolation from available data on the extent of microscopic extension from recurrent NPC tumours by Chan et al. [18] and data from other head and neck primaries [19–23].

(II) Rationale for additional anatomical editing

This is important for NPC particularly because of inadequate data on geometric expansion. Recommendations on inclusion/exclusion of anatomical structures, as discussed above regarding the common patterns of spread, are based on:

- Known natural behaviour of tumour invasion.
- Complex and intricate anatomic relationship between the nasopharynx and adjacent soft tissues.
- The concern that unlike other cortical bones, the skull base is not a strong barrier to tumour cell infiltration because it is perforated by various foramina and fissures.

Table 2
Comparison of published protocols.

	RTOG 0225 [7]	RTOG 0615 [8]	NRG HN001 [15]	PYNEH/HKU [9]	China [16]	AIRO [17]	Current
High dose clinical target volume (CTVp1)							
Margin from GTVp	GTVp + 5 mm	GTVp + 5 mm	GTVp + 3 mm	GTVp + 5 mm + whole NP	GTVp + 5–10 mm + whole NP	GTVp + ≥5 mm (can be 0–1 mm if anatomical barriers are present)	GTVp + 5 mm (±whole NP)
Minimal margin if tumour in close proximity to critical OARs	GTVp + 1 mm	GTVp + 1 mm	GTVp + 0 mm	GTVp + 1–2 mm	Not stated	Not stated	GTVp + 1 mm
High dose clinical target volume (CTVn1)							
Margin from GTVn	GTVn + 5 mm	GTVn + 5 mm	GTVn + 3 mm	GTVn(RP) + 5 mm GTVn (cervical) + 5–10 mm	GTVn(RP) + 5–10 mm GTVn (cervical) + 2–5 mm → PTV directly	Not stated	GTVn + 5 mm (consider 10 mm if ECE)
Intermediate dose clinical target volume (CTVp2)							
Margin from GTV	GTVp + 10 mm + whole NP	GTVp + 10 mm + whole NP	GTVp + 8 mm + whole NP	GTVp + 10 mm	GTVp + 5–10 mm	GTVp + ≥10 mm margin + whole NP (caudal border at soft palate)	GTVp + 10 mm + whole NP
Nasal cavity – Posterior part	1/3	1/3–1/4	1/4	1/3	5 mm from choana	1/3–1/4	At least 5 mm from choana
Maxillary sinuses – Posterior part	1/3	1/3–1/4	1/4	1/3	5 mm from posterior wall	1/3–1/4	At least 5 mm from posterior wall
Posterior ethmoid sinus	Not stated	Not stated	Not stated	Part	Part	Not stated	Include vomer
Skull base	+	Cover foramina ovale & rotundum	Cover foramina ovale & rotundum	Cover foramina ovale & rotundum & petrous tip	Cover foramina ovale & rotundum & lacerum	Cover foramina ovale & rotundum	Cover foramina ovale, rotundum, lacerum & petrous tip
Cavernous sinus	Not stated	If T3–4	If T3–4 (involved side only)	If T3–4	Not stated	If T3–4 or bulky disease involving the roof of NP	If T3–4 (involved side only)
Pterygoid fossae	+	+	+	+	+	+	+
Parapharyngeal spaces	+	+	+	+ (to styloid process)	+	+ (to styloid process & retrostyloid space)	Full coverage
Sphenoid sinus	Inferior	Inferior if T1–2; whole if T3–4	Inferior if T1–2; whole if T3–4	Inferior 1/2 if T1–2; whole if T3–4	Sphenoid floor	Inferior half; whole if T4	Inferior 1/2 if T1–2; whole if T3–4
Clivus	+	1/2–2/3 if no invasion; whole if invasion	1/3 if no invasion; whole if invasion	1/2 if no invasion; whole if invasion	1/3 (+ anterior 1/3 of vertebral body)	1/3 if no invasion; whole if invasion	1/3 if no invasion; whole if invasion
Minimal margin if tumour in close proximity to critical OARs	Not stated	Not stated	GTVp + 1 mm	GTVp + 2–3 mm	2 mm	Not stated	GTVp + 2 mm
Intermediate dose clinical target volume (CTVn2)							
Margin from GTVn	Not stated	GTVn + 10 mm	GTVn + 8 mm	GTVn (dubious) + 5 mm GTVn (gross) + 10–15 mm	GTVn (RP) + 5–10 mm	Not stated	CTVn1 + 5 mm
Lymph nodes – bilateral RP, level II, III & Va	+	+	+	+ plus at least ipsilateral one level below the involved levels	+	+	+, level VIIb plus at least ipsilateral one level below the involved levels
Level Ib	Not stated	Not stated	Optional if T1/2N0	• Ib LN + ve • Submandibular gland • Bulky level II LN (>2 cm) • ECE • Structures that drain to level Ib as 1st echelon site	• Ib LN +ve • IIa LN >3 cm • ipsilateral >4 levels involved • invasion to >1/3 nasal cavity/soft palate/alveolar	Include in case of neck node positivity	• Ib LN +ve • Submandibular gland • Level II LN with ECE • Structures that drain to level Ib as 1st echelon site • Otherwise Ib can be omitted ipsilaterally

Table 2 (continued)

	RTOG 0225 [7]	RTOG 0615 [8]	NRG HN001 [15]	PYNEH/HKU [9]	China [16]	AIRO [17]	Current
Low dose clinical target volume (CTVn3)							
Levels IV & Vb down to clavicle	+	+	+	+ if cervical LN involved/suspicious Omit if N0 or N1 based solely on RPLN involvement	+ if upper LN involved/suspicious Omit if N0	If level III is involved	+ if cervical LN involved/suspicious Omit if N0 or N1 based solely on RPLN involvement Note difference between 2013 LN consensus guidelines and 8th edition AJCC/UICC
Planning target volume (PTV)							
Margin from CTV	5 mm (reduce to 1 mm if CTV adjacent to BS)	5 mm (reduce to 1 mm if CTV adjacent to BS)	5 mm (3 mm if IGRT) (reduce to 0 mm if CTV adjacent to BS, SC)	All IGRT 3 mm – above caudal border of C1 5 mm – below caudal border of C1	2–5 mm	5 mm (3 mm if IGRT)	Not stated

Abbreviations: BS, brainstem; CTV, clinical target volume; ECE, extracapsular extension; GTV, gross target volume; IGRT, image-guided radiotherapy; LN, lymph node; NP, nasopharynx; PTV, planning target volume; RP, retropharyngeal; SC, spinal cord.

High risk primary tumour CTV (CTVp1) for full therapeutic dose

(1) CTVp1 = GTV + 5 mm margin (consider exclusion of the clivus if not involved). [Consensus: High (90%)]

This recommendation is based on a surgical series studying the extent of microscopic extension of recurrent NPC tumours by Chan et al. [18]: the mean diameters of tumour measured by histological examination were approximately 3–4 mm larger than those measured by MRI in both the transverse and longitudinal dimension, as well as data extrapolated from other head and neck primaries, where surgico-pathological data is available [19–23].

(2) CTVp1 = inclusion of whole nasopharynx (as well as GTV + 5 mm margin from (1)). [Consensus: Low (55%)]

This is a recommendation with major discord and only slightly more than half of the experts recommend including the whole nasopharynx in CTVp1. The argument for inclusion is based on a study by Sham et al. [24], which analysed 72 cases with biopsies taken from the roof, posterior and lateral walls of the nasopharynx, regardless of gross appearance on fibreoptic examination. This study revealed that 51.4% of patients had occult microscopic extension not detectable by endoscopy and another 13.8% showed a submucosal growth pattern. With the general principle of irradiating all sites with known disease to therapeutic dose, the CTV1 should include the whole extent of gross tumour depicted on endoscopic and radiological examinations, as well as sites with positive histological evidence of involvement. Hence, in view of this common involvement of multiple sites, covering the whole nasopharynx: including the roof, posterior and lateral walls to an extent of 5 mm from mucosal surface in CTV1-T is worth considering, but the soft palate (the anatomical floor of the nasopharynx) can be spared as this site is rarely involved. However, the cohort in Sham's study was not imaged with MRI; and it was highly plausible that if a MRI had been performed, the "occult" disease would have become visible on imaging. Work by King and colleagues [25] on 246 patients who underwent MR imaging, endoscopy and endoscopic biopsy, suggest that the sensitivity of MR imaging is 100%, a specificity of 93%, accuracy of 95% and a negative predictive value of 100%. This leads to the concern that covering the entire nasopharynx will result in a high dose to a large volume that may not require it, thus needlessly increasing the toxicity risk. Hence, the alternative recommendation is to cover only the GTVp with 5 mm expansion (as explained above) as CTVp1, and cover the whole nasopharynx in CTVp2. It should be noted that as a general trend, most NPC-endemic Asian centres would cover the nasopharynx in CTVp1 while most non-Asian centres cover it with CTVp2.

(3) Anatomical landmark to define the caudal limit of nasopharynx set at caudal border of C1 [Consensus: High (86%)]

There is little controversy regarding the superior, anterior and lateral borders; which are defined as the base of skull cranially, anteriorly to the junction with nasal choana superiorly and the medial pterygoid plate more inferiorly, sparing the soft palate where feasible, while the lateral borders are demarcated by the medial border of the parapharyngeal space. The caudal border of the nasopharynx however, is less clearly defined. Agreement on definition is needed, regardless whether it is to be included in CTVp1 or CTVp2. According to *Gray's Anatomy*, the oropharynx starts at the cranial border of C2 vertebrae, hence we recommend using the caudal edge of C1 as the most inferior limit of the nasopharynx [26].

Intermediate risk (prophylactic dose) CTV (CTVp2)

(1) CTVp2 = 5 mm expansion from CTVp1 [Consensus: Moderate (76%)]

Referencing again the histopathological study by Chan et al. [18] on resected specimens from 50 recurrent NPC patients, this study showed that the extent of cancer cells invading at the submucosal level varied from 7.4 mm to 13.8 mm; hence, the authors recommended 15 mm surgical resection margins as measured from the mucosal surface. However, this figure was obtained from operator-visualized gross tumour during surgery. The use of data from recurrent NPC might be considered a "worst case scenario" as previous treatment with radiotherapy or chemo-radiotherapy might have changed the pattern of local infiltration. An increase in expansion margin to 15 mm in RT will be technically difficult and inevitably incur increased toxicity to adjacent structures. Furthermore, there are no data on the incidence of marginal misses in the zone at 10–15 mm from GTVp. On the other hand, in terms of tighter margins, a study is ongoing to evaluate a margin expansion (with imaged-guided radiotherapy (IGRT)) of CTVp1 + 3 mm for CTVp2 (i.e. 8 mm from GTVp) [15]. Thus, on balance, we recommend using a 5 mm margin expansion from CTVp1 to create CTVp2.

Anatomical editing for inclusion of adjacent structures in CTVp2. The following sections address various contentious points regarding CTVp2 coverage progressing anatomically in all 3 dimensions. When relevant, this is also divided into individual recommendations for the respective T-categories.

Superiorly.

(2) Inclusion of the vomer and surrounding ethmoid sinus in CTVp2 [Consensus: High (90%)]

The posterior–inferior part of the ethmoid sinus is included to ensure coverage of the vomer, which is anatomically the superior border of the nasopharynx [26]. The extent of coverage of the posterior ethmoid sinus should be based on adjacent structure involvement – for example, the upper part of the posterior ethmoid sinus should be included if the sphenoid sinus is involved. Regardless, a substantial portion of the upper part of the posterior ethmoid sinus would be covered after expansions from GTVp to CTVp2 if the sphenoid sinus is involved. Elective coverage of the anterior and middle ethmoid sinuses is not necessary.

(3) Sphenoid sinus

T1 and T2 disease: Inclusion of the inferior part of sphenoid sinus

T3 and T4 disease: Inclusion of the whole sphenoid sinus. [Consensus: High (90%)]

This recommendation was extrapolated from treatment techniques and outcomes before the advent of IMRT, when conventional 3-beam RT was used. The upper borders of the treatment portals were set at the anterior clinoid process level for T1–2 disease, and even higher for T3–4 disease thus encompassing the whole sphenoid sinus, with good long-term treatment results [27,28]. Since the widespread use of IMRT, the same borders have been applied in view of this historical data. In rare instances of T4-category being solely related to inferior extension – such as to the hypopharynx, there is no necessity to cover the whole sphenoid sinus.

(4) Cavernous sinus

T1 and T2 disease: Spare the cavernous sinus

T3 and T4 disease: Cover the whole ipsilateral cavernous sinus. [Consensus: High (86%)]

The study by Liang et al. [13] on the local extension patterns in NPC showed that local disease tends to spread stepwise from proximal sites to more distal sites and the incidence rate of concurrent tumour invasion into bilateral sites was low at <10%. For the cavernous sinus specifically, the cumulative incidence rate of tumour invasion was 17.4%, and this structure was only at high risk when the tumour infiltrates the petrous apex or the foramen lacerum. Thus, we conclude that it is generally safe to spare cavernous sinus for T1–T2 disease, but we suggest covering the ipsilateral cavernous sinus in the case of T3–T4 tumours, in line with other guidelines. Again, in rare instances of T4-category being solely related to inferior extension – such as to the hypopharynx, there is no necessity to cover the cavernous sinus.

(5) Skull base foramina: Cover bilateral foramina ovale, foramina rotunda and foramina lacera irrespective of T-category. Spare jugular foramen and hypoglossal canal if no extensive postero-lateral infiltration of the primary tumour or high jugular lymphadenopathy. [Consensus: High (86%)]

The bilateral foramina ovale, rotunda and lacera are perforations in the skull base subject to tumour cell infiltration. In NPC, it has been demonstrated that tumours tend to extend quickly through privileged pathways such as these neural foramina [12–14]. Based on this risk and common practice, we recommend covering these basal foramina regardless of T-category. However, the jugular foramina and hypoglossal canals can be spared in the absence of extensive postero-lateral infiltration of the primary tumour or high jugular lymphadenopathy. Some have suggested to spare the foramina ovale in patients with low T-category, due to the observed pattern that NPC tends to spread stepwise so it is unusual to have involvement of a particular structure without first having involvement of the adjacent structure [13]. More data are needed to review this in future [29].

Anteriorly.

(6) Cover 5 mm of the posterior nasal cavity anteriorly from the choanae irrespective of T-category. [Consensus: Low (71%)]

The posterior nasal cavity is at risk of disease involvement given the fact that the nasal cavity is right next to the nasopharynx. There are discrepancies among the experts concerning the extent of elective coverage of the nasal cavity. Current guidelines [7–9,15,17] commonly state posterior 1/2–1/4, and data from Fujian Cancer Center [29] showed that 5 mm anterior coverage from the posterior nasal cavity choanae is adequate for achieving good tumour control with no increase in marginal misses, thereby forming the basis of our recommendation. It is important that clinician should take endoscopic photographs as a record of the extent of anterior extension of the tumour into the nasal cavity, which can also serve to guide extent of treatment.

(7) Cover 5 mm of the posterior maxillary sinus electively to ensure adequate inclusion of the pterygo-maxillary fissure and pterygo-palatine fossae, irrespective of T-category. [Consensus: Low (72%)]

The pterygo-maxillary fissure and pterygo-palatine fossae are 2 additional privileged pathways through which NPC can easily spread [13]. Recurrences in this area are difficult to treat and are often detected late. Once the tumour involves the pterygopalatine fossa, it can easily spread into the foramen rotundum along the maxillary nerve (V2) and the inferior orbital fissure, and beyond (as explained above).

Other areas further subject to tumour invasion are the infratemporal fossa, with perineural extension along the mandibular nerve (V3) into the foramen ovale, and the vidian canal along the pterygoidien nerve and further to the petrous apex [12]. Delineation of these 2 structures may not always be anatomically straightforward. Thus we recommend 5 mm coverage of the posterior maxillary sinus to ensure that both structures are included within the CTVp2. An alternative method recommended by some experts would be to only delineate the 2 structures and ensure that they are included within the CTVp2.

Laterally.
(8) Cover pterygoid muscle by 5 + 5 mm expansion from GTVp only (i.e. equivalent to CTVp1 + 5 mm) and not by muscle boundaries unless there is gross muscular invasion. [Consensus: High (95%)]
   None of the current guidelines specifically mention the extent of coverage of the medial pterygoid muscle, but a significant portion of this muscle will invariably be included in CTVp2 after expansions as we are electively covering the pterygoid fossae and the parapharyngeal space. There is no need to specifically cover the lateral pterygoid muscle, even if the parapharyngeal space is involved, since a 5 + 5 mm expansion from GTVp will generally be adequate. However, the whole muscle should be included if there is invasion of the deep fascia/epimysium of the pterygoid muscles.
(9) Cover entire parapharyngeal space. [Consensus: High (86%)]
   The parapharyngeal space is a high-risk site of involvement by NPC, with a cumulative incidence rate of involvement of 67.7% across all T-categories [13]. Expert consensus for full coverage of this area regardless of T category was high.

Posteriorly.
(10) Cover the anterior 1/3 of the clivus if not involved and cover the whole clivus if any clival involvement. [Consensus: High (86%)]
   The key concern for contouring clival coverage is to ensure posterior coverage without subjecting the brainstem to excessive radiation dose. For cases without clival involvement, we recommend covering the anterior 1/3 of the clivus to include any possible microscopic disease spread [13]. In cases where there is gross disease involvement of the clivus, the whole clivus should be included as marrow infiltration provides a pathway of reduced resistance for disease spread.

Other issues on CTVp1/2 delineation. This subsection addresses a number of contentious technical issues that might arise during CTVp1/2 delineation. Here we present our discussions on these subjects as well as the expert consensus opinions from our panel, but stop short of giving specific recommendations.

(1) No special attempt to shave out air cavity within the CTVp1/2 volumes. [Consensus: low (65%)]
   This is an issue with no clear resolution. Proponents for not editing away the air cavities feel that removing them from the treatment volume holds no clinical significance as the air cavities have no elements that need to be treated or spared. This may also not be practical for small curving regions such as the nasal cavity or paranasal sinuses. Furthermore, there is the concern from a physics dosimetric standpoint that air cavity removal may lead to under-dosing of the treatment volumes at the air–tissue interface regions where the target volumes are either wrapped around

or situated in close vicinity to an air cavity, as in the case of the typical NPC CTVp volumes [30]. This is due to the phenomenon of electronic disequilibrium near air–tissue interfaces, which results in radiation dose build-down and build-up near proximal and distal air–tissue interface regions, respectively. The likelihood of under-dosing has been shown to increase with the beam energy and decrease with the size of the radiation field. Thus, with the use of conformal treatment deliveries such as IMRT, which is essentially dose delivery using a large number of small high energy beamlets, the chances of under-dosing at the air–tissue interface increases with a smaller air margin, resulting in an increased risk of recurrence of cancer near air–tissue interfaces [31,32].

On the other hand, proponents holding the view that the air cavities should be trimmed away from the CTV-P argue that from the physio-pathological point of view, air is not part of the target tumour volume and should be removed since microscopic disease cannot possibly extend through the air spaces. Inclusion of the air cavities renders the total treatment volume to be larger, and hence may be associated with increased toxicity. Extrapolating from studies carried out on the association between target volume sizes and toxicities in head and neck squamous cell carcinomas, which arguably should also apply to NPC, these have demonstrated that RT to larger tumour volumes was associated with greater toxicity at all time points, and decreased treatment tolerability [33,34]; hence, target volumes should be rendered as small as possible by the removal of unnecessary coverage of air cavities. Furthermore, with the advent of proton beam therapy, large air cavities within the target volumes also result in dosimetric difficulties when planning for proton therapy treatment [35].

More specific to NPC, in a planning study on 9 patients, Liu at al. [36] showed that the presence of an air cavity induces a small but negligible increase in tumour and OAR doses and a dose build-up effect was observed within the tumour region posterior to the air cavity. In another planning study published in abstract by Lian et al. [37], no differences in dosimetric quality and treatment efficiency was found when comparing tomotherapy plans created with the use of three different ways of including the air cavity in the target volumes. However, the authors of the above paper also cautioned that the target coverage was more vulnerable to patient setup uncertainty when there was significant trimming of the air cavities.

No consensus has been reached on this point of whether to trim the air cavities or not, we attempt here to elaborate on the opinions of both sides, to enable the practising clinician to have a better understanding of the pros and cons to develop his own practice.

(2) The recommendation on margins for tumour abutting critical organs-at-risk (OARs). [Consensus: low (68% agree to use 1 mm margin for CTVp1 and 2 mm margin for CTVp2, 14% recommend 0 mm margins for both)]
   This is another area where achieving a consensus will be extremely difficult as this issue represents a weighing between the risk of having a marginal miss compared to the risk of incurring debilitating RT-induced damage, with marked individual differences in philosophy. It is also difficult to issue recommendations in this area as each case should be evaluated on a case-by-case basis, and patient factors such as the patient's pre-morbidities and attitudes towards disease and toxicity, in addition to clinician factors, play a big part.
   In terms of clinician philosophies, some will exceed OAR tolerances rather than compromise tumour coverage and dose

in order to minimize the risk of recurrence; while the majority will adopt the general principle of constraining the tumouricidal dose within the tolerance limit of critical OARs. The maximum acceptable doses of the most critical OARs (such as the optic chiasm brainstem and spinal cord) will be included as highest priority for dose optimization, thus target volumes abutting/invading these critical OARs will inevitably receive doses lower than the intended tumour dose [1].

There is no doubt that some trade-off is needed when the general 5 + 5 mm margin is impractical. In accordance with ICRU 83 [38], the CTV represents a margin to account for microscopic disease, so a minimum margin is expected even if gross tumour is abutting into critical OARs. Therefore, a minimum of 1 mm expansion for CTVp1 and 2 mm for CTVp2 serves as a compromise, so that dosimetrists know exactly the minimum CTV aimed for, and allow calculation of the actual volume of under-dose if unavoidable. The final decision on the difficult balance between the risks of locoregional recurrence versus OAR damage has to be made by the oncologist incharge together with informed discussion with the affected patient. While outside the scope of this set of recommendations, further work is awaited on prioritization and ranking of OARs.

Delineation of the nodal CTV

Recommendations and consensus guidelines

Although guidelines on target volume delineation of nodal levels have been previously published [39–41], there have been new studies on refining the selection of levels in node-negative NPC patients [42–44]. There are also controversies on details of contouring that warrant consideration. Therefore, in this recommendation, we will address some common areas with significant variation among experts for contouring the CTV for nodal coverage.

The diagnostic criteria used for defining LN involvement are:

- Retropharyngeal LNs > 5 mm or cervical LNs > 10 mm in shortest diameter (11 mm for subdigastric node) [45]
- Three or more contiguous and confluent LNs, each with shortest diameter of 8–10 mm [45]
- LNs of any size with central necrosis or a contrast-enhanced rim [45]
- LNs of any size with extracapsular extension [45]
- LNs of any size with overt FDG uptake on FDG-PET scan (a systematic review and meta-analysis by Vellayappan et al. on the accuracy of 18F FDG-PET in the staging of newly diagnosed NPC showed a sensitivity of 0.84 (95% confidence interval [CI] 0.76–0.91) and specificity of 0.90 (95% CI 0.83–0.97) for signifying malignant involvement) [46]

(Those LNs not fulfilling the above criteria are considered as equivocal)

The high risk nodal CTV for full therapeutic dose (CTVn1) is derived from expansion of involved nodes (GTVn). The prophylactic intermediate risk nodal region CTV (CTVn2), is defined by the cervical lymph node levels as set out in expert consensus guidelines in 2003 and updated in 2013 [39,40].

Geometric GTVn + 5 mm expansion for CTVn1 and GTVn + 5+5 mm expansion for CTVn2

(1) CTVn1 = GTVn + 5 mm in cases with no extracapsular extension (Consider 10 mm expansion if extracapsular extension present)

(2) CTVn2 = CTVn1 + 5 mm expansion (i.e. GTVn + 5 mm + 5 mm). [Consensus: Low (64%)]

These expansions were derived from common practice in major centres, common recommendation in current guidelines, and extrapolation from non-NPC head and neck cancers [47]. We have scanty surgico-pathological data on the extent of microscopic extension from NPC nodal metastasis. The only report on NPC comes from a clinic-pathological study by Wei on resected neck specimens from 27 patients with recurrence [48], showing that extra-capsular extension was common (84%) in this recurrent series; however, there were no data on the exact range of tumour infiltration beyond the capsule. Among the trial protocols (Table 2), margins ranging from 3 to 10 mm have been practiced. On the other hand, the previous guideline by Gregoire et al. [41] recommended that when an involved LN abuts a muscle (e.g. sternocleidomastoid or para-spinal) and/or shows clear radiological indication of muscular infiltration, this muscle at the vicinity of the node should be included in the CTV with at least with 10 mm margin in all directions. A wider margin is recommended for patients with gross extra-capsular extension, but data on margins >10 mm are lacking.

For simplicity, the majority of the experts agree that the 5 mm + 5 mm expansion from GTVn is acceptable for routine general practice. A tighter expansion of 3 mm from GTVn to CTVn1 may be considered especially in nodes that are small and clearly defined with no suspicion of extracapsular extension. The CTVn1/2 should be anatomically edited at the sternocleidomastoid muscle border, rather than just simple geometric expansion. On the other hand, consideration should be made for larger than 5 mm + 5 mm margins from GTVn to CTVn1/2 for cases with extra-capsular extension.

Hence, for involved LNs [45], we recommend using the geometric expansion of 5 mm for cases with no extracapsular extension, and 10 mm if extracapsular extension is present, for CTVn1 and another 5 mm expansion for CTVn2. For equivocal LNs not fulfilling the criteria of gross involvement, we do not have any specific recommendations on geometric margins.

Intermediate risk cervical lymph node levels (prophylactic dose) CTV (CTVn2)

The following points highlight our recommendations for anatomical editing of special lymph nodes as well as cervical lymph node level inclusions when delineating CTVn2.

(3) Prophylactic coverage of the retropharyngeal lymph nodes (RPLN) in CTVn2 should extend from the base of the skull to the caudal border of the hyoid bone or caudal border of C3 as the lower limit. Only the lateral nodes need prophylactic coverage. [Consensus: Moderate (77%)]

This recommendation was formulated as there is a need to specify an anatomical lower limit for elective retropharyngeal nodal coverage to avoid too much of the pharyngeal constrictors being unnecessarily irradiated. Routine coverage is confined to the lateral group of retropharyngeal LN. The medial group is not included as this is rarely involved: in a study of 3100 newly diagnosed NPC cases from Fudan University who underwent MR imaging as part of their staging workup; 75% (2012) had involved retropharyngeal lymph nodes of which only 6 (0.2%) were located in the medial retropharyngeal lymph nodal region [49]. This will ensure that part of the pharyngeal constrictors will be spared.

In addressing the setting of the lower borders, we based this upon the anatomical landmark using the caudal border of

the hyoid bone as stated in the previous guideline for nodal coverage by Gregoire et al. [39,40]. There are 4 studies that further address this [50–53]: in summary, approximately 75% of all RPLNs were located at the body of C1, 18% at C2 and probably less than 5% at the level of the body of C3. Thus, we recommend that the lower extent of the retropharyngeal lymph node region should ideally be at the caudal border of the hyoid bone or the caudal border of the body of C2, but consider extending to C3 if there are concerns about extensive involvement.

(4) Prophylactic coverage of ipsilateral Level Ib lymph node level in CTVn2 if there is:

- disease involvement of the submandibular gland, or;
- involvement of structures that drain to level Ib as the first echelon site (namely the oral cavity, anterior half of nasal cavity), or;
- involvement of level II LNs with extracapsular extension. [Consensus: High (91%)]
- level II nodal involvement with maximum nodal axial diameter greater than 2 cm (but no extracapsular extension. [Consensus: Low (68%)]

Otherwise level Ib can be omitted ipsilaterally.

There are marked variations in practice regarding the elective coverage of level Ib among different centres. The incidence of Level Ib LN involvement at presentation is rare (only 2.7% in the study by Ho et al. [54]). However, the level Ib lymph nodes receive efferent lymphatics from the submental lymph nodes, the medial canthus, the lower nasal cavity, the oral cavity including the hard and soft palate, lips, and the anterior tongue [39]. If there is bulky disease involving level IIa, this may also result in retrograde spread to level Ib [55].

There are some centres whose practice is to cover the level Ib when there are level IIa LNs with maximal axial diameter >2 cm (even without extracapsular extension). This is based on the studies by Zhang et al. [55] and Ou et al. [56]; which showed that the maximal diameter of level IIa LNs > 2 cm was an independent predictive factor for having level Ib metastasis. However, it should be noted that the total incidence of level Ib LN involvement in the studied cohort by Zhang was only 0.3% (40/1438 patients); and although more than half of the patients with level Ib LN involvement had level IIa LNs > 2 cm, only 6.9% (21/306) of patients with level IIa LNs > 2 cm had level Ib involvement. Reflecting this, the consensus for coverage of this level was low [66%].

There is no doubt that the whole level Ib nodal region should be covered in the case of any nodal involvement in this level. In addition, we recommend elective coverage of the ipsilateral level Ib lymph nodes within the CTVn2 if there is gross involvement of the:

- ipsilateral submandibular gland;
- structures that drain to level Ib as the first echelon site (oral cavity, anterior half of nasal cavity [40])
- ipsilateral level IIa LNs with extra-capsular extension
- consider if ipsilateral level IIa LNs with maximum nodal axial diameter greater than 2 cm

(5) Sparing the whole submandibular gland in the CTVp2 for level Ib coverage. [Consensus: Low (59%)]

Opinions were widely split on this issue within our expert panel. The proponents feel that the submandibular gland should not be included as part of the lymphatic system; its exclusion will help in reducing xerostomia; thus attempts should be made to trim off and spare parts of the gland where feasible.

However, it should be noted that the submandibular gland is included as part of level Ib treatment in both the neck nodal level consensus guidelines published in 2003 [39] and 2013 [40]. Furthermore, surgical neck dissections usually remove the submandibular gland as part of level Ib.

An MRI-based study by Poon et al. [57] to identify the most common locations of the head and neck lymph nodes showed that the location of the submandibular LNs appears to be limited to the space anterior and lateral to the submandibular gland, mostly along the inferior edge of the mandible. While this serves as a guide to the locations of the level IB nodes surrounding the gland, further studies are needed to confirm this issue.

Coverage of other cervical nodal levels and dose prescription

(1) Cover bilateral retropharyngeal LNs and cervical lymph node levels II, III and Va within CTVn2 for all T and N categories. [Standard practice, included for completeness]

All current guidelines recommend elective coverage of *bilateral retropharyngeal LNs and cervical nodal* levels II, III and Va within CTVn2 for all patients. Most centres would extend the coverage to one level beyond that with grossly involved nodes. Some recommend covering the entire nodal level with involved nodes to a high dose.

(2) The cranial border for nodal coverage is extended to the skull base in order that the retrostyloid nodes are always covered. [Consensus: Low (64%)]

Both the consensus guidelines published in 2003 and 2013 [39,40] defined the upper border of the cervical level II nodal region as the caudal edge of the lateral process of C1 and level VIIa (for retropharyngeal LN) at upper border of C1. However, there are published studies [55,58,59] which showed that 25% of NPC patients with involved level II lymph nodes actually had nodes that were located more cranially than the caudal edge of the lateral process of C1. Hence, proponents suggest that the upper border of level II should be extended to include the retrostyloid space in order to cover the retrostyloid nodes, up to the base of skull for NPC cases, regardless of the nodal status. This portion is actually denoted as level VIIb for covering the retro-styloid nodes in the 2013 Guideline [40].

(3) Allow 3 dose levels for CTVn (i.e. CTVn1 = full therapeutic dose, CTVn2 = intermediate prophylactic dose, and an optional low dose level, CTVn3). [Consensus: High (81%)]

While dose prescription is not the focus of this set of recommendations, we will briefly address this point to highlight practices within the different institutions within the expert panel, as well as for clarity in the explanation of (4) below. In general, we recommend treating CTVn1 to a dose of 70 Gy equivalent, and CTVn2 to a dose of 50–60 Gy equivalent. Some centres may choose to implement a 3rd low dose level, making it a total of 3 dose levels with that of 60 Gy equivalent given to CTVn2, while a lower dose of 50 Gy equivalent is given to the lower neck (i.e. CTVn3).

(4) Cover cervical lymph node levels IV and Vb ipsilaterally if there are any involved lymph nodes on the same side of the neck (excluding retropharyngeal lymph nodes). [Consensus: High (95%)]

Cervical nodal levels IV and Vb can be omitted ipsilaterally for patients with no cervical lymph nodes involvement on the same side; otherwise they should be covered within CTVn for prophylactic dose. Most centres set a CTVn3 for a lower prophylactic dose (about 50 Gy equivalent) for levels IV and Vb if nodal involvement is confined to level II nodes only, while others include them in CTVn2 for an intermediate prophylactic dose (about 60 Gy equivalent). (Two papers [60,61] describe the slight difference in definition of the lower neck between the 2013 consensus guideline [40]

and the 8th edition of the AJCC/UICC staging system for NPC.) For patients with grossly involved LN extending to levels IV or Vb, these nodes should be treated to high doses in CTVn1 with expansion. There is no resolution as to whether we should apply the principle of covering one level beyond the involved level, and hence recommend covering the upper mediastinum nodes in CTVn2 when such low neck nodes are involved, especially since the vast majority of these patients would die of distant metastases.

Discussion on treatment extent after induction chemotherapy

We include a brief discussion on the recommended target volumes for patients with induction chemotherapy given, because this is a common concern particularly for patients with tumour abutting critical OAR. Specific data on clinical–pathological correlation are lacking. This summary of consensus among international experts provides a guidance, but a full analysis is outside the main scope of this paper.

Induction chemotherapy can be a useful modality for NPC, in particular, for those cases where the tumour has extended close to critical OARs. There are an increasing number of randomized trials and meta-analyses which showed that induction followed by concurrent chemotherapy could improve progression-free survival [62–65]. There is however, substantial controversy on the optimal volume for contouring. The guidelines for non-NPC head and neck cancers by Salama et al. [66] recommended that all structures involved by tumour before induction chemotherapy should be included, even if they are no longer grossly involved after induction chemotherapy, and radiation doses should not be modified according to response. This recommendation can be extrapolated to NPC. Our panel of experts in general agree that ideally, the pre-induction volume should receive the full therapeutic dose regardless of post-induction chemotherapy shrinkage. This principle should be used for tumours with pre-induction volume that can be fully covered to the full therapeutic dose without exceeding the maximal tolerance of critical OARs.

However, for tumours that are technically difficult to irradiate to full therapeutic dose due to dose constraints of critical OARs, there are generally two different schools of thought. Some experts will continue to use the above principle of treating the pre-induction volumes to full doses, while others will compromise to avoid excessive risk of damage by using the post-induction volumes at the area(s) abutting the critical OARs if the involved structure(s) showed gross regression following chemotherapy.

There are however a few caveats and points to note when compromising the targets with post-induction volumes:

- it is important to ensure that the pre-induction gross tumour volume is still covered at least by CTVp2
- skull base involvement shown on MRI usually remain unchanged even after induction chemotherapy making it difficult to tell assess the extent of residual disease. It would be advisable to irradiate the pre-treatment skull base involvement to full therapeutic doses.
- soft tissue involvement, often leads to displacement of OARs, thus it is reasonable and even necessary to use the post-treatment scans for localization of OARs.

A recent randomized study by Yang et al. suggests that this strategy of restricting the full therapeutic dose to the post induction chemotherapy MRI volume, but ensuring that the pre-induction chemotherapy volume will receive at least an intermediate dose (64 Gy) appears not to compromise 3-year local, regional and distant control as well as overall survival but served to reduce late toxicities and overall health status in this cohort of 212 NPC patients [67]. Whether these results will continue to hold should an even lower dose be used (say to meet the critical OAR constraints) remains to be seen.

Concluding remarks

The current study reveals marked variation in philosophy and practice among international experts most experienced in radiation therapy for NPC. This provides a valuable platform for comprehensive review of available evidence and extensive exchange of opinions on various contentious issues to attain consensus on best possible recommendations for contouring of CTV for NPC, While there are limitations where clinical–pathological data specific for NPC are scanty or lacking, this set of consensus guidelines should serve as a practical reference for appropriate contouring to ensure optimal target coverage. We earnestly hope that our recommendations will help to minimize treatment variations between clinicians, and thus improve the quality of care for NPC patients across the world.

Disclaimer

This set of guidelines is not meant to be a dogmatic protocol. We aim to provide practical suggestions on appropriate of treatment volumes coverage for patients with accurate localization and delineation of gross tumour extent based on optimal investigations. However, wider margins may be needed in cases with suboptimal imaging or in case of doubt about possible tumour involvement. The final target volumes should be based on full consideration of individual patients' factors as well as the facilities of individual centre (including the quality of imaging methods and the precision of treatment delivery).

Conflicts of interest statement

All authors declare no conflicts of interests.

Author's contribution

VG, CG conceived of the idea. AWL, WTN, JJP and JTW developed and executed the consensus development. All authors participated in the consensus development. AWL, WTN, JJP, JTW, VG and SSP were involved in the writing phase of the manuscript. All authors reviewed and approved the final manuscript.

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Appendix A. Supplementary data

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