



# **Head and neck cancer**

## **RCR consensus statements**

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## RCR head and neck cancer consensus statements

These statements should be read in conjunction with with the *key points from the consensus meeting* and *further background notes* sections.

### 1. Gross tumour volume (GTV) to clinical target volume (CTV) margins

#### Primary site

- 1.1 Use the '5+5' technique to generate CTVs for well-defined head and neck cancer: a volumetric expansion of 5 mm from GTVp (the primary gross tumour volume) to define the high-dose CTV and a 10 mm margin from GTVp for a lower-dose CTV.
- 1.2 Consider using larger margins from GTV (eg 10–15 mm) if there are concerns regarding the certainty of GTVp determination based on the quality of imaging or clinical information.
- 1.3 Edit the CTVs to:
  - Exclude air cavities
  - Exclude structures limited by anatomical barriers that prevent microscopic disease extension boundaries (eg bone and fascia)
  - Include any other region at high risk of containing microscopic tumour.
- 1.4 Consider using a larger craniocaudal margin (eg 15 mm) from GTV for the lower-dose CTV in the case of hypopharyngeal posterior pharyngeal wall tumours, due to the risk of submucosal extension.

#### Lymph nodes

- 1.5 Delineate involved nodes as GTVn. Expand GTVn by 5 mm to form the high-dose CTVn, editing from bone and air as for CTVp.
  - 1.6 Use a 10 mm margin around nodes with obvious extranodal extension (eg into the sternocleidomastoid muscle) to form the high-dose CTV.
  - 1.7 Consider a larger margin (up to 20 mm) to include more of an involved muscle above and below the site of infiltration within a lower-dose CTV.
  - 1.8 Delineate the rest of an involved nodal level to form part of a lower-dose CTV, extending at least 10 mm craniocaudally from GTVn.
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## 2. Unilateral radiotherapy for cancer of the oropharynx

- 2.1 Offer unilateral curative radiotherapy for lateralised\* T1-2 squamous cell carcinoma of the tonsil in an N0 neck or with one involved ipsilateral neck node.
- 2.2 Consider unilateral curative radiotherapy for lateralised\* T1-2 squamous cell carcinoma of the tonsil with involved ipsilateral nodes but without significant nodal burden\*\* after discussing the benefit of reduced toxicity versus the possible risk of a contralateral neck recurrence with the patient.

### *\*Lateralised tumour*

Defined using TNM8 as a tumour confined to the palatine tonsil/tonsillar fossa/lateral pharyngeal wall with greater than 10 mm clearance from midline, not involving base of tongue or posterior pharyngeal wall and extending onto the adjacent soft palate by less than 10 mm – see key points from consensus meeting.

### *Non-lateralised tumour*

Tonsillar/lateral pharyngeal wall tumour that involves the adjacent base of tongue or involves the soft palate by greater than or equal to 10 mm or with less than 10 mm clearance from midline.

or

A tumour that arises from a midline structure (base of tongue, soft palate or posterior pharyngeal wall).

### *\*\*Significant nodal burden*

Many ipsilateral neck nodes (for example three or more) or large size (more than 3 cm) or located in levels other than II–III.

## 3. Reducing the CTV to improve organ sparing

- 3.1 Consider omitting the high level II lymph nodes from the elective target volume in an uninvolved contralateral neck when delivering radical or adjuvant radiotherapy for non-nasopharyngeal head and neck squamous cell carcinoma.
- 3.2 Omit the contralateral retropharyngeal lymph nodes from the elective target volume when delivering radical radiotherapy for oropharynx cancer if all the following apply:
  - No involved nodes in the contralateral neck
  - No ipsilateral involved retropharyngeal lymph nodes
  - GTVp does not involve the soft palate or posterior pharyngeal wall.

#### 4. Adjuvant contralateral neck irradiation following surgery for oral tongue cancer for patients planned for postoperative ipsilateral radiotherapy

- 4.1 Offer contralateral neck radiotherapy for patients having adjuvant ipsilateral radiotherapy for oral tongue squamous cell carcinoma who have had surgery to the primary site and an ipsilateral neck dissection if any of the following apply:
- T3 or T4 tumour
  - Primary is within 10 mm of the midline
  - Two or more pathological lymph nodes in the ipsilateral neck
  - Extranodal extension (ENE) is present in the ipsilateral neck.
- 4.2 Consider contralateral neck radiotherapy for patients having ipsilateral adjuvant radiotherapy for oral tongue squamous cell carcinoma who have had surgery to the primary site and an ipsilateral neck dissection if there is a single involved lymph node with no ENE in the ipsilateral neck.

#### 5. Induction chemotherapy

##### **Non-nasopharyngeal head and neck squamous cell cancer excluding sinonasal tumours**

- 5.1 Do not offer induction chemotherapy prior to definitive (chemo-) radiotherapy unless:
- There is an urgent need for a rapid response in advanced and symptomatic local disease
- or
- As part of a protocol for organ preservation.

##### **Nasopharyngeal cancer**

- 5.2 Consider induction chemotherapy for locoregionally advanced, node-positive nasopharyngeal cancer in suitably fit patients.

#### 6. Radical reirradiation in head and neck cancer

- 6.1 The risk–benefit ratio of radical reirradiation changes with time. Avoid reirradiation in patients who have recurrence with a short latency period (eg within 6–12 months of completing radiotherapy) or with significant late effects.
- 6.2 Treat the GTV with small margins (maximum GTV to CTV expansion of 5 mm). The reirradiated CTV should ideally be less than 50 cm<sup>3</sup>.
- 6.3 Do not include elective nodal areas within reirradiation treatment volumes.
- 6.4 Keep the cumulative spinal cord and other important organs at risk (OAR) doses as low as possible. Ensure a thorough radiobiology evaluation with advice from physicists has taken place with risks considered, discussed with patient and documented.

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## Introduction

The Royal College of Radiologists' consensus statements are produced to guide and support clinicians in controversial areas of practice that lack strong evidence. They aim to reduce unacceptable variation in UK radiotherapy. These head and neck consensus statements follow from excellent work done by the RCR in the areas of breast<sup>1-4</sup> and lung cancer.<sup>5-6</sup> They follow a robust process outlined below.

We are very grateful to Sarah Griffin and Emma Burgum for their support in producing this work. We acknowledge the time, effort and commitment of the committee and all the participants of the consensus meeting held in July 2021. We are also grateful to the various stakeholder associations and in particular to Chris Curtis, our patient representative from The Swallows charity.

The consensus statements should be read in conjunction with any National Institute for Clinical Excellence (NICE) guidance. We hope that they will contribute to delivering optimal care for our patients.

**Amen Sibtain, chair of the working group**

**Tom Roques, medical director for professional practice, CO Faculty, RCR**

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## What are consensus statements?

Consensus statements are developed by a group of experts on a topic for which 'consensus is sought using an explicit methodology to identify areas of agreement and disagreement'.<sup>7</sup> The consensus statements reflect the group's collective analysis and evaluation of the best available evidence as well as their expert opinion on a topic.

Clinical consensus statements are separate from clinical practice guidelines. While clinical consensus statements and clinical guidelines both provide recommendations on clinical practice, there are subtle but important differences between them. Clinical guidelines are usually based on a formal systematic review of high-level evidence, while consensus statements are most appropriate on topics where evidence is limited or lacking and therefore where a consensus approach offers the best way to address variability in clinical practice and improve patient outcomes.<sup>8,9</sup>

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## RCR consensus methodology

A working group of head and neck cancer experts were recruited to develop a series of consensus statements around head and neck cancer practice. The group was asked to focus on topics where there was current variation in the UK and was asked to avoid duplicating other guidelines unless there were good reasons for reiterating them. Six broad topic areas were selected. Following an appraisal of the available research literature, statements were drafted and refined over a nine-month period.

Head and neck leads from all of the UK cancer centres that deliver head and neck radiotherapy were invited to share the first draft statements with their multidisciplinary head and neck teams and to provide feedback. They also completed a survey on current head and neck radiotherapy practice.

Representatives from the following stakeholder organisations were also invited to comment on the first draft consensus statements: Society and College of Radiographers; Institute of Physics and Engineering in Medicine; Association of Cancer Physicians; The Swallows Head and Neck Cancer Group; and clinical trial leads (TORPEdO, CompARE and PATHOS).

All feedback received was reviewed in detail by the working group and the statements and accompanying notes revised for consideration at the July 2021 consensus meeting.

In advance of the consensus meeting these revised draft statements were circulated to all head and neck leads along with pre-recorded presentations by the working group summarising the evidence for each topic's statements.

On 6 July 2021 head and neck leads from each centre were invited to attend a virtual consensus meeting to discuss and vote on the draft statements. Fifty centres were represented, with a representative from The Swallows Head and Neck Cancer Group also in attendance.

Initial discussions were had in small breakout rooms followed by a whole-group discussion facilitated by the working group. Many statements were refined based on the meeting discussions. Representatives were then asked to vote on each statement on behalf of their centre, with one vote per centre. Some statements were redrafted and voted on again so that wording could be clarified.

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The following voting categories were agreed to indicate strength of voting. Consensus in the responses was defined as an agreement of at least 70% of participants.

Unanimous support	100%
Very strongly supported	90–99%
Strongly supported	70–89%
Majority support	60–69%
Equipose	50–59%
Rejected	<50%

Members of the working group took notes of the discussion.

The final statements were then approved by the RCR's Clinical Oncology Professional Support and Standards Board for publication.

### Wording the consensus statements

The RCR statements have been worded to make them concise, unambiguous and easy to translate into practice.

The wording of the RCR statements is based on the NICE technical manual.<sup>10</sup>

Each statement starts with a verb describing what the reader should do. The verb chosen reflects the strength of the recommendation:

- Statements that should (or should not) be offered use directive language such as 'offer' (or 'do not offer'), 'delineate', 'omit', 'treat' and so on.
- If there is a closer balance between benefits and harms the statement starts with 'consider'. These are recommendations for activities or interventions that *could* be used but where discussion with clinical teams and the patient, carefully considering the alternatives, is advised.



## References

1. The Royal College of Radiologists. *Postoperative radiotherapy for breast cancer: UK consensus statements*. London: The Royal College of Radiologists, 2016.
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1.  
GTV to CTV margins

## Statements

Statement	Voting outcome
<b>Primary site</b>	
1.1 Use the '5+5' technique to generate CTVs for well-defined head and neck cancer: a volumetric expansion of 5 mm from GTVp to define the high-dose CTV and a 10 mm margin from GTVp for a lower-dose CTV.	Very strongly supported
1.2 Consider using larger margins from GTV (eg 10–15 mm) if there are concerns regarding the certainty of GTVp determination based on the quality of imaging or clinical information.	Unanimous support
1.3 Edit the CTVs to: <ul style="list-style-type: none"> <li>– Exclude air cavities</li> <li>– Exclude structures limited by anatomical barriers that prevent microscopic disease extension boundaries (eg bone and fascia)</li> <li>– Include any other region at high risk of containing microscopic tumour.</li> </ul>	Strongly supported
1.4 Consider using a larger craniocaudal margin (eg 15 mm) from GTV for the lower-dose CTV in the case of hypopharyngeal posterior pharyngeal wall tumours, due to the risk of submucosal extension.	Very strongly supported
<b>Lymph nodes</b>	
1.5 Delineate involved nodes as GTVn. Expand GTVn by 5 mm to form the high-dose CTVn, editing from bone and air as for CTVp.	Very strongly supported
1.6 Use a 10 mm margin around nodes with obvious extranodal extension (eg into the sternocleidomastoid muscle) to form the high-dose CTV.	Very strongly supported
1.7 Consider a larger margin (up to 20 mm) to include more of an involved muscle above and below the site of infiltration within a lower-dose CTV.	Very strongly supported
1.8 Delineate the rest of an involved nodal level to form part of a lower-dose CTV, extending at least 10 mm craniocaudally from GTVn.	Very strongly supported

## Key points from consensus meeting

The statements refer to definitive upfront treatment without induction/neoadjuvant chemotherapy.

Small-group discussions highlighted that clinicians and their departments gain more confidence using smaller margins the more they use them.

### Statement 1.1

Most of the time T1 larynx cancer is excluded from a '5+5' technique. Instead the whole larynx is treated because of the likelihood of field change and the small target volumes used.

### Statement 1.2

Image quality is necessarily subjective, but a good contrast-enhanced planning CT scan with good diagnostic imaging and clinical information are usually enough to support the '5+5' technique. A planning MRI is not essential.

### Statement 1.3

The '5+5' consensus paper<sup>1</sup> provides further details about CTV editing by T-stage and by tumour subtype. This level of detail is out of scope for this consensus statements document.

### Statement 1.4

This statement is not intended to completely prohibit a clinician from using more than 15 mm. However, at the consensus meeting it was acknowledged that more than 15 mm would be a long way from the GTV.

### Statement 1.5

A standard definition of involved nodes is taken from the CompARE trial protocol. Lymph nodes should be presumed pathological and included in GTVn if any of the below criteria is fulfilled:

- Measure more than 10 mm in short axis diameter on pre-therapeutic imaging (5 mm in the case of retropharyngeal nodes)
- Contain necrotic cores
- Demonstrate evidence of extranodal extension
- Demonstrate increased uptake on staging PET-CT
- Any node that a head and neck radiologist/multidisciplinary team (MDT) feels is involved in the absence of the above criteria.

For a further discussion about radiologically involved nodes please see Elsholtz *et al.*<sup>2</sup>

The consensus group recognised that there may be other instances where nodes can be included in GTVn, for example by their number or where there is a small visible node very close to an involved node. The group reiterated the importance of individualisation on level of suspicion.

### Statement 1.6

It was recognised there was limited evidence on margins around nodes but statements 1.5–1.7 were felt to be pragmatic and in line with current clinical trial protocols. Clinicians should edit nodal CTVs from uninvolved bone, air and fascia planes.

The terms extranodal extension (ENE) and extracapsular spread (ECS) are often used interchangeably, although ENE is now the preferred terminology used in the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours publication.<sup>3</sup>

### Statement 1.8

It was noted that more UK centres use a low dose than an intermediate dose to treat the rest of an involved nodal level though both are acceptable.

## Further background notes

### Primary site

Until recently there have been two prevailing views on primary GTV expansion: geometric expansion as promoted by the Danish Head and Neck Cancer (DAHANCA) group and anatomical expansion reflecting the compartmentalisation of structures within the head and neck territory. The 2018 Grégoire *et al* consensus paper<sup>1</sup> is directing the radiation oncology community to a geometrical expansion approach. In their conclusion the authors state that '*Implementation of these guidelines in the daily practice of radiation oncology should contribute to reduced treatment variations from clinicians to clinicians, facilitate the conduct of multi-institutional clinical trials, and contribute to improved care of patients with head and neck carcinoma*'. Accurate imaging modalities are a prerequisite to ensure adequate delineation of the primary tumours. Any uncertainty will be a key factor in margin determination.

Several sources of evidence support margin reduction.

- The majority of recurrences occur within the GTV to CTV 10 mm margin – so it is safe to reduce to a geometric expansion.<sup>4</sup>
- Anatomy-based contours are significantly more heterogeneous and show larger volume differences between centres than geometric margins.<sup>5</sup>
- Surgical series indicate that microscopic tumour infiltration occurs within a distance of 10 mm from the edge of the GTV. (Three surgical series are summarised in the Grégoire paper 2018.<sup>1</sup>)
- It is recognised that CT, MRI and FDG-PET overestimate macroscopic tumour extent but underestimate microscopic tumour infiltration, hence the two-dose level geometrical expansion in the consensus paper.
- These recommendations relate specifically to GTV to CTV expansion in the primary treatment setting and thus do not apply in the case of recurrent disease and in the postoperative setting. Additionally, margins for internal target volume (ITV, organ movement) and planning target volume (PTV, set-up) need to be determined at institutional level.

## Lymph nodes

There are two key issues with regard to lymph nodes when treating head and neck squamous cell carcinoma: involved node delineation including CTV expansion and nodal-level selection according to primary site. Consensus on nodal-level selection has evolved through rigorous evaluation of studies on initial involvement at presentation and patterns of failure. Similarly, the updated delineation guidelines reflect a review of the original 2003 guidelines, which through their update should help to simplify and standardise head and neck contouring.

- Nodal selection is according to Biau *et al*<sup>6</sup> and involved node delineation is according to Grégoire *et al* (2013).<sup>7</sup>
- Nodal selection and delineation of the node-negative neck CTV is thus standardised but where there are involved nodes the nodal CTV is expanded volumetrically and adapted because of the risk of direct microscopic involvement.
- Most nodal infiltration into surrounding tissues in surgical series is <10 mm.<sup>8</sup>
- Larger margins (10–20 mm) where nodal GTVs abut key structures (eg sternocleidomastoid muscle, salivary glands) are recommended as a modification of the original Grégoire proposals<sup>9</sup> to take into account macroscopic or microscopic tumour infiltration outside of the node.

## References

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## 2. Unilateral radiotherapy for cancer of the oropharynx

### Statements

Statement	Voting outcome
2.1 Offer unilateral curative radiotherapy for lateralised* T1-2 squamous cell carcinoma of the tonsil in an N0 neck or with one involved ipsilateral neck node.	Very strongly supported
2.2 Consider unilateral curative radiotherapy for lateralised* T1-2 squamous cell carcinoma of the tonsil with involved ipsilateral nodes but without significant nodal burden** after discussing the benefit of reduced toxicity versus the possible risk of a contralateral neck recurrence with the patient.	Very strongly supported

#### \*Lateralised tumour

Defined using TNM8 as a tumour confined to the palatine tonsil/tonsillar fossa/lateral pharyngeal wall with greater than 10 mm clearance from midline, not involving base of tongue or posterior pharyngeal wall and extending onto the adjacent soft palate by less than 10 mm – see key points from consensus meeting.

#### Non-lateralised tumour

Tonsillar/lateral pharyngeal wall tumour that involves the adjacent base of tongue or involves the soft palate by greater than or equal to 10 mm or with less than 10 mm clearance from midline.

or

A tumour that arises from a midline structure (base of tongue, soft palate or posterior pharyngeal wall). \*\**Significant nodal burden*

Many ipsilateral neck nodes (for example three or more) or large size (more than 3 cm) or located in levels other than II–III.

### Key points from consensus meeting

#### Statement 2.1

- An earlier draft of this statement specified the one involved node should be a '*node in level II measuring less than 3 cm*'. This was removed at the consensus meeting as some would still treat unilaterally if one involved node was present in another level. Some argued for the inclusion of 'minimal base of tongue infiltration' in the definition of a lateralised tumour. Initially this had been included because evidence showed that Canadian groups have used less than 10 mm base of tongue invasion as a cut-off for defining a lateralised tumour. There was concern that such a precise distance would be very difficult to measure on imaging.
- For clarity the phrase 'tumour confined to palatine tonsil/tonsillar fossa/lateral pharyngeal wall' was used instead of 'palatine tonsil' or 'tonsillar fossa' as seen in previous versions.

### Statement 2.2

- There was debate about the number of nodes stated and the definition of 'many'. It was agreed that the cut-off in previous drafts of three nodes was arbitrary and therefore during the meeting this was changed to 'for example three nodes' to give more freedom to deviate at clinical discretion. This statement does not prevent treatment with ipsilateral radiotherapy when three or more pathological nodes are present.
- It was felt that there was no good evidence to suggest an increased risk of contralateral recurrence for greater than three nodes; but equally there was no good evidence there was not an increased risk of contralateral recurrence for greater than one node.
- The consensus group considered if ENE should be added as a factor to define 'significant nodal burden'; however, it was felt there was not good evidence to support its addition as a risk factor for contralateral nodal recurrence.

### Further background notes

The following recommendations are based on evidence from series on unilateral neck irradiation (UNI) in tonsillar cancers published between 1980 and 2019<sup>1-19</sup> including studies looking exclusively at postoperative UNI.<sup>20-22</sup> Published guidelines on the subject have also been taken into consideration.<sup>23-25</sup>

#### Rationale for UNI

Toxicity outcomes of unilateral versus bilateral treatment have been published by Jensen *et al*<sup>26</sup> (n=158) and McDowell *et al*<sup>27</sup> (n=136). UNI offers sparing of contralateral neck OAR including the salivary glands, the oral mucosa and pharyngeal constrictor muscles. This can lead to reduced frequency and severity of radiotherapy toxicity, and can in particular lead to lower rates of xerostomia, dysphagia, hoarseness, laryngeal oedema and skin fibrosis resulting in improved swallowing function, social functioning scores and quality of life.

UNI has been shown to be safe in selected tonsillar cancer patients with low rates of contralateral neck recurrences (CNR). A 2017 review of published literature by Al-Mamgani *et al*<sup>28</sup> showed low CNR rates (2.42%) among 1,116 patients selected for UNI with a successful salvage rate of 73%.

The 2020 analysis by the American Radium Society group<sup>25</sup> included 1,031 patients who had undergone either primary or postoperative UNI and showed that 26 developed a CNR (2.52%) of which 19 had a successful salvage (73%).

#### Potential risk factors for CNR

##### Primary tumour extent:

- Most studies included mainly patients with well-lateralised T1–2 tonsillar tumours. Only a small percentage of patients had T3 tumours.
- Most studies used the Toronto<sup>1</sup> definition for 'well lateralised', which involves tumours limited to the lateral one-third of the 'hemi-structure' of the base of tongue or soft palate (defined as  $\leq 10$  mm superficial mucosa of 'hemi-structure' extension, without muscle involvement or any suspicion of deeper penetration).
- The Al-Mamgani *et al* review suggested that involvement of the midline is one the most significant prognostic factors for CNR (p=0.001).<sup>28</sup>

*Nodal status:*

- Historic UNI studies included small percentages of N2b (TNM7) disease.<sup>24</sup> This probably reflects the lower prevalence of human papillomavirus (HPV)-positive disease in previous decades, which means less nodal involvement at presentation but also suggests a selection bias.
- The Norwich series showed a CNR of 14.3% (4/28) in the N2b (TNM7) subgroup (53% of patients had N2b disease).<sup>19</sup> In the Royal Marsden Hospital series, multiple ipsilateral involved neck nodes were associated with a higher risk of CNR as all six patients who developed a CNR had N2b (TNM7) disease at presentation (40% of patients had N2b disease).<sup>12</sup> However, other series including a good percentage of N2b (TNM7) patients did not confirm this (Koo *et al*, 40% of patients with N2b disease; Dan *et al*, 50.9% with N2b).<sup>10,13</sup>
- Two series looking at postoperative UNI showed no increased risk for CNR in patients with pN2b (TNM7) disease.<sup>20-21</sup> A third similar study showed a higher rate of CNR in the postoperative UNI group compared with the bilateral neck irradiation one but the difference did not reach statistical significance, numbers of patients were small (7.9% versus 0%, p=0.107) and impact on overall survival was limited with successful salvage treatment (five-year overall survival (OS) 92.8% versus 94%, p=0.985).<sup>22</sup>
- Another small surgical study showed that ipsilateral multilevel involvement was an independent factor with multivariate analysis as 29% (4/14) of patients treated with a bilateral neck dissection had occult disease in the contralateral neck.<sup>29</sup>

*Extranodal extension (ENE):*

- There is no data available on radiologically evident ENE and the risk of CNR. The only available evidence comes from series where a neck dissection preceded the UNI.
- In the Lynch *et al* series,<sup>12</sup> ENE was associated with a higher risk of CNR (five out of six patients with a CNR). Other postoperative ipsilateral neck radiotherapy series did not confirm an association between ENE and increased risk for CNR.<sup>20-22</sup>
- Due to the lack of sufficient evidence, ENE cannot be considered a significant factor when deciding on UNI.

*HPV:*

- There are studies suggesting that HPV-positive tumours are more likely to present with more advanced nodal disease and exhibit a higher propensity for CNRs.<sup>30-32</sup> Equally, there are studies reporting low rates of CNR irrespective of HPV status.<sup>13,16,33-34</sup>
- On current evidence, HPV status does not appear to be a significant factor for deciding on UNI versus bilateral neck radiotherapy.

*Smoking:*

- There is very little evidence on the effect of smoking in CNR risk. In the Lynch *et al* series,<sup>12</sup> a more than ten pack-year smoking history was associated with a higher risk of CNR (five out of six patients with a CNR).



## Further information

Further information can also be found in the following guidance documents.

### **ASTRO 2017**

- Unilateral radiotherapy should be delivered to patients with well-lateralised (confined to tonsillar fossa) T1–T2 N0–N1 (TNM7) tonsillar cancer.
- Unilateral radiotherapy may be delivered to patients with less than 10 mm of soft palate extension but with no base of tongue involvement T1–T2 N0–N2a (TNM7) tonsillar cancer without evidence of ENE, after careful discussion of patient preferences and the relative benefits of unilateral radiotherapy versus the potential for CNR and salvage treatment.

### **American Radium Society 2020**

#### *Definitive (chemo)radiotherapy:*

- Strongly recommend that unilateral neck radiotherapy is usually appropriate for a tonsil-confined tumour with a minimal burden of nodal disease (0 to 2 involved lymph nodes).
- Strongly recommend bilateral neck radiotherapy with extension to posterior pharyngeal wall and involved retropharyngeal nodes.
- Agreed on  $\leq 10$  mm of tumour invasion into soft palate or base of tongue.
- No agreement on definition of 'minimal burden of disease'.
- No agreement on single ipsilateral retropharyngeal pathological lymph node.
- No consensus on N2b (TNM7), clinical ENE or single greater than 6 cm node.

#### *Adjuvant (chemo)radiotherapy:*

- Strongly recommend bilateral neck radiotherapy in:
  - pN2b (TNM7)
  - Macroscopic ENE.
- Recommend unilateral radiotherapy as usually appropriate in well-lateralised tonsil primary tumours with pN1 (TNM7), irrespective of microscopic ENE or perineural invasion (PNI) and lymphovascular invasion (LVI) in primary.
- No consensus on UNI with a close ( $< 1$  mm) mucosal margin at base of tongue.

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### 3. Reducing the CTV to improve organ sparing

#### Statements

Statement	Voting outcome
3.1 Consider omitting the high level II lymph nodes from the elective target volume in an uninvolved contralateral neck when delivering radical or adjuvant radiotherapy for non-nasopharyngeal head and neck squamous cell carcinoma.	Unanimous support
3.2 Omit the contralateral retropharyngeal lymph nodes from the elective target volume when delivering radical radiotherapy for oropharynx cancer if all the following apply: <ul style="list-style-type: none"> <li>– No involved nodes in the contralateral neck</li> <li>– No ipsilateral involved retropharyngeal lymph nodes</li> <li>– GTVp does not involve the soft palate or posterior pharyngeal wall.</li> </ul>	Unanimous support

#### Key points from consensus meeting

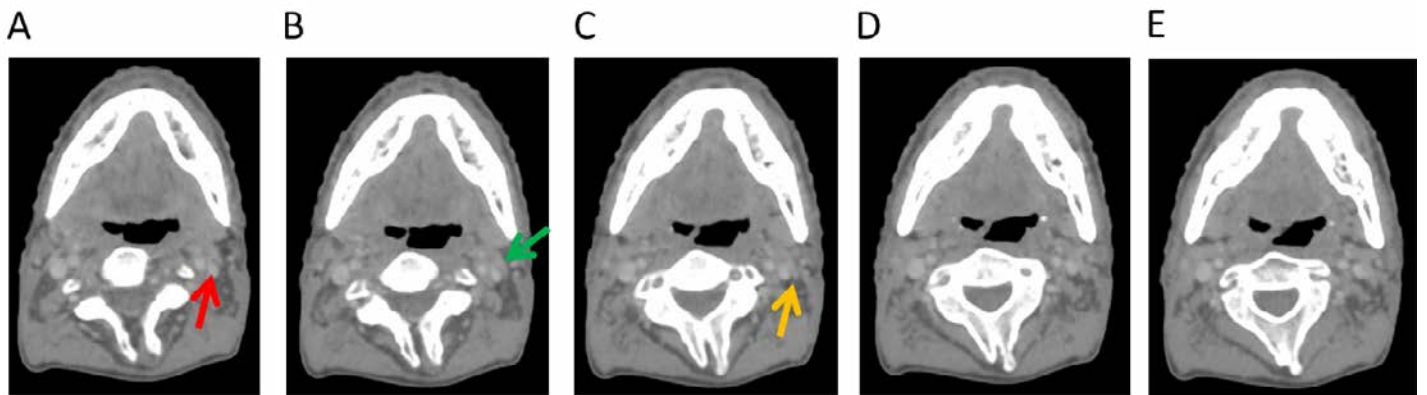
There was unanimous agreement for these statements.

#### Further background notes

Several series<sup>1,2,3</sup> have reported on non-nasopharyngeal head and neck squamous cell carcinoma (HNSCC) patients treated with radical or adjuvant radiotherapy in whom the contralateral high level II (HLII) lymph nodes in an uninvolved contralateral neck were omitted from target volumes; series reported by Eisbruch *et al*<sup>1</sup> included 133 radically treated HNSCC patients, Spencer *et al*<sup>2</sup> included 406 adjuvant and radically treated HNSCC patients, and Iyizoba-Ebozue *et al*<sup>3</sup> included 157 radically treated oropharyngeal cancer patients. No recurrences in the contralateral HLII were reported in any of these series (cumulative total of 696 patients).

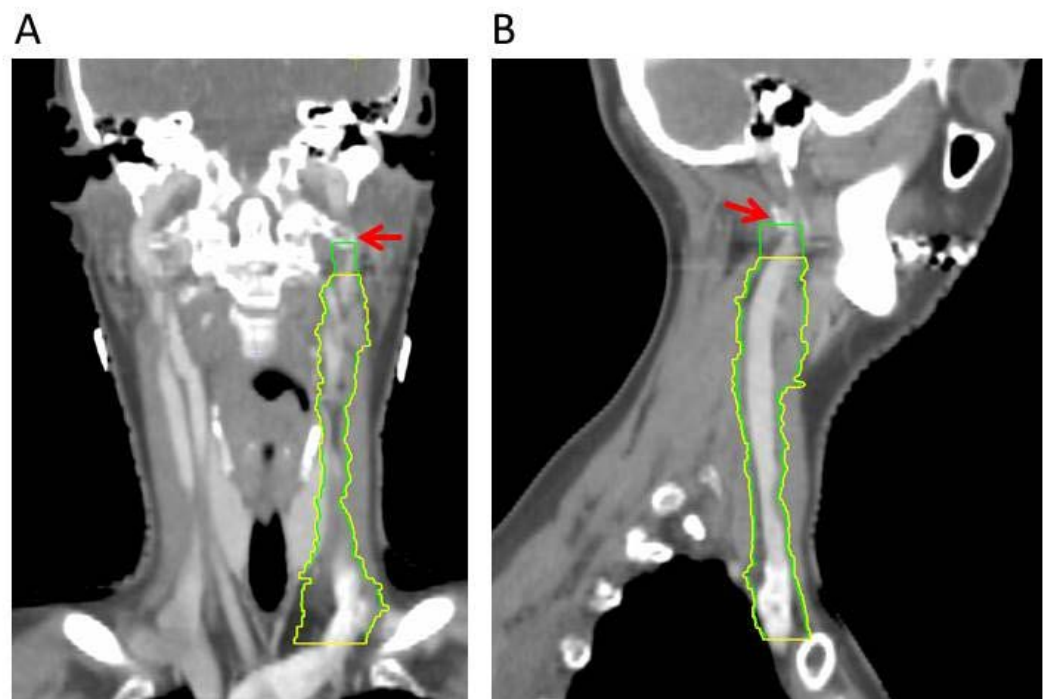
In retrospective analyses, omission of contralateral HLII was associated with improved contralateral parotid sparing<sup>1,3</sup> and superior quality of life.<sup>2</sup>

HLII is defined as the most cranial axial CT image where the posterior belly of the digastric muscle crosses the jugular vein, ensuring irradiation of the subdigastric lymph node.<sup>1</sup> The most superior CT slice for level II delineation when HLII is spared has been defined in the ongoing TORPEdO trial and by Iyizoba-Ebozue *et al* to be where the posterior belly of digastric crosses the posterior aspect of the internal jugular vein (see Figures 1 and 2).



**Figure 1.** Omission of HLII where posterior belly of digastric crosses the posterior aspect of internal jugular vein. Example of axial planning CT slices with intravenous contrast (2 mm slice thickness). A is the most caudal slice; A to E extends superiorly. The level where the posterior belly of digastric muscle crosses posterior aspect of internal jugular vein is shown in C, and would be the most superior slice of CTV delineation when HLII is omitted from elective CTVs.

Red arrow in A: internal jugular vein. Green arrow in B: posterior belly of digastric muscle. Yellow arrow in C: posterior belly of digastric crosses posterior aspect of internal jugular vein.



**Figure 2.** HLII sparing. Coronal (A) and sagittal (B) planning CT images showing elective lymph node level contouring of left neck levels II–IVa with (yellow contours) and without (green contours) sparing of HLII. Red arrow: transverse process of C1.

Several imaging series in patients with oropharyngeal carcinoma (OPC) demonstrate an extremely low rate of involvement of contralateral retropharyngeal lymph nodes (RPLN) without ipsilateral RPLN,<sup>4,5,6</sup> and in the absence of involvement of the contralateral neck, posterior pharyngeal wall or soft palate involvement.<sup>6</sup>

Outcomes of patients with OPC treated with radical radiotherapy with omission of the contralateral RPLN have been reported by Iyizoba-Ebozue *et al*<sup>3</sup> (n=175), Spencer *et al*<sup>7</sup> (n=117) and Leeman *et al*<sup>7</sup> (n=102), with no contralateral RPLN recurrences. In a series of 700 non-nasopharyngeal HNSCC patients (52% OPC) treated according to DAHANCA protocols in which RPLN were only treated in cases of posterior pharyngeal wall involvement, RPLN recurrences were only reported in two patients.<sup>8</sup>

Omission of contralateral RPLN from elective target volumes has been associated with improved quality of life<sup>2</sup> and reduced contralateral parotid doses.<sup>3</sup>

The 2019 lymph node selection guidelines recommend inclusion of the contralateral VIIa lymph node level for N0-2b(TNM7) disease with posterior pharyngeal wall involvement for p16-negative OPC and state that there is no data to suggest a different approach to p16-positive disease.<sup>9</sup>

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#### 4. Adjuvant contralateral neck irradiation following surgery for oral tongue cancer for patients planned for postoperative ipsilateral radiotherapy

##### Statements

Statement	Voting outcome
<p>4.1 Offer contralateral neck radiotherapy for patients having adjuvant ipsilateral radiotherapy for oral tongue squamous cell carcinoma who have had surgery to the primary site and an ipsilateral neck dissection if any of the following apply:</p> <ul style="list-style-type: none"> <li>– T3 or T4 tumour</li> <li>– Primary is within 10 mm of the midline</li> <li>– Two or more pathological lymph nodes in the ipsilateral neck</li> <li>– Extranodal extension (ENE) is present in the ipsilateral neck.</li> </ul>	Strongly supported
<p>4.2 Consider contralateral neck radiotherapy for patients having ipsilateral adjuvant radiotherapy for oral tongue squamous cell carcinoma who have had surgery to the primary site and an ipsilateral neck dissection if there is a single involved lymph node with no ENE in the ipsilateral neck.</p>	Strongly supported

##### Key points from consensus meeting

###### Statement 4.1

- General agreement that many oral tongue cancers are inherently aggressive and difficult to salvage following recurrence.
- Compelling evidence for high rates of contralateral recurrence if N2b (TNM7). DAHANCA suggests oral tongue cancer should be viewed as a midline structure.
- MDTs should consider the option of bilateral neck dissections in patients with oral tongue tumours, particularly for cancers approaching the midline.

###### Statement 4.2

- If the primary is well lateralised, resected with good margins and there is no ENE in lymph nodes some would not offer contralateral radiotherapy.
- There was discussion as to the strength of the statement between 'offer' and 'consider'. The wording was changed from offer to consider to allow for clinical assessment of individual cases. Using consider would give the freedom to discuss with patients the balance between treatment-related morbidity and risk of contralateral relapse.

### Further background notes

Cancer of the oral tongue has been associated with a worse prognosis compared with other oral cavity subsites.<sup>1</sup> Postoperative radiotherapy (PORT) after a curative surgical resection may improve survival.<sup>2</sup> However, the PORT treatment volume and the extent of inclusion of the surgical bed and elective regions has not been consistently defined. One area of debate is the PORT volume for oral tongue cancer that has received a primary resection and ipsilateral neck dissection. This topic considers when the PORT volume should be extended to the surgically undissected clinical (cN0) and radiological (rN0) lymph node-negative contralateral neck in the scenario that ipsilateral PORT is planned to the operated bed.

Contralateral neck radiotherapy in the case of the undissected c/rN0 neck may result in overtreatment of patients and there is debate as to whether it impacts disease recurrence or survival.<sup>3,4</sup> However, salvage rates and survival for patients with regional recurrent disease are low<sup>5</sup> and the possibility of PORT changing disease outcome is reasonable to consider. When a decision has been made to deliver ipsilateral PORT, delivering PORT to the undissected c/rN0 contralateral neck is based upon the pathological features of the primary cancer and ipsilateral nodal disease, which are thought to be indicators of occult contralateral disease and hence risk of contralateral lymph node recurrence (CLNR).

#### **Nodal burden and risk of CLNR**

The most highly consistent finding in series assessing risk of CLNR in oral tongue cancer is the ipsilateral nodal burden. The risk of CLNR based on pathological nodal status is biologically plausible due to the oral tongue being considered a midline structure with bilateral nodal drainage and because the presence of pathological nodes indicates a cancer with the propensity to spread.

Habib *et al* determined recurrence rates in the contralateral neck for well-lateralised oral tongue cancers receiving ipsilateral treatment by examining a range of pathological factors.<sup>6</sup> Patients with pathologically proven ipsilateral nodal metastases were at significantly higher risk of contralateral failure (hazard ratio (HR) 4.6, 95% CI 1.5–13.8,  $p=0.006$ ). Poor differentiation in addition to ipsilateral nodal disease conferred a 10% risk of contralateral failure.<sup>6</sup> All other factors including T-stage, margins, tumour grade, LVI and PNI, and ENE were not associated with CLNR.

Vergeer *et al* carried out a retrospective review of well-lateralised oral tongue cancers receiving surgery with ipsilateral radiotherapy.<sup>7</sup> In this Dutch series increasing volume of ipsilateral nodal disease predicted the risk of CLNR at five years; the following three groups of pN0, pN1/pN2a and pN2b (TNM7) carried the risk of contralateral recurrence of 1%, 12% and 27% respectively.

A retrospective series of oral cavity cancers after surgery and radiotherapy reported a contralateral relapse rate of 25% in patients with ipsilateral pN2b neck disease treated with ipsilateral surgery and PORT.<sup>8</sup> This led the authors to recommend bilateral neck irradiation in patients with N2b (TNM7) disease. Positive margins, increasing tumour size, the oral tongue subsite and increasing nodal status were associated with risk of cancer death in multivariate analysis. The significant number of failures within the radiotherapy field (68%) in the series suggests PORT may not modify disease course, especially in the setting of positive or close margins, which were 17% and 60% respectively in this series.



Retrospective oral cavity cancer series from Leeds, UK, analysing recurrence patterns also reported ipsilateral nodal burden as a predictor of CLNR.<sup>9,10</sup> Oral tongue cancers were found to be particularly prone to contralateral recurrence, with a failure rate of 33% in the presence of ipsilateral pN2 disease. The authors promote the need to consider comprehensive bilateral neck postoperative irradiation for oral tongue cancers, particularly in the presence of ipsilateral pN2a/b (TNM7) disease.

When considering N1 (single lymph node disease), contralateral failure rates of up to 12% have been reported.<sup>6,7,8,9,10</sup> This raises the possibility that patients with any ipsilateral nodal disease may benefit from bilateral PORT. The risk of CLNR is due to the bilateral lymph drainage of oral cancers, which was reported by the Sentinel European Node Trial (SENT) as 12% in early (T1–2) lateralised disease.<sup>11</sup>

It may be reasonable to omit contralateral neck radiotherapy for lateral oral cancers that are more than 10 mm from the midline and pN0.<sup>9,12,13</sup> Contreras *et al* omitted PORT to the neck in 14 pathologically negative (pN0) necks in patients with oral cavity cancer. While there was no occurrence of nodal relapse, 2 of 14 had an infield recurrence at the primary site. However, even in low-risk patients there is a risk of contralateral recurrence. Ganly *et al*<sup>14</sup> determined the incidence of locoregional failure in 164 patients with low-risk, pathologic T1–T2 N0, oral tongue cancer who underwent partial glossectomy and ipsilateral elective neck dissection without PORT. Regional recurrence occurred in 11% of patients and of these the relapsed disease was in the ipsilateral previously dissected neck in 61% and contralateral neck in 39% of patients. At a median of 66 months of follow up, patients who developed recurrence in the neck had a significantly poorer disease-specific survival compared with those who did not (33% versus 97%;  $p < .0001$ ).

The presence of ENE in ipsilateral lymph nodes may also be predictive of CLNR. Oral cavity cancer is common in India and a recent study reported ENE in an ipsilateral node as a significant predictor of contralateral recurrence<sup>15</sup> in addition to a cancer crossing the midline.

### **Tumour grade, PNI and LVI and risk of CLNR**

Habib *et al* determined that patients with poorly differentiated tumours have a significantly higher risk of contralateral failure (hazard ratio (HR) 3.6, 95% confidence interval (CI) 1.1–11.9,  $p=0.037$ ).<sup>6</sup> The rate of CLNR for oral tongue was 3.7% but increased to 6.9% in poorly differentiated disease. In a Taiwanese case series perineural invasion was associated with the CLNR rate.<sup>3</sup>

However, other studies report that poor tumour differentiation, perineural and lymphovascular space invasion are not significant factors in the adjusted analysis for risk of CLNR.<sup>6,8,15,16,17,18</sup> Poor pathological features may not on their own be considered independent risk factors for occult contralateral disease.

### **Tumour depth and risk of CLNR**

The depth of the primary tumour has also been suggested as a factor associated with regional recurrence. Ganly<sup>14</sup> reported in T1–2N0 oral tongue cancers treated with ipsilateral surgery alone a risk of neck recurrence was dependent on primary depth. The rate of regional recurrence at two years stratified by tumour thickness was 5.7% for patients who had tumours less than 4 mm thick and 24% for patients who had tumours more than 4 mm thick. The majority of recurrences were in the ipsilateral not contralateral neck. Tumour

depth was not associated with CLNR in other series<sup>15,17,18</sup> and cannot be suggested as a sole factor in considering bilateral neck PORT.

### **Tumour at or crossing the midline and risk of CLNR**

Oral tongue cancers approaching or crossing the midline are associated with CLNR and this is used as a factor to determine the requirement for bilateral PORT.<sup>4,15,17,19</sup> It is intuitive that a cancer approaching or crossing the midline be at risk of contralateral occult nodal disease. In one series, patients with tumours showing radiological evidence of extension crossing the midline at presentation were at a higher risk for contralateral neck disease (53.8%) than patients without an extension crossing the midline (10.3%).<sup>19</sup>

### **Tumour size T3–4 and risk of CLNR**

Kurita *et al* investigated factors associated with contralateral nodal recurrence in oral cavity cancers and showed that the T-stage and number of ipsilateral neck lymph node metastases were independent and significant predictors.<sup>19</sup> The risk of CLNR increased with advancing T-stage, with risks for T1, T2, T3, T4 disease being 0%, 12.2%, 11.8% and 31.4% respectively. Similar findings have been reported elsewhere<sup>5,17</sup> and may relate in part to larger tumours approaching and crossing the midline.

### **International consensus guidelines**

Three international consensus guidelines were identified that consider in the scenario that PORT is planned that the fields should include the operated ipsilateral neck and the undissected c/rN0 contralateral neck.

Grégoire has recently suggested that unilateral neck radiotherapy may be reasonable for the lateral border of the mobile tongue (not approaching the midline by less than 10 mm). But contralateral neck treatment may be advisable in oral cavity tumours with stage pN2a (TNM7) or more.<sup>20</sup>

American Society of Clinical Oncology (ASCO) clinical practice guideline recommendation 3.2 suggests contralateral neck radiotherapy should be administered to treat potential microscopic disease in patients with oral cavity cancers who have undergone ipsilateral neck dissection only and are at substantial risk of contralateral nodal involvement (tumour of the oral tongue and/or floor of mouth that is T3–4 or approaches the midline).<sup>21</sup>

The DAHANCA 2020 radiotherapy guideline states that oral tongue cancers should be treated as midline structures and thus for any nodal status including pN0 tumours, bilateral elective regions should be treated.<sup>22</sup>

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5.  
Induction chemotherapy

## Statements

Statement	Voting outcome
<b>Non-nasopharyngeal head and neck squamous cell cancer excluding sinonasal tumours</b>	
5.1 Do not offer induction chemotherapy prior to definitive (chemo-) radiotherapy unless: <ul style="list-style-type: none"> <li>– There is an urgent need for a rapid response in advanced and symptomatic local disease</li> <li>or</li> <li>– as part of a protocol for organ preservation.</li> </ul>	Unanimous support
<b>Nasopharyngeal cancer</b>	
5.2 Consider induction chemotherapy for locoregionally advanced, node-positive nasopharyngeal cancer in suitably fit patients.	Unanimous support

## Key points from consensus meeting

- These statements are for *squamous cell cancer* and not other variants such as small cell.
- Docetaxel, cisplatin and 5 fluorouracil (TPF) was acknowledged as the 'best' evidenced regime; however, the consensus view was to not explicitly specify it within the consensus statements due to concerns over its toxicity.
- The wording of statement 5.2 was changed to reflect the decision to consider chemotherapy in node-positive patients, not just in stage III and IV disease.
- Age alone should not be a reason to omit induction chemotherapy where it is indicated. Patients who are suitably fit should be considered regardless of chronological age.

## Further background notes

**Non-nasopharyngeal head and neck cancer**

Randomised evidence comparing cisplatin and fluorouracil alone (PF) with TPF in patients with stage III–IV head and neck cancer demonstrates improved median progression-free survival (PFS) and OS but more acute toxicity with TPF.<sup>1,2</sup> Subsequent studies randomising stage III–IV head and neck patients to induction chemotherapy or no induction chemotherapy have demonstrated no difference between OS and PFS but with more toxicity and febrile neutropenia in the TPF arm.<sup>3,4</sup> Specific circumstances in which induction chemotherapy has been shown to be of possible benefit include laryngeal preservation and sinonasal disease. For example, laryngeal preservation has been shown to be higher in a TPF induction chemotherapy group but with similar OS.<sup>5</sup> In sinonasal cancers induction chemotherapy produces a partial response in 67% of patients, with surgery performed in 52% after induction chemotherapy.<sup>6</sup> Improvements in outcomes, however, come at increased toxicity, with up to 30% of patients not proceeding to chemoradiotherapy (CRT).<sup>7</sup>

Induction chemotherapy is therefore not recommended as standard care and should only be considered in specific circumstances.

### Nasopharyngeal cancer

Two trials have shown a benefit of concomitant and adjuvant chemotherapy compared with radiotherapy alone for locally advanced nasopharyngeal cancer.<sup>8,9</sup> However, a subsequent study did not demonstrate an improvement when adjuvant chemotherapy was added to chemoradiation.<sup>10</sup>

Induction chemotherapy is better tolerated than adjuvant chemotherapy, with increasing evidence demonstrating a benefit with the addition of induction chemotherapy to CRT. TPF added to CRT in locoregionally advanced disease improves OS.<sup>11,12</sup> The gemcitabine and cisplatin (Gem-Cis) combination has also been shown to improve overall survival and recurrence-free survival compared with CRT alone in locally advanced disease, with OS 94.6% versus 90.3%. The patient cohort were stage III to IVB disease, and <65 years old.<sup>13</sup> In direct comparison, there was no difference between Gem-Cis and TPF induction chemotherapy in terms of three-year survival rate, but there was a significant difference with either induction regimen compared with CRT alone. Furthermore, there is reduced grade 3–4 toxicity with the Gem-Cis regimen compared with TPF.<sup>14</sup>

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## 6. Radical reirradiation in head and neck cancer

### Statements

Statement	Voting outcome
6.1 The risk–benefit ratio of radical reirradiation changes with time. Avoid reirradiation in patients who have recurrence with a short latency period (eg within 6–12 months of completing radiotherapy) or with significant late effects.	Very strongly supported
6.2 Treat the GTV with small margins (maximum GTV to CTV expansion of 5 mm). The reirradiated CTV should ideally be less than 50 cm <sup>3</sup> .	Very strongly supported
6.3 Do not include elective nodal areas within reirradiation treatment volumes.	Unanimous support
6.4 Keep the cumulative spinal cord and other important organs at risk (OAR) doses as low as possible. Ensure a thorough radiobiology evaluation with advice from physicists has taken place with risks considered, discussed with patient and documented.	Very strongly supported

### Key points from consensus meeting

- A recent Red Journal publication was noted: 'International recommendations on reirradiation by intensity-modulated radiation therapy for locally recurrent nasopharyngeal carcinoma'.<sup>1</sup> The paper refers to nasopharyngeal cancer but its recommendations would also apply to other subsites.
- Reirradiation was recognised as a very complex area with increasing numbers of patients likely to be considered for this in the future. The purpose of these statements is to ensure both that there is equity of access to reirradiation for patients who fit criteria for it but also, most importantly, that reirradiation is delivered as safely as possible.
- Reirradiation needs to be approached with caution and with careful supervision and partnership from suitably experienced radiotherapy teams. The consensus group strongly favoured a more organised and network-based approach to management of these complex head and neck cases. It is not appropriate for reirradiation to be delivered by all head and neck centres.
- There was concern that reirradiation represents a very small number of cases for an individual oncologist's practice. It was posed that reirradiation should be considered as a new technique and should be approached as such.
- Peer review of reirradiation case selection, volumes and dosimetry should take place taking into account overall cumulative radiation doses. Patients need to be selected for reirradiation very carefully and risks must be carefully discussed with each individual patient and recorded on a consent form.
- The risk of reirradiation is greater the shorter the length of time since previous radiotherapy treatment. It was acknowledged that while one would avoid offering reirradiation within 12 months, there is no strong evidence for a specific time cut-off and the group therefore did not wish for the statement to be overly prescriptive.

- There was discussion as to whether reirradiation could be one of the referral routes into the NHS England proton centres. It was reported that reirradiation is not on the routinely commissioned list; commissioned indications are for skull base tumours, adenoid cystic carcinoma cancers, TORPEdO and teenager and young adult (TYA) patients.<sup>2</sup> It was also noted that proton reirradiation may not be better at reducing dose to OAR than volumetric modulated arc therapy (VMAT) reirradiation.
- One centre reported the provision of a brachytherapy service for reirradiation of recurrent head and neck cancers.

#### Statement 6.4

- There was recognition of the need to balance OAR priorities. Refer to the Ng *et al*/ Red Journal paper for more detailed information.<sup>1</sup>
- The consensus group acknowledged it was not possible to give specific cord dose or OAR dose values and therefore opted for 'as low as possible'. Involvement of radiotherapy physicists is paramount.
- Consideration of additional risks should be carefully discussed with the patient.

#### Further background notes

The emergence of second primary cancers or locoregional recurrence following radical treatment for HNSCC ranges from 20–40%. Treatment options for locoregional recurrence or second primary cancers include surgical resection plus adjuvant radiotherapy, radical reirradiation or palliative systemic therapy. Careful patient selection prior to embarking on aggressive retreatment strategies is paramount. Informed consent must outline the high risk of treatment failures and long-term grade 3+ toxicities for all individuals.

The radical reirradiation consensus statements assume the following:

- Patient performance status (PS) is 0–1.
- Distant metastatic disease has been excluded.
- Thorough radiobiological evaluation with a physics team has taken place with risks considered, discussed with the patient and documented.
- Cases are discussed in regional networks/MDTs, with additional peer review (cross-centre if required) of proposed radiotherapy contours/plan in order to develop individual expertise and gain support.

The collection and dissemination of patient outcome data after receiving reirradiation through local and national audit is strongly encouraged.

#### Patient selection

A prolonged interval between radiotherapy courses presumes the existence of radiosensitive disease and allows for recovery of previously irradiated normal tissues, translating to a reduction in long-term severe toxicities and improved chance of cure. In RTOG 96-10, Spencer *et al* concluded that those who had more than three years' interval between radiotherapy courses had improved one-year survival rates of 48% compared with 35% if treated within three years.<sup>3</sup> Tanvetyanon *et al* confirmed the prognostic implications of the time to reirradiation and produced a nomogram to aid patient selection taking into account other clinical factors such as comorbidities and presence of organ dysfunction (eg reliance on feeding tubes).<sup>4</sup>



Ward *et al* retrospectively identified 412 patients who had been treated with reirradiation after presenting with recurrent/second primary HNSCC and published three prognostic subgroups to guide patient selection when considering reirradiation in the intensity-modulated radiation therapy (IMRT) era.<sup>5</sup> This multi-institution reirradiation consortium (MIRI) concluded that there were three distinct subgroups with worsening outcomes as patients accumulated more competing risks.

- **Class I** – Patients over two years from initial radiotherapy course who had undergone surgical resection of recurrent disease: two-year OS 61.9% (95% CI 51.9–73.9%).
- **Class II** – Patients over two years from initial radiotherapy course who had unresectable tumours or those less than two years from initial radiotherapy course who did not have organ dysfunction: two-year OS 40% (95% CI 33.9–47.2%).
- **Class III** – Patients less than two years from initial radiotherapy course who had unresectable tumours with organ dysfunction: two-year OS 16.8% (95% CI 10.0–28.1%).

A retrospective review conducted by Takiar *et al* of 227 patients receiving reirradiation with definitive IMRT reported an actuarial rate of  $\geq$  grade 3 toxicities of 32% at two years and 48% at five years. A retreatment CTV volume greater than 50 cm<sup>3</sup> was predictive of the development of  $\geq$  grade 3 toxicity (HR 3.11 95% CI 1.46–6.65). No patients with retreatment volumes less than 25 cm<sup>3</sup> developed  $\geq$  grade 3 toxicity.<sup>6</sup>

### SABR

The use of stereotactic ablative body radiotherapy (SABR) in the treatment of recurrent head and neck cancer is an emerging field with series reporting lower rates of late grade 3+ toxicity and reported two-year local control rates from approximately 30% up to 60%.<sup>7–10</sup> Rwigema *et al*<sup>11</sup> and Vargo *et al*<sup>10</sup> reported improved locoregional control and OS in patients with recurrent, previously irradiated head and neck cancer with GTV volumes less than 25 cm<sup>3</sup> treated with SABR. Tumour volumes of over 25 cm<sup>3</sup> were associated with higher rates of acute toxicity.<sup>11,12</sup> Cengiz *et al* noted an elevated risk of carotid blowout in patients whose disease encompassed  $>180^\circ$  of the carotid. The absence of carotid blowout syndrome was also noted in those with maximum dose  $<34$ Gy.<sup>13</sup>

### Patterns of failure

Hoebbers *et al* demonstrated the most frequent pattern of failure post reirradiation was in field after a completing retrospective review of 58 patients who underwent definitive reirradiation (with preceding salvage surgery in 47%); 82% of locoregional recurrences occurred within a high-dose area with none in the electively treated neck.<sup>12</sup> Similarly Popovtzer *et al*'s reirradiation series showed that 96% of recurrences occurred within the retreated GTV after using a 5 mm margin from GTV to PTV.<sup>14</sup> Caudell *et al* performed a retrospective cohort study to investigate the impact of including elective nodal areas when reirradiating patients with recurrent head and neck cancer. Elective nodal irradiation did not reduce the risk of two-year locoregional failure or two-year OS regardless of stratifying to postoperative or definitive reirradiation.<sup>15</sup>

### Concurrent chemotherapy

In the Radiation Therapy Oncology Group (RTOG) 9610 report Spencer *et al* investigated the feasibility of reirradiation with concurrent chemotherapy and used a regime of four weekly cycles of 5-fluorouracil (5-FU) and hydroxyurea with 60Gy in 1.5Gy bi-daily fraction.<sup>3</sup> They

reported a one- and two-year survival estimate of 41.7% (95% CI 30.6–52.8) and 16.2% (95% CI 7.3–25.0) with acute G4 toxicity rates 23%.<sup>3</sup> In Langer *et al*'s RTOG 99-11 chemotherapy was substituted with cisplatin and paclitaxel with an estimated two-year survival of 25.9% and acute G4+ toxicity rate of 28%.<sup>16</sup> Janot *et al* focused on the postoperative setting and randomly assigned patients to receive either postoperative reirradiation with 5-FU and hydroxyurea or observation. Again an increase in disease-free survival was observed with close to a third of patients experiencing G3 or G4 long-term toxicity.<sup>17</sup> Subsequent retrospective series have come to similar conclusions with studies showing improved locoregional control with the use of concurrent chemotherapy and reirradiation without an OS benefit and increased G4 toxicity. For example, Takiar *et al* noted a significant association between the use of concurrent chemotherapy and improved locoregional control (HR 0.44,  $p=0.02$ ) after retrospectively examining a series of 206 patients radically treated with reirradiation (135 (66%) received chemotherapy). In this study concurrent chemotherapy was also associated with increased risk of developing grade 4 toxicities (HR 1.78,  $p=0.035$ ).<sup>6</sup>

### Spinal cord tolerance

Rates of myelopathy following spinal cord irradiation have been reported at <1% and 6% for those receiving 50Gy and 60Gy respectively to the full cross-section of the cord at 2Gy per fraction.<sup>18</sup> Preclinical studies have suggested partial recovery of occult spinal cord injury following spinal cord reirradiation, which is evident within the first year and increases further from one to three years.<sup>19</sup> Kirkpatrick *et al* suggested a recovery of at least 25% cord tolerance at six months and Nieder *et al* reported a safe tolerance if an overall BED  $135.5 \text{ Gy}_2$  is used (provided if each course  $\text{BED} < 98 \text{ Gy}_2$  and treatment interval is more than six months).<sup>18,20</sup> Sulman *et al*<sup>21</sup> presumed a threshold of 50% recovery if the treatment interval is over 12 months when reporting their retrospective review. Alternative approaches to spinal cord dose constraints have been used in other HNSCC reirradiation studies, without reported cases of myelopathy. These include:

- Cumulative doses of 50Gy (2Gy equivalent)<sup>3,16,22</sup>
- Cumulative doses of 60Gy (2Gy equivalent)<sup>23</sup>
- Cumulative dose of 50Gy (2Gy equivalent) including 50% recovery for retreat interval  $\geq 12$  months<sup>6,12,21,24</sup>
- Cumulative dose of 60Gy (2Gy equivalent) including 50% recovery for retreat interval  $\geq 12$  months.<sup>25</sup>

Other, more complex spinal cord retreatment dose tolerance models exist and may be useful to consider in planning treatment for individual cases. For example, Wooley *et al*<sup>26</sup> estimate tolerance doses by using a range of elapsed time measures up to three years after the initial course of treatment.

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## Acknowledgements

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### RCR consensus project team

- Emma Burgum, professional support and standards administrator, RCR
- Sarah Griffin, clinical oncology projects and development officer, RCR

### Consensus participants

The following centres were represented at the virtual RCR head and neck cancer consensus meeting held on 6 July 2021.

Aberdeen Royal Infirmary	Beatson West of Scotland Cancer Centre
Bristol Haematology and Oncology Centre	Colchester General Hospital
Dorset Cancer Centre	Edinburgh Cancer Centre
Gloucestershire Oncology Centre, Cheltenham General Hospital	Guys and St Thomas Hospital NHS Trust
Imperial College Cancer Centre (Charing Cross)	Ipswich Hospital
James Cook University Hospital, Middlesbrough	Kent Oncology Centre
Leeds Cancer Centre	Leicester Royal Infirmary
Mount Vernon Cancer Centre	Musgrove Park Hospital
New Cross Hospital (The Royal Wolverhampton NHS Trust)	Norfolk and Norwich University Hospital

North Middlesex University Hospital	North Wales Cancer Treatment Centre, Glan Clwyd Hospital
North West Cancer Centre, Altnagelvin Hospital	Northampton General Hospital
Northern Centre for Cancer Care (NCCC), Freeman Hospital	Northern Ireland Cancer Centre, Belfast City Hospital
Nottingham University Hospital, City Hospital Campus	Oxford Cancer Centre, Churchill Hospital
Plymouth Oncology Centre	Queen Alexandra Hospital, Portsmouth Oncology
Queen Elizabeth Hospital (Birmingham)	Queen's Hospital, Romford
Raigmore Hospital	Royal Cornwall Hospital
Royal Derby Hospital	Royal Devon and Exeter Hospital
Royal Preston Hospital	Royal Shrewsbury Hospital
Royal Surrey County Hospital, Guildford	Royal Sussex County Hospital (Brighton)
Royal United Hospital Bath	South West Wales Cancer Centre
St Bartholomew's Hospital (Barts Health NHS Trust)	The Christie Hospital
The Clatterbridge Cancer Centre	The Royal Marsden Hospital
Torbay Hospital	University College London Hospital
University Hospital Southampton	Velindre Cancer Centre
Weston Park Cancer Centre, Sheffield	Worcester Oncology Centre

We are also very grateful to Chris Curtis, chief executive officer and founder of The Swallows Head and Neck Group, who attended on the day to provide a patient perspective.

The first draft of the consensus statements was circulated to all of the UK cancer centres that deliver head and neck radiotherapy to discuss with the multidisciplinary head and neck teams and to provide feedback. Feedback received was incorporated into the draft voted on at the 6 July consensus meeting.

### Stakeholder consultation

Representatives from the following stakeholder organisations were invited to comment on the first draft of consensus statements prepared by the working group.

- Society and College of Radiographers
- Institute of Physics and Engineering in Medicine
- Association of Cancer Physicians
- The Swallows Head and Neck Cancer Group
- Clinical trial leads (TORPEdO; CompARE and PATHOS)

We are very grateful for all feedback received. All comments were carefully considered by the working group and helped shape the subsequent draft statements, which were discussed and voted on by head and neck leads during the consensus meeting.



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