Treatments for Locally Advanced Oropharyngeal Cancer: A Systematic Review of Clinical Effectiveness and Cost-Effectiveness - Project Protocol
Rationale and Policy Issues

Head and neck squamous cell carcinoma (HNSCC) encompasses multiple sites of origin — the oral cavity, oropharynx, and larynx — with diverse drivers of carcinogenesis and diverse clinical outcomes. Oropharyngeal cancer, the subtype of HNSCC that originates in the oropharynx, is associated with human papillomavirus (HPV) infection, alcohol use, and tobacco use, and is the 13th most common diagnosed cancer and the 15th most common cause of cancer death for adults in Canada. An estimated 4,400 Canadians (2,900 men and 1,450 women) were diagnosed with HNSCC in 2015, and 1,200 Canadians will die of the disease. In 2010, 210 Canadians (170 men and 40 women) were diagnosed with oropharyngeal cancer. In light of the morbidity associated with open surgical approaches to excising tumours of the oropharynx, non-surgical treatments have, in most centres, become the mainstay of treatment. A 2003 trial by Adelstein et al. established concurrent cisplatin and conventional fractionation radiotherapy as the standard of care over radiotherapy alone with a 13% improvement in three-year survival. Of the population of HNSCC patients included in this study, 59% had oropharyngeal cancer. More recently (2008), another radiosensitizing agent, cetuximab, has been made available in Canada as an alternative to cisplatin as part of concurrent chemoradiotherapy for HNSCC. With some exceptions — namely, the open surgical experience in Alberta (particularly Edmonton) — most locally advanced oropharyngeal cancers have been treated with either radiation or chemoradiation therapy with or without salvage surgery. In 2015, an Alberta Health Clinical Practice Guideline on oropharyngeal treatment recommended either surgery followed by radiotherapy or chemotherapy, or concurrent chemoradiotherapy for locally advanced oropharyngeal cancer. The chemotherapy options are single-agent cisplatin or cetuximab in the concurrent chemoradiotherapy setting, and cisplatin in the adjuvant setting. Intensity-modulated radiotherapy that delivers precise radiation doses to the tumour while sparing surrounding structures is the accepted standard of care (the recommended radiation dose is 66 to 70 Gy when part of concurrent chemoradiotherapy, or 60 to 66 Gy when following surgery in the adjuvant setting). Altered fractionation schedules have been explored, including accelerated fractionation, which reduces the total treatment time, and hyper-fractionation, which involves daily administration of two reduced-dose fractions. Relatively recent advances in minimally invasive techniques, namely Transoral Robotic Surgery (TORS) and Transoral Laser Microsurgery (TLM), are increasingly being incorporated as favourable options for early-stage oropharyngeal cancer. For oropharyngeal cancer that is at a more advanced stage, treatment with these minimally invasive techniques is still associated with functional impairment. For residual or recurrent oropharyngeal cancer, the more traditional open surgical approach via mandibulotomy or lateral pharyngotomy is used. In these cases, microvascular reconstruction of the subsequent defect is almost universally required.

The superiority of initial surgery or initial chemoradiotherapy in the treatment of oropharyngeal cancer in terms of oncologic, functional outcomes, toxicities, complications, and quality of life is not apparent. The cost-effectiveness of the two regimens is also unclear.

Objectives

This systematic review aims to compare the clinical effectiveness of primary surgical therapy (with or without adjuvant radiation and chemotherapy) with primary chemoradiotherapy (with or without salvage surgery) for locally advanced oropharyngeal cancer. The cost-effectiveness of the two treatment strategies will also be examined.

Research Questions

1. What is the comparative clinical effectiveness of primary surgery (with or without adjuvant radiotherapy and chemotherapy) versus primary chemoradiotherapy (with or without salvage surgery) for the treatment of adults with a diagnosis of locally advanced oropharyngeal cancer?
2. What is the cost-effectiveness of primary surgery (with or without adjuvant radiotherapy and chemotherapy) for the treatment of adults with a diagnosis of locally advanced oropharyngeal cancer?
3. What is the cost-effectiveness of primary chemoradiotherapy (with or without salvage surgery) for the treatment of adults with a diagnosis of locally advanced oropharyngeal cancer?

Methods

The protocol for this systematic review was written a priori and will be followed throughout the review process.

Search Strategy
A limited literature search was conducted on key resources including PubMed, OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, and Canadian and major international health technology agencies, as well as with a focused Internet search. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2006 and October 6, 2016. A supplemental search was performed, which was limited to English-language documents published from January 1, 2001 to November 17, 2016. See Appendix 1 for the detailed search strategy.

**Selection Criteria**

Selection criteria are outlined in Table 1.

**Table 1: Selection Criteria**

| **Population** | Adult patients (aged ≥ 18 years) with biopsy-proven primary locally advanced oropharyngeal carcinoma (American Joint Committee on Cancer stage III, IVa, or IVb) |
| **Intervention** | Concurrent primary chemoradiotherapy (with or without salvage surgery) |
| **Comparator** | Primary surgery (with or without adjuvant radiotherapy and chemotherapy) |

**Outcomes**

- **Oncologic outcomes**
  - Overall survival, recurrence-free survival, local-regional control (LRC, freedom from local progression)

- **Functional outcomes**
  - Rate of percutaneous feeding tube dependence at 2 years; rate of tracheostomy dependence at 2 years

- **Quality-of-life outcomes**
  - Quality of life, anxiety, recreation, pain, saliva, dry mouth, swallowing, taste, and speech measured with a standardized scale

- **Toxicities**
  - Mortality rates due to chemotherapy-induced neutropenia, rates of skin and mucosal toxicity, osteoradionecrosis, soft tissue necrosis, cerebellar necrosis, xerostomia

- **Complications**
  - Fistula formation, post-operative hemorrhage, hematoma formation, surgical-site infections, pneumonia

- **Cost-effectiveness outcomes**
  - Cost of primary surgery with or without adjuvant radiotherapy and with or without adjuvant chemotherapy
  - Cost of primary chemoradiotherapy with or without salvage surgery
  - All specific related costs
  - Quality-adjusted life-years (QALYs)
  - Incremental cost-effectiveness ratio (ICER)

**Study Design**

Randomized controlled trials, non-randomized studies with a comparator group, cost studies

**Screening and Selecting Studies for Inclusion**

Two reviewers (CH and KS) will independently screen the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria, will order the full text of any articles that appear to meet those criteria. The reviewers will then independently review the full text of the selected articles, apply the selection criteria to them, and compare the independently chosen included/excluded studies. Disagreements will be resolved through discussion until consensus is reached. Duplicate publications of the same study will be excluded unless they provide additional outcome information of interest. The study inclusion/exclusion form is provided in Appendix 2. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.10

Articles will be excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2001, or if they are duplicate publications of the same study. A list of excluded studies, with reasons for exclusion, will be provided for each research question.

**Data Extraction**
A data extraction form for the review will be designed a priori to document and tabulate relevant study characteristics. Data will be extracted independently by reviewers (CH and KS), and any disagreements will be resolved through discussion until consensus is reached. Study authors will be contacted in case of missing or unclear data. A draft of the a priori data extraction form for the clinical and cost studies is provided in Appendix 3. A calibration exercise will be conducted to ensure consistency in data extraction.

**Methodological Assessments**

The quality of clinical studies and cost evaluations will be assessed using Downs and Black and Drummond checklists, respectively. Quality assessment will be done by the lead researcher, and verified by a second researcher. Any disagreements will be resolved through discussion until consensus is reached. Studies will not be excluded based on methodological assessments, but assessments will be used to explain any potential differences across study results.

**Summary of Evidence**

**Description of Study Characteristics and Findings**

For each question, a narrative summary will be undertaken to report on the quantity of studies by design, intervention, comparator, settings, and outcome measures, where applicable. Tables will accompany the narrative summary, to ensure the consistency of the presented information across all studies and facilitate study comparisons by the reader.

**Description of Methodological Assessments**

A narrative summary of the results of the methodological assessments will be presented separately for each research question, including an overall impression of the quality of included studies. Tables outlining the strengths and limitations of each study will accompany the narrative summary, to ensure consistency of presented information across all studies and facilitate study comparisons by the reader. Separate tables will be created for each study design, or tabulated data will be separated within the same table by the use of subheadings.

**Data analysis methods**

Tables will be created to summarize quantitative findings for each outcome listed in Table 1. Data will be synthesized separately for each question, by outcome.

Head-to-head trials between the two treatment strategies will be included. Since discrepancies in patient demographics, such as clinical stage and comorbidities between the two intervention groups, may lead to bias in outcomes, meta-analyses will be performed only from data from randomized controlled trials (RCTs); in that case, results will be pooled. If meta-analysis is deemed inappropriate owing to lack of RCTs, or the heterogeneity of the clinical trials and methodological characteristics of included studies, a narrative summary of the included study findings will instead be constructed. Clinical experts may be consulted to determine whether important clinical heterogeneity exists.

If meta-analysis is deemed appropriate, meta-analyses will be carried out using Cochrane Review Manager software to derive pooled estimates of interest. A random-effects model will be used. Forest plots will be presented for all evidence syntheses to supplement reported estimates.

Time-to-event data (e.g., hazard ratios or continuous time-to-event measurements) will be presented, where appropriate, and will be pooled according to the methods described by Tierney et al.\(^\text{11}\) If pooling is deemed to be inappropriate, time-to-event data will be presented in tabular format and described narratively.

Analyses of dichotomous outcomes will be summarized using relative risks and 95% confidence intervals (CIs), and analyses of continuous outcomes will be summarized using mean differences and 95% CIs. Findings will be reported as “not statistically significant” if the CI of the overall estimate includes unity for dichotomous outcomes, or if the CI of the overall estimate includes null for continuous outcomes. The chi-square test will be used to assess effect size variance, with \(P < 0.10\) indicating significant heterogeneity across trials.

Planned subgroup analyses based on use of additional treatments (i.e., surgery alone or surgery with adjuvant chemotherapy or radiotherapy; primary chemoradiotherapy with or without salvage surgery), surgical approach, chemotherapy agent (cisplatin or cetuximab), and based on patient characteristics such as HPV status, smoking habit, and alcohol use will be performed when sufficient data are available. When significant heterogeneity is identified and sufficient data are available, further subgroup analyses will be made to identify the primary sources of heterogeneity. Additional sensitivity analyses dealing with outlying data points, study quality, study size, and other factors will also be considered to establish the robustness of findings.

For the economic review, costs and cost-effectiveness outcomes of primary surgery with or without adjuvant chemoradiotherapy, and of primary chemoradiotherapy with or without salvage surgery from the available evidence, will be
summarized and reported narratively and in tables. No primary economic evaluation will be performed.

**Areas for Potential Amendments**

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data according to the amendments.

**References**


**Appendix 1: Literature Search Strategy**

**Clinical Database Search**
### OVERVIEW

<table>
<thead>
<tr>
<th>Interface</th>
<th>Ovid</th>
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<tbody>
<tr>
<td>Study Types:</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, cohort studies, economic studies, and guidelines</td>
</tr>
</tbody>
</table>
| Limits: | Publication date limits:  
- Randomized controlled trials, controlled clinical trials, cohort studies, and economic studies — 2001-present  
- Health technology assessments, systematic reviews, meta-analyses and guidelines — 2001-present  
Language limit: English  
Conference abstracts: excluded  
Humans |

### SYNTAX GUIDE

- `/`: At the end of a phrase, searches the phrase as a subject heading
- `.sh`: At the end of a phrase, searches the phrase as a subject heading
- `MeSH`: Medical Subject Heading
- `exp`: Explode a subject heading
- `*`: Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
- `?`: Truncation symbol for one or no characters only
- `adj#`: Adjacency within # number of words (in any order)
- `.ti`: Title
- `.ab .kw`: Abstract Author keyword
- `.hw`: Heading word; usually includes subject headings and controlled vocabulary
- `.pt`: Publication type
- `.rn .yr`: CAS registry number Publication year
- `.la`: Language
- `pmez`: Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
- `oemezd`: Ovid database code; Embase 1974 to present, updated daily

### Multi-database Strategy

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</table>
(meta regression* or metaregression*).ti,ab,kf,kw.

(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.

(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.

(cochrane or (health adj2 technology assessment) or evidence report).jw.

(meta-analysis or systematic review).md.

(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.

(outcomes research or relative effectiveness).ti,ab,kf,kw.

((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.

or/59-75

(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.

(Randomized Controlled Trial/.

exp Randomized Controlled Trials as Topic/

"Randomized Controlled Trial (topic)"/

Controlled Clinical Trial/.

exp Controlled Clinical Trials as Topic/

"Controlled Clinical Trial (topic)"/

Randomization/.

Random Allocation/.

Double-Blind Method/.

Double Blind Procedure/.

Double-Blind Studies/.

Single-Blind Method/.

Single Blind Procedure/.

Single-Blind Studies/.

Placebos/.

Placebo/.

Control Groups/.

Control Group/.

(random* or sham or placebo*).ti,ab,hw,kf,kw.

((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.

((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.

(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.

(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.

allocated.ti,ab,hw.

((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.

(or/77-102

Economics/.

Cost/.

exp Health Economics/.

Budget/.

budget*.ti,ab,kw.

(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmacoeconomic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.

(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmacoeconomic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.

(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.

(value adj2 (money or monetary)).ti,ab,kw.

Statistical Model/.
Multi-database Strategy

Line #

114 economic model*.ab,kw.
115 Probability/
116 markov.ti,ab,kw.
117 monte carlo method/
118 monte carlo.ti,ab,kw.
119 Decision Theory/
120 Decision Tree/
121 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw.
122 or/104-121
123 Economics/
124 exp "Costs and Cost Analysis" /
125 Economics, Nursing/
126 Economics, Medical/
127 Economics, Pharmaceutical/
128 exp Economics, Hospital/
129 Economics, Dental/
130 exp "Fees and Charges" /
131 exp Budgets/
132 budget*.ti,ab,kf.
133 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-
    economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
134 /freq=2
135 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
136 (value adj2 (money or monetary)).ti,ab,kf.
137 exp models, economic/
138 economic model*.ab,kf.
139 markovchains/
140 markov.ti,ab,kf.
141 monte carlo method/
142 monte carlo.ti,ab,kf.
143 exp Decision Theory/
144 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf.
145 or/123-144
146 exp clinical pathway/
147 exp clinical protocol/
148 exp consensus/
149 exp consensus development conference/
150 exp consensus development conferences as topic/
151 critical pathways/
152 exp guideline/
153 guidelines as topic/
154 exp practice guideline/
155 practice guidelines as topic/
156 health planning guidelines/
157 exp treatment guidelines/
158 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
159 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.
160 (standards or guideline or guidelines).ti,kf,kw.
Multi-database Strategy

Line #

161 (practice or treatment* or clinical) adj guideline*,ab.
162 (CPG or CPGs).ti.
163 consensus*,ti,kf,kw.
164 consensus*.ab. /freq=2
165 (critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*).ti,ab,kf,kw.
166 recommendat*.ti,kf,kw.
167 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.
168 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.
169 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.
170 or/146-169
171 76 or 103 or 122 or 170
172 76 or 103 or 145 or 170
173 53 and 171
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175 173 or 174
176 remove duplicates from 175
177 176 use oemzd
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179 177 not conference abstract.pt.
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OTHER DATABASES

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<td>PubMed</td>
<td>Same MeSH, keywords, and limits will be used as per MEDLINE search, with appropriate syntax used. PubMed will be searched for citations not found in MEDLINE.</td>
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<tr>
<td>Cochrane Library</td>
<td>Same MeSH, keywords, and limits will be used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Cochrane Library databases.</td>
</tr>
<tr>
<td>Trial registries (Clinicaltrials.gov)</td>
<td>Same keywords and limits will be used as per MEDLINE search. Search limited to completed trials.</td>
</tr>
</tbody>
</table>

Grey Literature

Dates for Search: October 2016

Keywords: Oropharyngeal neoplasms (cancer, carcinoma, malignancy), chemoradiotherapy, surgery (salvage, primary)

Limits: January 2001–present; English language only

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), will be searched:

- Health Technology Assessment Agencies
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Clinical Practice Guidelines
- Health Economics
- Databases (free)
- Statistics/Prevalences
- Internet Search
- Open Access Journals.
Appendix 2: Article Screening Checklist

Treatments for Locally Advanced Oropharyngeal Cancer: A Systematic Review of Clinical Effectiveness and Cost-Effectiveness

Title:

First author and year:

Reviewer: C. Ho _______ K. Seal _______

INCLUSION CRITERIA:

1. **Population**: yes____ no____ can’t tell____
   Adult patients (aged 18 years) with biopsy-proven locally advanced oropharyngeal carcinoma (American Joint Committee on Cancer stage III, IVa, or IVb)

2. **Intervention**: yes____ no____ can’t tell____
   Primary surgery with or without adjuvant radiotherapy and with or without adjuvant chemotherapy
   Primary chemoradiotherapy with or without salvage surgery

3. **Comparator**: yes____ no____ can’t tell____
   Primary chemoradiotherapy +/- salvage surgery
   Primary surgery +/- adjuvant radiotherapy +/- adjuvant chemotherapy
   Any alternative treatment regimen

4. **Outcome Measures** (any of): yes____ no____ can’t tell____
   **Oncologic outcomes**
   Overall survival
   Recurrence-free survival
   Local-regional control (LRC)
   **Functional outcomes**
   Rate of percutaneous feeding tube dependence at 2 years
   Rate of tracheostomy dependence at 2 years
   **Quality of life outcomes**
   Anxiety, recreation, pain, saliva, dry mouth (xerostomia), swallowing, taste, and speech
   **Toxicities**
   Mortality rates due to chemotherapy-induced neutropenia, rates of skin and mucosal toxicity, osteoradionecrosis, soft tissue necrosis, cerebellar necrosis, xerostomia
   **Complications**
   Fistula formation, post-operative hemorrhage, hematoma formation, surgical-site infections, pneumonia
   **Cost-effectiveness outcomes**
   Cost of primary surgery +/- adjuvant radiotherapy +/- adjuvant chemotherapy
   Cost of primary chemoradiotherapy +/- salvage surgery, QALY, ICER

5. **Study Design**: yes____ no____ can’t tell____
   Randomized controlled trials (RCTs), non-randomized studies, cost studies
Appendix 3: Data Extraction Form

Reviewer: C. Ho ________ K. Seal ________

| Study title:      |                                      |
| Author:          |                                      |
| ID #: Year:      |                                      |

### Methods

<table>
<thead>
<tr>
<th>Study design</th>
<th>Study duration</th>
<th>Population - Number of patients recruited - Number of patients completing the study</th>
<th>Diagnosis</th>
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<table>
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<tr>
<th>Eligibility criteria</th>
<th>Country of origin</th>
<th>Industry sponsorship</th>
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<thead>
<tr>
<th>Baseline characteristics of study Participants, and details of treatment regimens</th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
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<tr>
<td>Proportion male/female (%)</td>
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<tr>
<td>Diagnosis (T-stage, N-stage, tumor subsite proportions)</td>
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<tr>
<td>Smoking status and proportion (%)</td>
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<td></td>
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<tr>
<td>Alcohol consumption and proportion (%)</td>
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<td>Proportion HPV positive (%)</td>
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<tr>
<td>- Details of treatment regimens (type of chemotherapy and dose, number of cycles, radiation dose, surgical approach)</td>
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<th>Other</th>
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### Outcomes

<table>
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<th>Intervention</th>
<th>Comparator</th>
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<tbody>
<tr>
<td>Oncologic outcomes and definition</td>
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<tr>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td>Recurrence-free survival</td>
<td></td>
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<tr>
<td>Local-regional control (LRC)</td>
<td></td>
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</tbody>
</table>

| Functional outcomes                                                 |            |
| Rate of percutaneous feeding tube dependence at 2 years             |            |
| Rate of tracheostomy dependence at 2 years                         |            |

| Quality-of-life outcomes and measurement scale used                 |            |
| Quality of life, anxiety, recreation, pain, saliva, dry mouth (xerostomia), swallowing, taste, and speech | |

| Toxicities                                                          |            |
| Mortality rates due to chemotherapy-induced neutropenia, rates of skin and mucosal toxicity, osteoradionecrosis, soft tissue necrosis, cerebellar necrosis, xerostomia | |

| Complications                                                       |            |
| Fistula formation, post-operative hemorrhage, hematoma formation, surgical-site infections, pneumonia | |

| Cost-effectiveness outcomes                                          |            |
| Cost of primary surgery +/- adjuvant radiotherapy +/- adjuvant chemotherapy Cost of primary chemoradiotherapy +/- salvage surgery QALY ICER | |

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