Methods/Supplementary Material

I. Literature Search Strategy

A literature search strategy was developed using medical subject headings (MeSH) related to adjuvant therapy for head and neck cancer. On 01/10/2019 Ovid MEDLINE® and Embase® were searched using a strategy to capture all published studies that included head and neck cancer and sub-sites AND adjuvant therapy either in the title, keyword, or abstract. The detailed search strategies are shown below.

Ovid MEDLINE® search strategy: The search strategy utilized MeSH vocabulary for indexing articles in PubMed.

1 “Head and Neck Neoplasms”/or “Mouth Neoplasms”/or “Gingival Neoplasms”/or “Palatal Neoplasms”/or “Tongue Neoplasms”/
2 exp “Hypopharynx”/or “Mouth” /or “Mouth Floor” /or “Mouth Mucosa” /or exp “Oropharynx” /or exp “Palate” /or “Pharynx” /or “Tongue” /or (buccal or gingiva* or “head and neck” or “hypo pharynx*” or hypopharyngeal or hypopharynx or laryngeal or larynx or mouth or oral or oropharyngeal or oropharynx or palate or palatal or pharyngeal or pharynx or tongue or tonsil*).tw,kf.
3 “carcinoma, Squamous Cell” /or (cancer or cancers or cancerous or carcinoma* or tumor or tumors or tumour or tumours).tw,kf.
4 2 and 3
5 1 or 4
6 ((“after surg*” or “following surg*” or “post operative*” or postoperative* or “post surg*” or postsurg*) adj3 (“chemo radi*” or “chemo therap*” or chemoradi* or chemotherapy* or cisplatin or “combined modalit*” or irradiation or “multi modal*” or multimodal or radiation or “radio chemotherap*” or “radio chemotherapy*” or “radio therapeutic*” or “radio therapy” or radiochemotherap* or radiotherapeutic* or radiotherapy)).tw,kf.
7 (“Chemotherapy, Adjuvant”/or “Combined Modality Therapy”/ or exp “Chemoradiotherapy”/ or “Radiotherapy, Adjuvant”/) and (exp “Head and Neck Neoplasms/surgery”/ or “Postoperative Period”/)
8 6 or 7
9 5 and 8

Embase search strategy: The vocabulary utilized in the Ovid Medline search was translated to Embase-compatible terminology and is detailed below. The search includes ‘head and neck cancer’ terms (1) + ‘adjuvant’ terms (2).

(1) ‘head and neck cancer’/de OR ‘mouth carcinoma’/de OR ‘mouth squamous cell carcinoma’/de OR ‘pharynx carcinoma’/exp OR ‘tonsil carcinoma’/de OR ‘tongue carcinoma’/de OR ‘gingiva tumor’/de OR ‘larynx carcinoma’/exp OR ['pharynx'/exp OR ‘mouth floor’/de OR ‘mouth mucosa’/exp OR ‘tongue’/exp OR ‘palate’/exp OR ‘larynx’/exp OR (buccal OR gingiva* OR ‘head and neck’ OR ‘hypo pharynx*’ OR hypopharyngeal OR hypopharynx OR laryngeal OR larynx OR mouth OR oral OR oropharyngeal OR oropharynx OR palate OR palatal OR pharyngeal OR pharynx OR tongue OR tonsil*):ab,ti AND ‘squamous cell carcinoma’/de OR (cancer OR cancers OR cancerous OR carcinoma* OR tumor OR tumors OR tumour OR tumours):ab,ti]
AND

(2) ['adjuvant chemotherapy'/exp OR 'multimodality cancer therapy'/de OR 'chemoradiotherapy'/exp OR 'adjuvant radiotherapy'/exp) AND ('head and neck surgery'/de OR 'postoperative period'/de) OR (('after surg*' OR 'following surg*' OR 'post operative*' OR postoperative* OR 'post surg*' OR postsurg*) NEAR/3 ('chemo radi*' OR 'chemo therap*' OR chemoradi* OR chemotherap* OR cisplatin OR 'combined modalit*' OR irradiation OR 'multi modal*' OR multimodal OR radiation OR 'radio chemo therap*' OR 'radio chemotherap*' OR 'radio therapeutic*' OR 'radio therapy' OR radiochemotherap* OR radiotherapeutic* OR radiotherapy))]:ab,ti]

Search Results
The Medline search yielded 3,720 results and Embase yielded 4,524 results. The results were combined and saved in an Endnote ® library where duplicates were removed yielding a final 5,689 results. The Endnote ® library was transferred to Covidence ® systematic review software.

II. Systematic review strategy (as per PRISMA-P)
The methodologic protocol for this systemic review was guided by the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) and includes all 17 core items of the PRISMA-P checklist (Shamseer, Moher, Clarke et al. BMJ 2015).

Studies were excluded if they were in non-English languages, case reports, case series, retrospective studies, large database studies (e.g. Surveillance, Epidemiology and End Results, National Cancer Database), abstracts for which a full manuscript was not published, preliminary analyses for which a final analysis was published, narrative reviews, modeling studies, cell-line or non-clinical/non-human studies. Articles were included if they met the following criteria:

Participants: Adult patients (age 18 years or older) with stage I-IVB SCCHN and no distant metastases (DM), who had no prior head and neck RT and were treated with curative-intent surgery. The following disease sites were included: oral cavity, oropharynx, hypopharynx, and larynx. Studies were excluded if they did not include at least 20 patients treated with surgery and postoperative therapy or the population was predominantly composed of nasopharyngeal carcinoma, paranasal sinus cancer, cancer of unknown primary, nasal cavity cancer, recurrent head and neck cancer, or patients treated with re-irradiation with or without chemotherapy
**Intervention:** The intervention of interest was PORT including all RT modalities (e.g. brachytherapy, cobalt, photons, particle therapy), chemo-PORT, or postoperative systemic therapy, including chemotherapy, biologic therapy, targeted therapy, and immunotherapy. Studies focused on the influence of timing of postoperative therapy were also included. Studies that focused on the impact of preoperative (e.g. neoadjuvant or induction) therapy on outcome were excluded.

**Comparators:** The effect of postoperative therapy was compared to surgery alone or other postoperative modalities (e.g. PORT compared to chemoPORT). Studies that did not have a comparison arm were also included. Surgery-alone studies were excluded.

**Outcomes:** Primary endpoints for the literature search included overall survival (OS), local, regional, and distant recurrence. Secondary endpoints included toxicity as captured by observer-rated, patient-reported, and functional measurements related to speech, swallow, or other relevant functions related to SCCHN treatment.

**Selection Process:** Selection was performed using Covidence® software. Title and abstract screening were performed by one author (DNM) using the PICO inclusion and exclusion criteria outlined above. Full text was obtained for all titles/abstracts that met inclusion criteria and for studies where there was uncertainty based on the title/abstract screening. Full text review was performed by two independent reviewers (DNM, AGS) blinded to each other’s judgment. Disagreement was resolved through discussion regarding study relevance related to the inclusion/exclusion criteria and concordance was obtained. Each study was graded using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence Table 1.

**Voting:** Clinical variants with corresponding treatment options were created to represent commonly encountered clinical scenarios, including those for which management is controversial. These were reviewed by all panelists prior to voting. Variants were circulated for voting whereby panelists rated each treatment using a score of “1-9”, representing “usually not appropriate” (1-3), “may be appropriate” (4-6), and “usually appropriate” (7-9). Panelists were blinded to each other’s votes. The results were reviewed and discussed, maintaining anonymity of voting. A second round of voting was performed, and results were again reviewed and discussed prior to finalizing votes. The median score was determined and agreement was determined as per the BIOMED Concerted Action on Appropriateness definition outlined in the RAND/UCLA methodology2 whereby agreement was defined as ≤3 votes outside the 3-point region containing the median (1-3;4-6;7-9), for a panel of 11-13, and ≤4 votes outside the 3-point region containing the median for a panel of 14-16. The strength of recommendations was graded using the GRADE system3.

**Search results:**

The process of study identification is summarized in Figure 1. A total of 5,689 studies were identified using Ovid MEDLINE® and Embase ®. After removal of duplicates, 5,660 studies were screened using the
title and abstract leading to 201 studies assessed for relevance using full-text review. After limitation to the eligibility criteria, 96 studies were identified. An additional five eligible studies were added, including four that were published after the cut-off date of 01/10/2019⁴²,⁴⁴,⁷⁵,¹¹⁶ and one randomized trial that was not identified through the literature search⁵².

Figure 1: Study selection QUOROM flow diagram

Records identified through Ovid MEDLINE® and Embase® search: (N=5689)

Records after duplicates removed: (N=5660)

Records screened using title and abstract screening (N=5660)  Records Excluded (N=5469)

Full-text articles assessed for eligibility (N=191)  Full text articles excluded, with reasons N=95

Not in English: 5
Not study population: 2
Not intervention of interest: 27
Not an included study design: 54
Not an outcome of interest: 1
Sample size <20: 6

Recommended by Panel due to relevance and met pre-defined literature search eligibility criteria.

Final studies included in qualitative synthesis: N=101

Details:
Systematic reviews: 13
RCTs: 29
Prospective phase I/II: 22
Prospective cohort studies: 28
Post-hoc analyses of RCT: 9

Studies published since 01/2019 cut-off (N=4)

Relevant RCT not identified in search (N=1)