The use of international radiotherapy consensus guidelines for primary clinical target volume delineation for oropharyngeal carcinoma: case series with recurrence pattern analysis

Abstract

Background: International consensus guidelines for head and neck cancer primary clinical target volume (CTV) delineation based upon a geometric '5+5' expansion and anatomical editing were published in 2018. Analysis of recurrence patterns in relation to target volumes is required to validate this approach.

Methods: Patients with oropharyngeal carcinoma treated between 2019-22 with definitive (chemo)radiotherapy using the guideline approach to primary CTV delineation were identified. Patterns of locoregional recurrence were analysed using combined spatial and dosimetric analysis. Central, high dose recurrences were defined by mapped a centroid of the volume of recurrence (Vrec) to within the high dose planning target volume (PTV) and >95% of Vrec receiving >95% of prescribed dose to high dose PTV.

Results: 133 patients were treated using the consensus outlining guidelines. Median follow up was 3.9 years. 78.9% had p16 positive disease. 3-year local and regional control rates were 96% and 94.7y. Locoregional recurrence occurred in 6/133 (4.5%) of patients including 3 patients with primary site recurrences. All primary site recurrences were classified as central high dose recurrences.

Conclusions: All primary tumour site recurrences were within the high dose volume with no evidence of marginal or out-of-field recurrences. There results provide evidence for the safety of the consensus outlining approach for primary tumour CTVs.

Keywords: oropharynx cancer; radiotherapy; clinical target volume; recurrence pattern.

Introduction

Methods of primary tumour clinical target volume (CTV-P) delineation for definitive head and neck radiotherapy represent a balance between ensuring inclusion of adequate surrounding tissue to avoid edge recurrences, versus avoidance of treatment of excessive normal tissue to minimise toxicity. Historically, there have been two broad approaches to CTV-P delineation. Anatomical/compartmental outlining is based upon knowledge of typical patterns of tumour extension, and was used in several clinical trials reflecting standard practice at the time [1, 2]. Geometric outlining is an alternative approach based upon concentric margins with minor modifications for obvious anatomical barriers eg, air and bone and formed the basis of the Danish DAHANCA guidelines in 2013 termed a 5+5mm expansion [3]. These variable approaches led to wide inter-observer variability in CTV-P delineation [4].

International consensus guidelines for the delineation of CTV-P for definitive radiotherapy were developed by expert consensus and published in 2018 [5]. These guidelines were based upon the concept of an initial 5mm geometric expansion from gross tumour volume (GTV) to a high dose CTV (CTV-P1), with a second geometric expansion by 10mm from GTV to a lower dose CTV (CTV-P2) with anatomical editing based upon natural anatomical boundaries, knowledge of complex anatomical relationships and likely routes of spread. This approach requires expert clinical examination and up to date imaging to facilitate accurate GTV delineation [5]. The rationale for these guidelines with the size of the recommended expansion was based upon a very limited evidence base of a small pathology and radiology studies, along with comparison with margins obtained in surgical series [5]. Doubts were raised over both whether the geometric margins were large enough and whether the dose to CTV-P2 was adequate to avoid disease recurrence [6]. The requirement for high quality clinical examination/imaging raises questions regarding the applicability to routine clinical practice.

Analysis of disease outcomes and recurrence patterns is essential to address the safety of this outlining approach in routine clinical practice. In 2018 our institutional protocols were adapted to allow the option of '5+5' delineation with anatomical editing according to the consensus guidelines, based upon clinician choice. Here we present mature results of recurrence pattern analysis of patients treated using the delineation approach in the international consensus guidelines.

Methods

Study population

This single centre retrospective study was approved by the institutional governance board (LeedsCAT REC Reference 19/YH/0300). Patients with squamous cell carcinoma of the oropharynx who received definitive radiotherapy +/- chemotherapy between 2019-2022 were identified from an electronic database. Patients with a history of prior head and neck cancer or prior therapeutic surgery were excluded. Staging scans routinely included MRI neck and PET-CT. Radiotherapy records/plans were reviewed to determine whether contouring had been according to the consensus guidelines.

Chemotherapy

Patients <70 years old with a good performance status with either T3+ or N+ disease were considered for concurrent chemotherapy. Standard concurrent chemotherapy was cisplatin 100mg/m^2 for 2-3 cycles. In the event of a contraindication to cisplatin, carboplatin was substituted.

Radiotherapy

All treatment during the study period was delivered by volumetric modulated arc therapy (VMAT). Patients were treated supine with a 5-point thermoplastic mask. Planning CT scans were acquired with intravenous CT contrast and 2mm CT slices. Deformable co-registration of diagnostic MRIs was available [7]. Primary tumour CTV delineation was according to consensus guidelines [5]. Elective lymph node levels were defined according to consensus guidelines [8]. The planning target volume (PTV) was created by auto-expansion of the CTV by 4 mm. Standard dose fractionations as per Royal College of Radiologists dose fractionation guidelines [9] were 70Gy in 35 fractions over 7 weeks or an option of 65Gy in 30 fractions over 6 weeks (the latter used in our practice for patients treated without concurrent chemotherapy). All contours were submitted for team-based prospective quality assurance prior to planning [10].

Response assessment and follow-up

Response was routinely assessed 4 months after treatment by clinical examination, naso-endoscopy if indicated and FDG PET-CT. Patients were routinely followed up for at least 5 years.

Recurrence analysis

Locoregional recurrence analysis was performed for patients with radiological evidence of recurrence which was confirmed by either pathology or subsequent clinical progression. The volume of recurrence (Vrec) was contoured on the original planning scan using information documented from clinical examination at the time of recurrence and imaging acquired at the time of relapse (using side-by-side visual interpretation of imaging). A 4mm centroid, presumed as the origin of recurrence, was generated based upon the calculated central Vrec voxel [11].

Patterns of failure classification

Recurrences were analysed in relation to either the primary tumour (primary recurrences) or lymph node risk levels (regional recurrences) depending upon anatomical location. The relevant PTV for analysis for each recurrence was determined by comparison of the anatomical site of the recurrence with the original PTVs. Dose volume histograms (DVH) were obtained for the Vrec and coverage of Vrec by 95% of the corresponding PTV prescription dose was documented. Mean dose and location of the centroid was compared with PTVs. Recurrences were classified into 5 types using combined spatial and dosimetric criteria [12]:

A. Central, high dose: mapped centroid of Vrec originating in high dose PTV and >95% of Vrec receiving >95% of prescribed dose to high dose PTV

B. Peripheral, high dose: mapped centroid of Vrec originating in high dose PTV and <95% of Vrec receiving >95% of prescribed dose to high dose PTV

C. Central, elective dose: mapped centroid of Vrec originating in elective dose PTV and >95% of Vrec receiving >95% of prescribed dose to elective dose PTV

D. Peripheral, elective dose: mapped centroid of Vrec originating in elective dose PTV and <95% of Vrec receiving >95% of prescribed dose to high dose PTV

E. Extraneous dose: mapped centroid of Vrec originating outside of all PTVs.

Statistical analysis

Follow up and survival outcomes were calculated from the first day of radiotherapy. Overall survival (OS), progression free survival (PFS), local control, regional control and distant metastases-free survival (DMFS) were considered as endpoints and were calculated using the Kaplan–Meier method via RStudio.

Results

133/622 (21.4%) of patients receiving definitive (chemo)radiotherapy for oropharynx cancer between 2019-22 were treated using the '5+5' approach according to the international guidelines. The proportion of patients treated according to the guideline '5+5' approach was 33% in 2019, 27% in 2020, 28% in 2021 and 36% in 2022. The proportion of patients treated using the approach varied according to the treating clinician from 12/90 (13%) patients to 47/137 (34%) of patients. Patient and disease characteristics are shown in Table 1. 105/133 (78.9%) patients had p16 positive disease.

102/133 (76.7%) received concurrent chemotherapy. Median follow up was 3.9 years (interquartile range 2.9-4.9).

120/133 (90.2%) of patients had a complete response to treatment based upon clinical and radiological assessment. 3 year local control, regional control, distant metastatic disease free, progression free survival and overall survival rates were, 96% (95%CI: 92.6%, 99.5%), 94.7% (95%CI: 91%, 98.6%), 94.2% (95%CI: 90.1%, 98.5%), 98.1% (95%CI: 95.5%, 100%), and 96.4% (95%CI: 93%, 100%) respectively. 6/133(4.5%) patients had locoregional recurrence following an initial complete response to treatment: 1 primary site only, 1 primary and nodal, 1 primary site and distant disease, 1 nodal combined with distant disease, 2 nodal only. Distant recurrence with no evidence of local recurrence occurred in 8 patients. Median time to locoregional recurrence was 8.5months (IQR 8.25-21.5months).

Of the 3 patients with local disease recurrence, none were salvageable, and all died with active disease. Of the 2 patients with isolated regional recurrence, 1underwent salvage surgery , later developing further regional recurrence and commenced systemic treatment . The other died with active disease.

Analysis of recurrence patterns

Recurrence pattern analysis by spatial and dosimetric criteria was performed for the 3 patients with local disease recurrence; all 3 (100%) were classified as type A (central, high dose). An example is show in Figure 2. For the 4 patients with regional recurrence, 3 were classified as type A and 1 as type C (central, elective dose).

Discussion

Implementation of international guidelines has led to an increase in delineation uniformity [13], with smaller margins than those previously used [1, 2]. Detailed analysis of recurrence patterns is needed to evaluate changes in radiotherapy delineation. Recurrence analysis from the DAHANCA centres showing local recurrences were predominantly in-field, provided some reassurance regarding the safety of these margins but were based upon differing approaches [14].

In our series, local control rates were high. Recurrence pattern analysis demonstrated that in all cases primary site recurrence, disease was within the central high dose region (pattern A). Therefore, there was a zero rate of marginal or out-of-field failure in the primary site. These data suggest that the '5+5' approach to CTV margin delineation along with anatomical editing, provides adequate CTV coverage, and that treatment failures are due to radioresistance. Similarly for regional lymph node disease, the pattern of treatment failure was of recurrence within high dose volumes with only one central elective dose recurrence (category C).

During this time period of 2018-22, 21.5% of patients were treated using the guideline approach. This limited rate of uptake partly relates to clinician unfamiliarity/concern regarding the risk of CTV reduction. The guidelines were only later recommended by the UK's Royal College of Radiologists in 2022 [9]. Rates of use of the guidelines varied by clinician from 34% to 13% reflecting the influence of clinician preference. Additional reasons are likely to have related to concerns over how easily the GTV-P could be defined; inaccurate GTV delineation coupled with a reduction in high dose CTV would lead to the potential risk of missing microscopic disease. Of note, although deformable registration of diagnostic MRI was available with the associated limitations [7], MRI simulation was not used in this time period. One way in which radiation oncologists attempt to mitigate this risk, is only employing the CTV guidelines in situations in which they are confident in delineating the GTV-P eg. well defined on clinical examination and imaging [13]. The use of the approach varied only by a small amount according to the year of treatment, although it is notable that by 2022, the highest proportion (36%) of patients were treated using the guideline approach. The gradual uptake of the guidelines is reflected elsewhere. In a survey of Belgian centres in 2022 found that 88% reported that they considered they had implemented the guidelines, although only 65% delineated all cases according to the guidelines; concern over the reduction of the high dose CTV and the potential risk of missing microscopic disease was highlighted as the main reason for not employing the guidelines.
[13].

In summary, these data show that the use of the international CTV guidelines based upon ‘5+5’ outlining and anatomical editing are associated with high rates of local control. Reassuringly, we did not find any cases of marginal primary tumour recurrences by volumetric or point-of-origin analysis.

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Figures

Figure 1: Example of a type A central high dose recurrence (Group A): Patient with p16+ve squamous cell carcinoma left oropharynx T2N1M0 treated with concurrent cisplatin-radiotherapy. A) '5+5' contouring around primary tumour. B) MRI showing recurrence 9 months post treatment. C) Site of recurrence contoured on original planning CT scan. D) Isodoses shown with site of recurrence (orange = 95% of prescription dose).

Tables

Table 1: Patient and disease characteristics

	n=133	%
Mean age/years (range)	61	
Gender • Male • Female	 102 31	 76.7 23.3
Subsite • Tonsil • Base of Tongue • Soft palate • Post pharyngeal wall • Vallecula	 64 62 3 2 1	 48.1 46.6 2.2 1.5 1.5
T stage • T0 • T1 • T2 • T3 • T4	 1 9 52 32 39	 0.9 6.7 39.1 24.0 29.3
N stage (p16 +ve) (n=105) • N0 • N1 • N2	 14 65 25	 14.2 61.9 23.8
N stage (p16 -ve/unknown) (n=28) • N0 • N1 • N2a • N2b • N2c • N3	 5 9 2 7 2 3	 17.9 32.1 7.1 25 7.1 10.7
P16 status • positive • negative • unknown	 105 27 1	 78.99 20.1 3.0
Smoking status at diagnosis • Never smoker • Smoker • Ex-smoker • Unknown	 26 26 35 46	 19.4 19.4 26.1 34.5

Radiotherapy only	31	23.3
Concurrent chemotherapy Chemotherapy agent • Cisplatin • Carboplatin • Cisplatin and carboplatin	102 76 8 18	76.6 74.5 7.8 17.6
Radiotherapy dose • 65Gy/30 fractions • 70Gy/35 fractions	 32 102	 24.1 75.9

Highlights

- Head and neck clinical target volume delineation guidelines were published in 2018.
- Patients with oropharyngeal cancer treated according to guidelines analysed.
- High rates of local control
- Recurrence pattern analysis shows all primary site recurrences in high dose area.
- Provides validation for use of delineation guidelines.

Declaration of competing interests:

The authors have no competing interests to declare.

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Ethics statement:

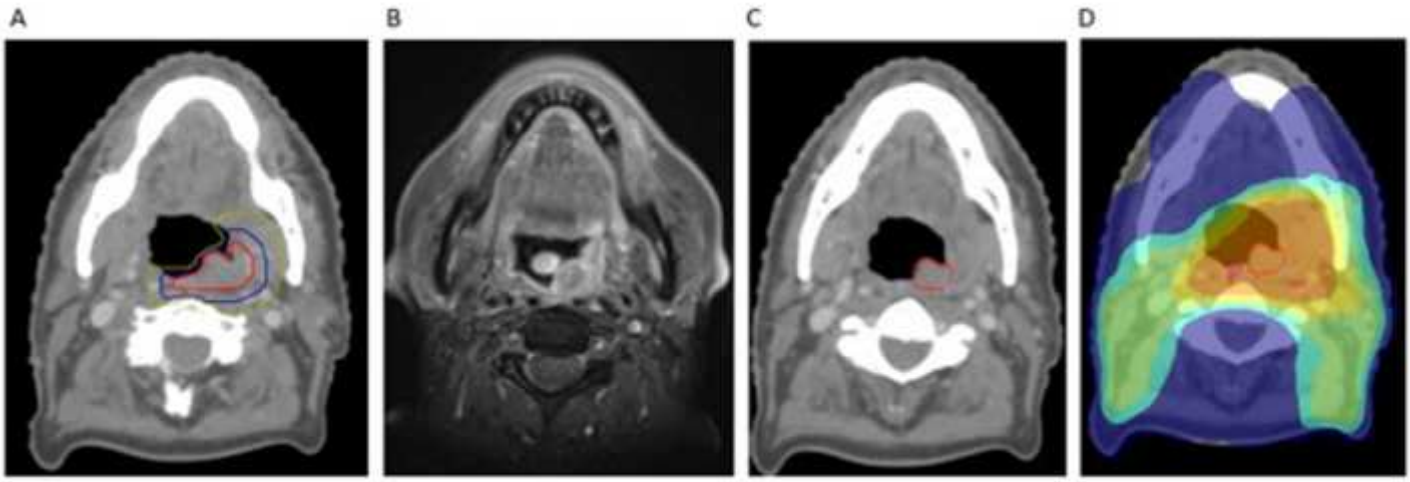
This single centre retrospective study was approved by the institutional governance board (LeedsCAT REC Reference 19/YH/030). Data supporting
the findings of this study are available upon reasonable request.

Patient consent:

This report includes no identifiable information or photographs, thus written informed consent from the patients was not obtained.

Figure

Click here to access/download;Figure;Figure 1.jpg



The use of international radiotherapy consensus guidelines for primary clinical target volume delineation for oropharyngeal carcinoma: case series with recurrence pattern analysis

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