Chapter 5

The effect of induction chemotherapy on tumor volume and organ-at-risk doses in patients with locally advanced oropharyngeal cancer

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Abstract

Background and Purpose: To retrospectively report changes in gross tumor volume (GTV) and organ-at-risk (OAR) doses after induction chemotherapy (IC) in oropharyngeal cancer using different contouring strategies.

Materials and Methods: GTV and OARs were delineated on pre- and post-IC planning CT. Two post-IC GTV contours were made: (1) a ‘consensus set’ using published guidelines (GTV_{consensus}), and (2) ‘visible set’, delineating only visible post-IC GTV (GTV_{visible}). Pre-IC interactively optimized volumetric modulated arc therapy plans were generated. The pre-IC planning constraints served as the starting point for both post-IC plans. Results reflect pooled data from all 10 patients.

Results: Mean reduction in volume post-IC was 24% and 47% for consensus and visible primary tumor and 57% and 60% for consensus and visible nodes. Compared to pre-IC plans, average mean OAR dose for post-IC GTV_{consensus} plans was significantly lower for CL parotid. For GTV_{visible} plans both parotids, upper/lower larynx, inferior pharyngeal constrictor and cricopharyngeal muscles were significantly lower. However reductions compared with post-IC GTV_{consensus} plans were modest (1.6/1.5/1.2/3.7/5.9/2.6Gy respectively).

Conclusion: IC in patients with oropharyngeal carcinoma results in substantial reductions in GTVs. If post-IC GTVs are used, which is contrary to current consensus, statistically significant but relatively small OAR dose reductions are observed.

Introduction

Most patients with head and neck cancer (HNC) present with a locally advanced (LA) tumor requiring multimodality treatment [1]. Concurrent chemoradiotherapy (CRT) is superior to radiotherapy alone and is considered standard of care for non-surgical treatment of LA-HNC [2].

Although it remains a controversial area, the last decade has seen renewed interest in the use of induction chemotherapy (IC) prior to CRT in LA-HNC [2-6]. Since IC often results in tumor reduction and anatomy changes [7], target volume delineation, although challenging, also presents opportunities for modification (reduction) of the pre-IC target volume, with the aim of reducing doses to organs-at-risk (OAR) and improving patient-specific outcomes. Such strategies are not advocated for routine clinical use and require further careful investigation to evaluate efficacy and safety. However the hypothesis that using IC combined with delineation strategies that are based on post-IC target volumes might facilitate relevant gains in OAR dosimetry nonetheless merits testing. Although this seems intuitive, it has not been examined in detail, nor is it clear that all patients will benefit or that such OAR gains will be
clinically meaningful. The question is of interest given the growing recognition that head and neck cancer patients are heterogeneous and may benefit from more individualized therapy [8] as evidenced by the recent interest in dose de-escalation in patients with HPV positive tumors (http://clinicaltrials.gov/show/NCT01530997).

Therefore, using a uniform cohort of patients with LA oropharyngeal cancer, this planning study tested the impact on organ-at-risk (OAR) doses using 2 different delineation strategies, one based on pre-IC and the other on post-IC target volumes.

**Materials and methods**

**Patient characteristics**

This retrospective in silico planning comparative (ISPC) study was performed using routine clinical data from 10 patients with locally advanced oropharyngeal carcinoma (LA-OC) previously treated with IC. Five patients treated on the EORTC 24061 protocol received 4 cycles of TPF IC 3-weekly and cetuximab; one patient also on this protocol (patient 1) developed a bowel perforation after cycle 1 and received no further IC. The remaining 4 patients treated off protocol received 2 cycles of TPF (Table 1).
Table 1: Patient characteristics and volume results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stage</th>
<th>IC</th>
<th>HPV</th>
<th>Smoking</th>
<th>Pre-IC</th>
<th>Post-IC</th>
<th>Post-IC</th>
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<tr>
<td>1</td>
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<td>10.8</td>
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<td>neg</td>
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<td>27.5</td>
<td>13.9</td>
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<td>47 py</td>
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<td>25.4</td>
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<td>11.0</td>
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<td>18 py</td>
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<td>134.3</td>
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<td>40.9</td>
<td>25.7</td>
<td>26.7</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Mean: 63.4, 48.4, 33.7, 38.0, 16.3, 15.1
Av red: 24%, 47%, 57%, 60%
St dev: 38.6, 35.4, 39.2, 47.7, 21.8, 18.4


Patients 1-6 received also cetuximab. Volumes in cc

Radiotherapy delineation

All patients were immobilized in a thermoplastic mask and had a contrast-enhanced pre-chemotherapy planning CT (pre-IC CT) with 2.5 mm slice thickness. In all patients a pre-IC MRI and in all but 1 patient a pre-IC PET/CT was rigidly co-registered with the pre-IC CT for delineation of pre-IC volumes. The MRI and PET/CT scans were diagnostic scans performed without immobilization.

The pre-IC gross tumor volume (GTV) was defined as the primary tumor and involved lymph nodes, using information from all imaging and clinical examination, including panendoscopy under general anesthesia. FDG-PET was mainly used to localize the primary tumor and involved lymph nodes. The border of the primary tumor was delineated with CT and MRI information and CT was used to contour involved lymph nodes and lymph node regions. The boost clinical target volume (CTVboost) comprised the GTV with a margin of 0.5 cm. The elective CTV (CTVelect) included the CTVboost and bilateral elective lymph...
nodes: at least levels II-V, and level I, VI and/or retropharyngeal nodes when indicated. Both CTVs were edited for anatomical boundaries. An additional margin of 4 mm was added to each CTV to create the planning target volumes (PTV_{boost} and PTV_{elect}).

The following OARs were delineated: both parotid glands (PG), contralateral submandibular gland (CL SMC) if the contralateral neck was macroscopically uninvolved, and swallowing organs at risk (SWOARs, i.e. superior, middle and inferior pharyngeal constrictor muscle, cricopharyngeal muscle, esophagus inlet muscle, upper and lower larynx) according to guidelines [9].

Two weeks after completion of IC, patients had a repeat contrast-enhanced planning CT (post-IC CT). Three patients also had a repeat diagnostic MRI which was co-registered with the post-IC CT for delineation.

We evaluated the effect of IC on OAR doses using two different GTV contouring strategies:

(1) Post-IC 'consensus' set: in accordance with published consensus guidelines [10], the pre-IC GTV was rigidly projected to the post-IC CT. The primary tumor GTV was then edited for bone and air. For pathologically involved lymph nodes the post-chemotherapy volume was used, unless there was evidence of extracapsular extension.

(2) Post-IC 'visible' set: the GTV was delineated on the post-IC CT. As in the pre-IC scenario, only the visible, macroscopic tumor and involved lymph nodes were delineated.

For both strategies, the CTV and PTV structures were generated as previously described. The post-IC OARs were delineated again as previously described. All contouring was done by a single, experienced head and neck radiation oncologist (PD).

Planning objectives and techniques

Volumetric modulated arc therapy plans (RapidArc [RA], Varian Medical Systems) were generated using the pre-IC CT and previously published techniques [11,12]. Briefly, dose prescription was 54.25 Gy in 1.55 Gy/fraction to the PTV_{elect} and 70.00 Gy in 2.00 Gy/fraction to the PTV_{boost} delivered as a simultaneous integrated boost (SiB). A standard constraint set was used for RA optimization, aiming to deliver at least 95% of the boost dose to 99% of the PTV_{boost} and 95% of the elective dose to 98% of the PTV_{elect}, while minimizing the boost and elective volumes receiving >107% of the prescribed dose. The maximum doses to the spinal cord and spinal cord +3 mm were set to 36 and 40 Gy, respectively. Five dose objectives were used for both PG and CL SMC and 4 for each (uninvolved) SWOAR. Priorities were set to 120-130 for PTV structures, 80 for salivary glands and 70 for swallowing structures. All dose constraints were adapted interactively during the optimization process with the aim of lowering the mean doses in the OARs. No specific constraints were used for the other healthy tissues, but a 1-cm wide ring was created around the
PTV\textsubscript{elec} to enforce a steep dose fall-off. The resulting pre-IC constraint set was then applied to both post-IC structure sets, with further interactive adaptation during optimization.

RA optimization was performed with the Eclipse treatment planning system (v10.0.28, Varian Medical Systems). Final dose calculations were performed using the Anisotropic Analytical Algorithm (AAA) with a 2.5mm calculation grid.

\textit{NTCP modeling}

To model the impact of changes in dosimetry, mean CL parotid gland doses from all plans for each patient, and their baseline xerostomia data were entered into an NTCP model designed to predict moderate-to-severe patient-rated xerostomia [13].

\textit{End-points}

1. Pre and post-IC volumes were compared for primary tumor, nodal GTV and selected OARs.

2. Pre and post-IC mean OAR doses were compared according to delineation strategy.

3. NTCP values to explore the possible decrease of patient-rated xerostomia were calculated.

\textit{Statistics}

Results are presented using descriptive statistics. Statistical analysis was performed using the Wilcoxon Signed Rank test, SPSS software package (version 20.0, SPSS, Inc., Chicago, IL).
Results

Volumetric changes after IC

Changes in tumor and lymph node volumes are shown in Table 1. For the primary site, the average reduction in GTV volume after IC using the consensus guideline approach to delineation was 24% compared with 47% when contouring the visible post-IC tumor alone. For pathological lymph nodes the average reductions in volume were 57% and 60%, respectively. For both primary tumor and lymph nodes, the post-IC GTV_{consensus} volumes were significantly smaller than the pre-IC volumes (p=0.005 and 0.008, respectively). The post-IC GTV_{visible} primary tumor volume was also significantly smaller (p=0.005). There was no significant difference in mean volume reduction of the primary tumor or lymph nodes between patients who received 4 cycles of TPF (n=5) versus 1 or 2 (n=5). There was also no difference in volume reduction for both primary tumor and lymph nodes between HPV+ (n=4) and HPV- (n=4) tumors. For the primary site, using the consensus and visible delineation strategies, the reduction was 26%/23% and 56%/50% respectively.

OAR doses

The average and standard deviations (SD) of the mean OAR doses (in Gy) for all 10 patients are shown in Table 2. Contouring and dose distributions for patient 3 are shown in Fig. 1.
<table>
<thead>
<tr>
<th>OAR (number of cases with possible sparing with either consensus or visible strategy)</th>
<th>PRE-IC</th>
<th>POST-IC</th>
<th>POST-IC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GTV consensus</td>
<td>CTV visible</td>
</tr>
<tr>
<td>IL parotid gland (10/10)</td>
<td>mean</td>
<td>31.3</td>
<td>29.9</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>8.6</td>
<td>8.2</td>
</tr>
<tr>
<td>CL parotid gland (10/10)</td>
<td>mean</td>
<td>23.2</td>
<td>20.7*</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>4.5</td>
<td>3.6</td>
</tr>
<tr>
<td>CL submand gland (5/10)</td>
<td>mean</td>
<td>54.7</td>
<td>54.9</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>18</td>
<td>17.2</td>
</tr>
<tr>
<td>upper larynx (5/10)</td>
<td>mean</td>
<td>57.7</td>
<td>56.7</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>13.9</td>
<td>15.2</td>
</tr>
<tr>
<td>lower larynx (8/10)</td>
<td>mean</td>
<td>35.9</td>
<td>35.8</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>19.9</td>
<td>21.2</td>
</tr>
<tr>
<td>superior PCM (5/10)</td>
<td>mean</td>
<td>65.3</td>
<td>64.7</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>8</td>
<td>9.2</td>
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<tr>
<td>medial PCM (2/10)</td>
<td>mean</td>
<td>66.5</td>
<td>66.3</td>
</tr>
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<td></td>
<td>st dev</td>
<td>7.5</td>
<td>8.1</td>
</tr>
<tr>
<td>inferior PCM (9/10)</td>
<td>mean</td>
<td>48.4</td>
<td>48.8</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>16.7</td>
<td>16.7</td>
</tr>
<tr>
<td>cricopharyngeal M (9/10)</td>
<td>mean</td>
<td>30.2</td>
<td>28.5</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>16.7</td>
<td>16.3</td>
</tr>
<tr>
<td>esophageal inlet M (10/10)</td>
<td>mean</td>
<td>21.6</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>st dev</td>
<td>10.7</td>
<td>9.9</td>
</tr>
</tbody>
</table>

*Abbreviations: IC: induction chemotherapy. GTV: gross tumor volume. st dev: standard deviation. IL: ipsilateral, CL: contralateral. PCM: pharyngeal constrictor muscle. M: muscle. Doses in Gray (Gy). *: p<0.05 (statistically significant)
Re-planning with interactive optimization on the post-IC GTV\textsubscript{consensus} datasets only resulted in a statistically significant decrease in mean CL parotid gland dose (p=0.021), whereas for the post-IC GTV\textsubscript{visible} plans, statistically significant differences were seen for both parotid glands (IL p=0.007, CL p=0.005), upper and lower larynx (p=0.043 and p=0.012), inferior pharyngeal constrictor muscle (p=0.012) and cricopharyngeal muscle (p=0.015). Nonetheless, in most cases the difference between the average mean OAR dose for the post-IC GTV\textsubscript{visible} and post-IC GTV\textsubscript{consensus} was modest (Table 2), with the largest differences observed for certain swallowing muscles (lower larynx, inferior PCM and cricopharyngeal muscle).
NTCP of xerostomia at six months

Individual patient NTCP values for xerostomia at 6 months are depicted in Fig. 2. Mean NTCP pre-IC was 42% (range 37-54%), compared to 38% (range 33-48%) in the post-IC consensus dataset, and 37% (range 32-47%) in the post-IC visible dataset. The difference between the pre-IC and both post-IC datasets was statistically significant (p=0.021 and 0.005, for the consensus and visible datasets respectively). In general there was little difference between the estimated xerostomia risk for the post-IC consensus and visible plans.

Figure 2: Normal tissue complication probability (NTCP) of xerostomia at 6 months

Discussion

The purpose of this detailed in silico study was to investigate the volumetric changes in GTV after IC and the subsequent dosimetric effect on OARs when using 2 different delineation strategies, one based on the pre-IC target volumes and the other on the post-IC target volumes.
Substantial reductions in primary tumor and nodal volumes after TPF induction chemotherapy for LA-OC were achieved, whether delineating with consensus guidelines or using visible post-IC target volumes alone. Although subsequent reductions in OAR doses were, on average and in most patients, rather modest and perhaps unlikely to be of clinical benefit for many patients, they were more substantial for certain individual patients, especially when using the post-IC target volumes (for which the largest average differences compared with the consensus approach were seen for some of the swallowing muscles). In some cases this may have enabled clinically relevant reductions in specific OAR doses. Using the ‘consensus’ delineation strategy (which does not take maximum advantage of volume reduction) appears to limit the potential for dosimetric gain, with the absence of a substantial reduction in OAR doses suggesting that in most cases the underlying OAR/PTV geometry remains relatively unfavorable.

This is illustrated by the findings in relation to the swallowing muscles (Table 2) for which the post-IC consensus plans were on average no different from the pre-IC plans, but for which the post-IC visible plans were associated with their largest dose reductions relative to the consensus plans. When correcting the post-IC primary tumor only for hard boundaries, as per consensus guidelines, the original extension cranio-caudally and toward the soft tissues of the neck (and therefore PTV\textsubscript{boost}) remained largely intact. Consequently, it is unlikely that certain OAR doses, in this case the swallowing muscles, will decrease significantly. Indeed, considering the whole group, it was only possible to achieve a statistically significant reduction in the mean CL parotid gland dose (from 23.2 Gy to 20.7 Gy) when using the consensus approach. While recognizing its limitations, using NTCP modeling, this translated into a reduction in the probability of patient-rated xerostomia for the whole group from 41% pre-IC to 38% post-IC for consensus contouring. Although this average reduction is relatively modest, for individual patients, such as patient 3 the difference was larger, with a 6.4% reduction. This patient had a large reduction in both primary tumor and nodal volume. Patient 6, who had a large reduction in nodal volume alone, achieved a 4.5% reduction in probability of xerostomia. While in general the difference in estimated xerostomia risk pre- and post-IC was relatively similar for the consensus and visible delineation strategies, the post-IC visible plans for patients 1 and 7 did have a lower risk, suggesting that selected patients might gain something from this approach.

Although guidelines advocate using the pre-IC GTV volume projected on the post-IC planning CT scan, it is unclear if it is imperative to give the whole pre-IC GTV the full boost dose. Loo et al. recently reported on patterns of failure after IC in 52 patients with LA oropharyngeal cancer [14]. Post-IC primary tumor was delineated following consensus guidelines but taking into account pre-IC anatomy, resulting in small post-IC volumes in some patients. Post-IC lymph node dimensions were used to delineate nodal GTV. With a median follow up of almost 3 years, no marginal recurrences were noted, suggesting that using larger post-IC volumes were unlikely to improve local control rates.

A 3-dose level plan, with full dose on the post-IC GTV\textsubscript{visible}, intermediate dose to the post-IC GTV\textsubscript{consensus} and the lowest dose to elective lymph node levels may merit investigation; however it is important that outcomes are not compromised. Salama et al. reported a dose de-escalation study using IC and giving progressively lower dose to high, intermediate and low-risk areas in 3 patient cohorts. They found a shorter time to progression in the lowest dose cohort, but similar survival and loco-regional/distant
control [15]. In all cohorts the pre-IC GTV received >70 Gy, but in the lowest dose cohort the intermediate and low-risk areas received only 51 and 36 Gy.

There are little data published about the volumetric and dosimetric impact of IC however 2 recent abstracts are relevant. Gupta et al. reported a mean reduction in the composite volume containing the primary tumor and grossly involved nodes of 52% in 31 patients (20 with oropharynx tumors) [16]. As in the present study, they described the use of multi-modality pre-IC imaging, however, they used pre-IC diagnostic contrast-enhanced CT and the post-IC volumes were defined on non-contrast radiotherapy planning CT scans. From the abstract it appears that their delineation strategy more closely resembles the ‘visible’ strategy in the present paper. If this is the case then the relative volume reduction is comparable between the two studies (52% reduction in composite volume versus 47% for primary tumor and 60% for nodes in our study). Regarding OAR doses, Caudell et al. [17] found significant dose differences for both parotid glands and the larynx before and after IC, with a mean dose reduction of 9.4 Gy for the IL parotid gland, compared to a modest 3 Gy difference in the present study. However in their study only 5/16 patients had a mean IL parotid dose <39 Gy pre-IC (rising to 12/16 post-IC), while in our series the average mean dose of 31.3 Gy pre-IC was already substantially lower.

Although our study is distinguished by the fact that it explores different delineation strategies in a homogeneous group of LA-HNC patients treated with IC, unfortunately not all patients had post-IC MRI and PET imaging. While this may have resulted in suboptimal post-IC contours and affected the volumetric comparison, the work of Geets et al. suggests that the impact may have been modest [18,19]. The present study has not examined other possible benefits of IC-related volume reduction such as whether or not it is associated with a reduction in the likelihood of re-planning during radiotherapy. In this study, only 1 patient needed re-planning during CRT. Although we did not see a complete tumor response in the patients within this analysis, this has been reported after IC [3,4] and the delineation strategy would need to be clearly addressed in any protocol incorporating post-IC based target volume delineation.

Despite some 30 years since early studies of IC in HNC [20], its role in LA-HNC is still not conclusively defined and it continues to be investigated as a way of improving upon CRT alone (e.g. CONDOR trial, ClinicalTrials.gov NCT00774319). However, the heterogeneity in tumor outcome and possibly also the response to treatment in patients with LA-HNC is now becoming more apparent and highly conformal photon-based radiotherapy treatments coupled with improved tumor and normal tissue imaging techniques are becoming more widely available. Contemporary IC trials could provide an opportunity to further investigate the most appropriate delineation, treatment planning and dose/fractionation strategies in sub-groups of patients with LA-HNC. This will help to define the gain in functional OAR preservation and quality of life that is possible without compromising local tumor control and survival.
Conclusions

Induction chemotherapy in patients with locally advanced oropharyngeal carcinoma results in statistically significant, and often substantial, volume reductions in primary tumor and lymph nodes. However, contrary to clinical practice, if post-induction gross tumor volumes are used, statistically significant dose reductions are observed in more OARs than if the current consensus approach to delineation is used. On average the absolute reduction in OAR doses compared with the consensus plans are modest suggesting that they may not translate into additional, clinically relevant gains for most patients and that only selected patients may benefit. NTCP modeling for xerostomia was consistent with this. Before new delineation strategies can enter routine clinical use they require to be tested in well-designed protocols to identify patients (and PTV-OAR geometries) that might benefit, in which patient groups they may be appropriate, and to ensure that local control and survival are not compromised.
References


