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Impact of post-chemoradiotherapy superselective/selective neck dissection on patient reported quality of life

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SUMMARY

Objectives: To describe patient-reported quality of life (QoL) for patients with HPV/p16-positive oropharyngeal squamous cell carcinoma undergoing post-chemoradiation (CRT) superselective or selective neck dissection (ND) as part of a prospective de-intensification study.
Materials and methods: Patients received 60 Gy IMRT with concurrent weekly cisplatin (30 mg/m^2), followed by preplanned neck dissection of only originally involved nodal levels. QoL measures were assessed using the EORTC QLQ-C30 (general), EORTC H&N-35 (head and neck specific), EAT-10 (swallowing), and NDII (Neck Dissection Impairment Index) questionnaires. Early and late post-ND time points were compared to baseline and post-CRT/pre-ND time points.
Results: 37 patients underwent post-CRT superselective or selective ND. Median # of levels and nodes dissected were 2 and 12, respectively. EORTC QLQ-C30, H&N-35, and EAT-10 QoL scores worsened after CRT but continued to improve thereafter despite post-CRT ND. NDII score worsened initially after ND at the early post-ND time point ($p = 0.023$) but had recovered by the late post-ND time point ($p = 0.672$). Initial decrease in NDII was greater with $\geqslant$12 nodes dissected ($p = 0.007$) and was correlated with the total number of nodes dissected (Spearman $p = 0.027$).
Conclusion: Use of post-CRT superselective and selective ND did not prevent recovery of most QoL metrics to near baseline. There was early but not late decrement in neck dissection specific QoL (NDII), more pronounced with more nodes dissected.

Introduction

Planned neck dissection (ND) was the historical standard of care after definitive radiation for head and neck cancer due to moderate rates of residual nodal disease in patients with positive nodes at diagnosis [1,2]. However, routine post-radiation neck dissection may subject patients with pathologic complete response in the neck to the morbidity of surgery without any added benefit. During the 1990s, concurrent chemotherapy with radiation was shown to significantly improve outcomes, ushering a paradigm shift with increased usage of nonoperative definitive chemoradiation (CRT), especially in the setting of oropharyngeal and laryngeal cancer [3]. In addition, there has been an increasing prevalence of HPV-associated oropharyngeal cancer, which carries a better prognosis and response to treatment [4].

There have also been many recent improvements in imaging techniques used to evaluate response to chemoradiation. Post-treatment CT and PET/CT are increasingly used to decide whether patients need a post-treatment neck dissection. In the setting of more effective treatments incorporating concurrent chemotherapy and more favorable tumor biology (i.e. HPV-association), numerous studies have shown that patients with a radiographic complete

Abbreviations: QoL, quality of life; CRT, chemoradiation; ND, neck dissection; NDII, Neck Dissection Impairment Index.

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response in the neck may be spared the morbidity of surgery with a low risk of recurrence [2,5–9]. Planned neck dissections have therefore declined in favor of an image-guided approach. A standard practice now is to obtain a PET/CT scan at 3 months post-treatment, reserving neck dissection for patients with evidence of residual disease.

The clinician-reported morbidity of a neck dissection has been previously documented in patients undergoing definitive surgery for head and neck cancer, with greater extent of dissection associated with greater morbidity [10–13], and further QoL decrements in patients with prior radiation [14–17]. In a pooled analysis of several Radiation Therapy Oncology Group studies, post-CRT neck dissection was a significant predictor of grade 3 or higher late toxicity [18]. However, the extent of neck dissections performed after radiation is evolving from the use of modified radical to selective and superselective (removal of 1–2 neck levels – i.e. only those initially harboring disease) dissections [19]. There is increasing evidence that post-CRT superselective and selective neck dissections are safe and efficacious [9,19–22]. The impact of these limited post-CRT neck dissections on patient reported QoL is unknown, but may be useful to clinicians considering how to manage possible residual nodal disease after definitive chemoradiation.

We conducted a Phase II trial in which patients with HPV/p16-positive squamous cell carcinoma of the oropharynx received de-intensified chemoradiotherapy, followed by a superselective/selective neck dissection directed at pre-treatment positive lymph node levels. We collected a robust battery of patient reported QoL outcomes before CRT, before neck dissection, and at several time points after neck dissection. The purpose of this manuscript is to investigate the impact of superselective/selective neck dissection on changes in patient reported QoL after prior definitive chemoradiation.

Materials and methods

Study design and eligibility

This was a multi-institutional Phase II study examining de-intensified CRT. Full details can be found in our recent report [23]. Informed consent was obtained from all patients. Inclusion criteria were as follows: Patients with untreated T0-3, N0-2c, M0 HPV and/or p16 positive squamous cell carcinoma of the oropharynx/unknown primary, $\leqslant$10 pack-years smoking or >5 years abstinence from smoking, $\geqslant$18 years of age, ECOG performance status 0–1, absolute neutrophil count $\geqslant$1800 cells/mm^3, platelet count $\geqslant$100,000 cells/mm^3, hemoglobin $\geqslant$8.0 g/dl, serum creatinine <2.0 mg/dl, and negative pregnancy test in women of childbearing potential. Exclusion criteria were as follows: Prior history of head and neck cancer or head and neck radiation, pre-existing grade 2 neuropathy or hearing loss, known HIV-positive, and recent (within 6 months) severe comorbidity including unstable angina, congestive heart failure exacerbation, myocardial infarction, and/or COPD exacerbation.

Study treatment and planned surgical evaluation

Study treatment consisted of de-intensified CRT followed by biopsy of the primary site and limited neck dissection. The planned post-treatment surgery was chosen to provide a robust pathologic endpoint as well as to ensure safety in patients receiving both de-intensified radiation and de-intensified chemotherapy. All patients were treated with intensity modulated radiation therapy to 60 Gy (2 Gy per fraction) to areas of gross disease and 54 Gy (1.8 Gy per fraction) to regions considered at risk for subclinical disease. Radiation was delivered over six weeks, five days a week. Chemotherapy consisted of concurrent weekly cisplatinum, 30 mg/m^2 for a total of six weekly doses. At 4–8 weeks post-CRT, patients received a response assessment including physical exam, fiberoptic nasolaryngopharyngoscopy, and diagnostic CT. Within 6–14 weeks after CRT, patients underwent the planned surgical evaluation. Patients with a complete clinical response at the primary site underwent a biopsy, followed by transoral surgery only if residual disease was present. All patients with initially node-positive disease received a superselective or selective neck dissection, defined as the removal of at least all previously involved nodal levels. Patients found to have residual nodal disease did not undergo any further neck surgery. Starting one month after surgery, all patients received massage therapy.

Quality of life assessment

Four validated questionnaires were used to assess patient-reported quality of life: the EORTC QLQ-C30 assessment of general QoL, the EORTC H&N-35 assessment of head and neck specific QoL, the EAT-10 assessment of swallowing, and the NDII (Neck Dissection Impairment Index) assessment of neck dissection-specific QoL. These are discussed in further detail below. The study schema is shown in Fig. 1. The QLQ-C30, H&N-35, and EAT-10 were collected pre-CRT, 6 weeks post-CRT (pre-neck dissection), and post-neck dissection at each subsequent follow-up visit. The NDII was collected at 6 weeks post-CRT (pre-ND) and at subsequent post-ND follow-up visits, but not pre-CRT. For the purposes of this study, we defined four distinct time points: Pre-CRT (Baseline), Pre-ND (Post-CRT), Early Post-ND (First QoL assessment after neck dissection) and Late Post-ND (Closest QoL assessment to 1.5 years post neck dissection). To assess the specific impact of the neck dissection, we compared the Pre-ND (Post-CRT) time point with the Early and Late Post-ND time points.

1. EORTC QLQ-C30 [24]: The EORTC QLQ-C30 is a core questionnaire that is a reliable and valid measure of the quality of life of cancer patients. It incorporates nine multi-item scales: five function scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and an overall global QoL scale. Several single-item symptom measures are also included. Higher numbers represent better QoL for the global and function scales, but worse QoL for the symptom scales and items.
2. EORTC H&N-35 [25]: The EORTC QLQ H&N-35 is a validated questionnaire designed to assess the quality of life of head and neck cancer patients in conjunction with the general cancer-specific EORTC QLQC-30. The H&N-35 incorporates additional single-item symptom measures of particular relevance, i.e. mouth opening, dental health, speech, dry mouth, etc. Higher raw scores represent worse QoL.
3. EAT-10 [26]: The EAT-10 is a validated self-administered instrument for documenting dysphagia severity. This questionnaire uses symptom-specific scores to assess dysphagia with solids,

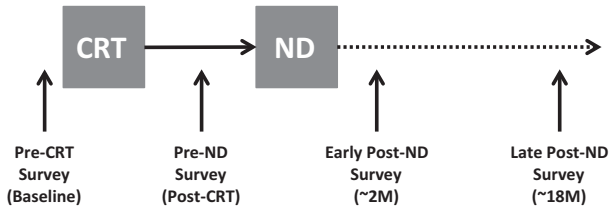

Fig. 1. Study schema showing the four collected QoL time points.