NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transoral carbon dioxide laser surgery for primary treatment of oropharyngeal malignancy

Tumours in the oropharynx (the part of the throat that includes the back of the tongue, the soft upper part of the back of the mouth and the tonsils) can be treated with combinations of surgery, radiotherapy and chemotherapy. Transoral carbon dioxide laser surgery uses laser energy to remove tumours in a procedure that is done through the open mouth.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2013.

Procedure name

- Transoral carbon dioxide laser surgery for primary treatment of oropharyngeal malignancy

Specialist societies

- British Association of Oral and Maxillofacial Surgeons
- British Association of Head and Neck Oncologists.

Description

Indications and current treatment

Malignancies in the oropharynx (which includes the tonsils, the base of the tongue and the soft palate) are usually squamous cell carcinomas originating in the epithelial cell lining. The incidence of these malignancies has increased significantly in younger patients, probably because of the increased prevalence of human papillomavirus infection. Presenting features include a persistent sore throat, a lesion in the mouth or throat, white or red patches that may be swollen or bleeding and pain in the ear. Patients tend to present with advanced or sometimes metastatic disease.

Patients with oropharyngeal cancers can be treated by surgery (using open or minimally invasive approaches for tumour resection and reconstruction), radiotherapy, chemotherapy, or a combination of these methods. Surgical resection may include neck dissection to remove lymph nodes. When the malignancy is considered to be unresectable, palliative chemotherapy and radiotherapy can be used. Treatment largely depends on tumour size, stage and histological assessment after surgery.

What the procedure involves

Transoral carbon dioxide (CO_2) laser surgery is a minimally invasive endoscopic approach for treating tumours in the oropharynx. It is usually performed under general anaesthesia, with the patient supine and tilted head-down. The tumours are visualised using a modified mouth gag and/or an endoscope. The carbon dioxide laser device is coupled to an operating microscope and the laser beam is used to excise the tumour completely, together with a reasonable margin of tissue all around it. Large tumours are removed in 2 or more pieces as multiblock resection.

Fibre-optic carbon dioxide lasers, flexible delivery systems and robots have been developed, all of which increase the range of angles of approach that can be used to achieve tumour resection.

Laser resection of tumours is sometimes combined with neck dissection if there is cervical lymphadenopathy or a suspicion of occult metastases. Adjuvant radiotherapy and/or chemotherapy is also offered to some patients, based on a number of factors such as T-stage, nodal status, extracapsular spread of tumour, margin status and histology.

Clinical assessment

Oropharyngeal tumours are staged by the Union Internationale Contre le Cancer (UICC): TNM Classification of Malignant Tumours. This classification is based on the depth of tumour invasion (T), lymph node involvement (N) and metastatic spread (M)[8].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transoral carbon dioxide laser surgery for primary treatment of oropharyngeal malignancy. Searches were conducted of the following databases, covering the period from their commencement to 23 July 2013: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with oropharyngeal malignancy.
Intervention/test	Transoral carbon dioxide laser surgery for primary treatment.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This IP overview is based on 558 patients from 4 prospective case series [1, 3, 5, 7], 2 retrospective case series [4, 2] and 1 retrospective comparative case series[6].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on transoral carbon dioxide laser surgery for primary treatment of oropharyngeal malignancy

Abbreviations used: AJCC, American Joint Committee of Cancer; AT, Adjuvant Therapy; CO_2, Carbon dioxide; CRT, Chemoradiotherapy; FOSS, Functional Outcome Swallowing Scale; HPV ISH, Human PapillomaVirus in situ hybridization; HR, hazard ratio; NA, Not Applicable; NED, No Evidence of Disease; ND, Neck Dissection; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; TLS, Transoral Laser Surgery; UICC, Union Internationale Contre le Cancer; W, watts.

Study details

Haughey BH (2011)[1]

Prospective case series

USA

Recruitment period: 1996-2006

Study population: patients with advanced oropharyngeal carcinoma (stage III and IV)

n = **204**

AJCC stage III 49; stage IV 155 (106 base of tongue, 98 tonsil + soft palate)

Age: mean 58 years (range 35-86)

Sex: 89% (181/204) male

Patient selection criteria: patients managed with TLS + neck dissections as primary management with curative intent, a biopsy proven AJCC stage III or IV oropharyngeal SCC (T3N0, T1-3N1, T4-4aN2, T4a, n3), with minimum follow-up of 2 years.

Technique: TLS (single excision or multiblock resection for large tumours) + ND in a single session (96%, 197/204) + adjuvant therapy in 74% (150/204) patients, 117 (58%) had RT alone, 33 (16%) had CRT.

Follow-up: **mean 48 months**

Conflict of interest/source of funding: not reported

Key efficacy findings

Number of patients analysed: **203 (53 TLS ± ND vs 150 TLS + ND + adjuvant treatment: radiotherapy 117; CRT 33)**

Overall survival (OS), Disease-specific survival (DSS) and disease-free survival (DFS) for the whole cohort (n=203)

Interval	OS % (95% CI)	DSS % (95% CI)	DFS % (95% CI)
2 year	89 (84-93)	91 (86-94)	85 (79-89)
3 year	86 (80-90)	88 (82-92)	82 (76-86)
5 year	78 (70-84)	84 (76-88)	74 (66-80)

Overall survival by use of adjuvant therapy

Adjuvant RT (in 117/150 patients) reduced the risk of death by >50% (HR 0.33-0.48) relative to receiving no adjuvant treatment (in 53/150 patients). Addition of chemotherapy to radiotherapy had no further risk reduction.

Overall survival prognostic factors: Low T classification (p=0.025), low N classification (p=0.006), negative margins (p=0.030), HPV ISH positivity (p=0.013), p16 staining positivity (p<.0001) and addition of any adjuvant therapy (p=0.047) were found to be significant factors to have an association with overall survival.

Disease free survival (DFS) by use of adjuvant therapy

Patients with adjuvant RT had a reduction of 62% in the risk of recurrence or death relative to those with no adjuvant therapy (HR=0.38; CI 0.20-0.73). Addition of chemotherapy to radiotherapy had no further risk reduction.

Disease free survival (DFS) prognostic factors: Age >75 years (p=0.0023), high N classification (p=0.048), positive margins (p=0.029), histologic tumour typing (p<.0001), HPV ISH positivity (p=0.0055), p16 positivity (p<.0001) and the use of adjuvant therapy

Key safety findings

Complications of TLS	n
Death (not treatment related, but due to myocardial infarction on day 17).	1
Bleeding (3 incidences on days 3, 6, 27 required return to the operating room, details of other 3 incidences not reported)	6
Airway lost in 1 patient during reresection of a positive margin, needed an operative cricothyrotomy.	1
Bilateral hypoglossal nerve paresis (stretch-related complication of endoscopic approach to the pharynx)	1
Postoperative velopharyngeal incompetence (not severe to prevent oral intake or good speech)	11
Tracheotomy at TLS	18%

Comments

Study design issues:

- 3 tertiary centres
- Postoperative HPV status: p16 was negative in 10% (18/185) and ISH histopathology was negative in 26% (44/174) patients.
- Swallow function was assessed by gastrostomy tube placement and FOSS (ranking from 0-5, with 0 being normal function and 4-5 being gastrostomy tube dependent).
- G-tube data is provided only for a subset of patients.

Study population issues:

- 3 cases of basoloid SCC and 1 adenoSCC were included.
- Patients with prior history of head and neck aerodigestive tract cancer or distant metastases were excluded.

Other issues:

- 3% (7/204) patients had open procedures for inaccessible tumours.

Abbreviations used: AJCC, American Joint Committee of Cancer; AT, Adjuvant Therapy; CO_2, Carbon dioxide; CRT, Chemoradiotherapy; FOSS, Functional Outcome Swallowing Scale; HPV ISH, Human PapillomaVirus in situ hybridization; HR, hazard ratio; NA, Not Applicable; NED, No Evidence of Disease; ND, Neck Dissection; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; TLS, Transoral Laser Surgery; UICC, Union Internationale Contre le Cancer; W, watts.

Study details

Key efficacy findings

(p=0.0088) were found to be significant factors to have an association with DFS.

Disease recurrence by type of postoperative adjuvant therapy (n=203)

12.7% (26/203) patients* had disease recurrence at any site and it occurred in more than 1 site in 4 patients.

	No adjuvant therapy n=53	Adjuvant RT (n=117)			CRT (n=33)	
Site of recurrence		**Primary alone n=4**	**Neck alone (n=45)**	**Primary + neck n=68**	**RT to primary +neck**	**Total**
Local^	5	2	1	0	0	8
Regional^	6	0	1	2	2	11
Distant ^^	4	1	3	3	1	12
Total	15	3	5	5	3	31

*12 patients had no adjuvant therapy, 12 had RT, and 2 had CRT,

^at a median interval of 10 months from surgery, ^^at a median interval of 14 months from surgery.

Swallowing function at 48 months (mean) (n=202)

FOSS score (0-5)	**No adjuvant therapy n (%)**	**Adjuvant RT n (%)**	**CRT n (%)**	**Total n**
0-2	**47 (90.0)**	**103 (88)**	**26 (78.7)**	**176**
3-5	**5 (9.6)**	**14 (12)**	**7 (21.0)**	**26**
Total	**52**	**117**	**33**	**202**

Significant differences in median FOSS score existed between treatment categories (p=0.0022), i.e. between patients with no adjuvant treatment and adjuvant RT alone (p=0.012) and between patients with no adjuvant treatment and CRT (p=0.0006).

Key safety findings

or within 30 days	(30/204)

Comments

Abbreviations used: AJCC, American Joint Committee of Cancer; AT, Adjuvant Therapy; CO_2, Carbon dioxide; CRT, Chemoradiotherapy; FOSS, Functional Outcome Swallowing Scale; HPV ISH, Human PapillomaVirus in situ hybridization; HR, hazard ratio; NA, Not Applicable; NED, No Evidence of Disease; ND, Neck Dissection; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; TLS, Transoral Laser Surgery; UICC, Union Internationale Contre le Cancer; W, watts.

Study details

Grant DG (2006)[2]

USA

Prospective case series

Recruitment period: 1997-2005

Study population: patients with pathologically confirmed untreated primary SCC of the tongue base (Tonsil 11, pharyngeal wall 10, epiglottis 4, vallecula, parapharyngeal space, soft palate 3 each, aryepiglottic fold, oral tongue 2 each, floor of the mouth, extraparapharyngeal space, pyriform sinus and laryngeal framework 1 each.

n=59

AJCC TNM staging: T1, 16; T2, 23; T3, 12 and T4, 8. Stage I, 4; II, 7; III, 12, IV, 36

Age: mean 65 years

Sex: 91% (54/59) male

Patient selection: biopsy proven untreated primary SCC of the tongue base

Technique: TLS with curative intent in all patients. Resection done in a piecemeal fashion under frozen control. A selective or modified radical neck dissection was performed n 83% (49/59) patients. 47% (28/59) had adjuvant radiotherapy.

Follow-up: mean 31 months

Conflict of interest/source of funding: none reported.

Key efficacy findings

Number of patients analysed: **59**

Oncologic results of TLS vs TLS combined with adjuvant RT

	Local recurrence ^ % (n)	Locoregional recurrence % (n)	Regional recurrence# % (n)	Distant metastases* % (n)
TLS +ND alone	10 (3/31)	0	3 (1/31)	3 (1/31)
Combined therapy	4 (1/28)	0	0	4 (1/28)
Total	7 (4/59)	0	2 (1/59)	3 (2/59)

^ At primary site between 6 and 22 months follow-up. * Patients had stage IV disease. # In a patient who had TLS alone with no ND.

Organ function (speech and swallowing) (pre and postoperative follow-up of 12 months or more; n=41)

The median preoperative FOSS stage was 0, (normal function) and at 1 year or more after treatment changed to stage 1 (normal function and symptomatic dysphagia). Combined therapy resulted in greater change in swallow stage than TLS alone. The median preoperative speech stage was 0 and at 1 year or more after surgery remained stage 0.

Key safety findings

No major complications

Complications	% (n)
Temporary tracheotomy* (16 for adequate airway at surgery, 2 for adequate tumour exposure, 2 postoperatively for airway obstruction, 1 to avoid hazardous intubation,1 for anticipated aspiration after extensive resection)	37 (22/59)
Permanent tracheotomy	2 (1/59)
Minor bleeding at1,7 and 14 days after surgery (no intervention needed)	5 (3/59)
Feeding tube at surgery	75 (47/59)
Long term tube feeding^	8 (5/59)

* 1 more had prior to surgery. ^ all had RT.

Comments

Study design issues:

- 2 tertiary care centres
- 11 patients declined adjuvant treatment.
- Organ function (speech and swallowing) before and after surgery was assessed using a clinical FOSS staging from 0 (normal function and symptomatic) to 5 (non-oral feeding for all nutrition) and Communication Scale (CS) staging from 0, normal speech to 5, no speech.

Study population issues:

- Contraindications include inadequate endoscopic access or tumour extension in presence of lymphadenopathy, or would cause risk of aspiration.

Abbreviations used: AJCC, American Joint Committee of Cancer; AT, Adjuvant Therapy; CO_2, Carbon dioxide; CRT, Chemoradiotherapy; FOSS, Functional Outcome Swallowing Scale; HPV ISH, Human PapillomaVirus in situ hybridization; HR, hazard ratio; NA, Not Applicable; NED, No Evidence of Disease; ND, Neck Dissection; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; TLS, Transoral Laser Surgery; UICC, Union Internationale Contre le Cancer; W, watts.

Study details	Key efficacy findings	Key safety findings	Comments
Eckel HE (1995)[3] Germany **Prospective case series** Recruitment period: 1986-1989 Study population: patients with oral and oropharyngeal carcinomas **(64 SCC of oral cavity, 53 SCC of oropharynx)** **n=117** Age: median 56 years Sex: 76% (89/117) male Patient selection criteria: histologically proven oral and oropharyngeal SCC, suitable for surgery, adequate tumour exposure, absence of bone invasion or deep invasion of primary, resectability of cervical metastases and no lymph node metastases. Technique: transoral laser resection (CO_2 laser in 113 patients and argon laser in 4 patients) of the primary tumour + staged ND (within 1-3 weeks) was performed in all patients. Argon laser was hand held and CO_2 laser was coupled with an operating microscope. Larger vessels that could not be coagulated by laser were managed by cautery or ligation. Excised area was allowed to heal by secondary intention. Additional postoperative radiotherapy was given 4-5 weeks later for patients with stage III and II disease. **Follow-up: median 56 months (range 36-85)** Conflict of interest/source of funding: none reported.	Number of patients analysed: **53** **Survival** **5-year survival in patients with oropharynx carcinomas (n=53)** Tumour-related 5-year survival is 86% for stage I and II cancers of the oropharynx and 65% for stage III disease of the oropharynx. **Local and regional control during follow-up** **Oropharynx** / **Recurrences* % (n)** / **Deceased % (n)** Soft palate: 24 (4/17) / 24 (4/17) Tonsil: 46 (12/26) / 35 (9/26) Posterior wall: 50 (1/2) / 50 (1/2) Base of tongue: 62 (5/8) / 62 (5/8) Total: 42 (22/53) / 36 (19/53) *some patients were treated by a second laser resection or salvage surgery. Some had radiotherapy or palliative treatment only.	**Complications for the whole cohort (n=117)** Postoperative bleeding (on 3rd, 5th and 6th day) reported in 3 patients with tumours in the oropharynx, required operative suture ligation. 2 patients with oral cancer had severe trismus (reduced mouth opening) after laser resection of buccal cavity carcinoma (not clear if this was due to scar contraction of the check or an early sign of recurrence).	**Follow-up issues:** All patients followed up for 3 years or more unless they died. **Study design issues:** • TNM staging according to AJCC staging system. • 5-year survival rates for stage IV disease for both oral and oropharynx cancers are presented together because of small numbers. Therefore not reported here. • Functional scores evaluated in a random subgroup of patients (with oral and oropharynx cancers). Therefore not reported. • Results not reported for oral cavity carcinomas as they are not the indication of this review.

Abbreviations used: AJCC, American Joint Committee of Cancer; AT, Adjuvant Therapy; CO_2, Carbon dioxide; CRT, Chemoradiotherapy; FOSS, Functional Outcome Swallowing Scale; HPV ISH, Human PapillomaVirus in situ hybridization; HR, hazard ratio; NA, Not Applicable; NED, No Evidence of Disease; ND, Neck Dissection; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; TLS, Transoral Laser Surgery; UICC, Union Internationale Contre le Cancer; W, watts.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Karatzanis AD (2012)[4]
Germany
Retrospective comparative case series
Recruitment period: 1976-2005
Study population: previously untreated patients with T1 oropharyngeal carcinoma (SCC) (sites: base of tongue (34), soft palate (83), tonsillar fossas (87), and lateral and posterior pharyngeal wall (19))
n= 223 (53 transoral CO_2 laser surgery (TLS) vs 170 electrocautery)
Age: mean 55.9 years
Sex: 82% (182/223) male
Patient selection criteria: patients with T1 oropharyngeal carcinoma and with minimum follow-up of 24 months.
Exclusion criteria: patients with previous treatments, systemic disease, second primary tumours at time of diagnosis and histology other than SCC.
Technique: standard transoral CO_2 laser surgery (resection) in 53 (23.7%) and simple use of electrocautery (en bloc resection) in 170 cases (76.2%) performed. Over all 76% (169/223) patients had NDs simultaneously or after histology assessments. 60% (134/223) patients received postoperative adjuvant treatment.
Follow-up: mean 65 months
Conflict of interest/source of funding: none reported.</td>
<td>Number of patients analysed: 53 vs 170

5-year disease-specific survival (DSS) and local control (LC) according to surgical technique
5-year DSS and LC were 89% and 95% for TLS and 87% and 91% for electrocautery (p>.05).</td>
<td>
<table>
<tr><th>Adverse event</th><th>TLS % (n)</th><th>Electro cautery % (n)</th></tr>
<tr><td>Bleeding (treated in operating room)</td><td>3.7 (2/53)</td><td>2.5 (4/170)</td></tr>
<tr><td>Aspiration</td><td>2 (1/53)</td><td>.58 (1/170)</td></tr>
<tr><td>Fistula</td><td>2 (1/53)</td><td>1.1 (2/170)</td></tr>
<tr><td>Nerve injury</td><td>0</td><td>.58(1/170)</td></tr>
<tr><td>Wound healing problem</td><td>0</td><td>1.1(2/170)</td></tr>
<tr><td>Total</td><td>7.5 (4/53)</td><td>5.8 (10/170)</td></tr>
</table>
Tracheostomy
<table>
<tr><th></th><th>TLS % (n)</th><th>Electrocautery</th></tr>
<tr><td>Temporary</td><td>7.5 (4/53)</td><td>2.3 (4/170)</td></tr>
<tr><td>Permanent</td><td>3.7 (2/53)</td><td>2.9 (5/170)</td></tr>
<tr><td>Total</td><td>11.3 (6/53)</td><td>5.3 (9/170)</td></tr>
<tr><td>Permanent gastrostomy</td><td>0</td><td>0</td></tr>
</table>
</td>
<td>Study design issues:
• 31 patients received postoperative chemotherapy in addition to radiotherapy.
• Biases include selection bias, various modifications made to treatment protocols over years.
• DSS and LC results according to anatomical sites were presented for all patients but not according to surgical technique. Therefore not reported here.
• Tumour clearance recurrence rates and status of surgical margins were given for all patients. Therefore not reported here.

Study population issues:
• Patients with early disease only included.
• Most common sites were tonsillar fossas and the soft palate.</td>
</tr>
</table>

Abbreviations used: AJCC, American Joint Committee of Cancer; AT, Adjuvant Therapy; CO_2, Carbon dioxide; CRT, Chemoradiotherapy; FOSS, Functional Outcome Swallowing Scale; HPV ISH, Human PapillomaVirus in situ hybridization; HR, hazard ratio; NA, Not Applicable; NED, No Evidence of Disease; ND, Neck Dissection; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; TLS, Transoral Laser Surgery; UICC, Union Internationale Contre le Cancer; W, watts.

Study details	Key efficacy findings	Key safety findings	Comments
Grant DG (2009)[5] **Retrospective case series** USA Recruitment period: 1996-2008 Study population: patients with previously untreated T1-T3, N0 to N2 SCC of the oropharynx of whom **74% (44/69) had no indication for adjuvant RT and 36% (25/69) had an indication for adjuvant RT to the neck but declined**. Primary tumour sites: tonsil 41% (28), tongue base 41% (28), pharyngeal wall 12% (8), soft palate 6% (4), and vallecula 1% (1). n = **69** Age: not reported Sex: 84% (58/69) male Patient selection criteria: previously untreated patients Technique: TLS for primary tumour resection in all patients and with selective or modified radical ND in 83% (59/69) patients using a microscopic mounted CO_2 laser or a hollow flexible fibre CO_2 laser (Omniguide) Excision performed either circumferentially or in a piecemeal fashion to ensure adequate surgical margins. Follow-up: **mean 44 months** Conflict of interest/source of funding: none reported.	Number of patients analysed: **69** **Overall and disease specific survival** * 21 patients had stage IVa disease. 11 patients were alive at last follow-up, 3 disease-related deaths, and 5 died of other causes, 1 lost to follow-up. **Local control:** 96% (66/69) patients had no recurrence at primary site. 4% patients (3/69) had recurrence at primary site between 9 and 21 months after surgery. All successfully salvaged with further TLS ± RT. 1 patient had multiple recurrences of carcinoma in situ at several sites within the oropharynx and was alive 6 years after primary surgery. **Locoregional control**: in TLS not indicated for AT, 9% (4/44) of recurrences in the neck were salvaged and disease free at last follow-up (2-7 years). In the AT declined group 16% (4/25) had recurrence. Overall 5-year local control rate was 94%. For T1 tumours it was 90% and 94% for T2 tumours. No statistically significant difference between recurrence rates in these groups. 5-year locoregional control rate in TLS not indicated for AT group was 82%, for stage I, II, III disease were 90%, 73% and 70% respectively. TLS for AT declined group was 74%. **Swallow function:** 71% (49/69) patients were alive and disease free at last follow-up. No patient required tracheostomy or a permanent feeding tube. 98% (48/49) patients had normal or near normal (stage 0 or 1) and 1 patient had a stage 2 swallow function (stable with a modified diet).	No major complications relating to TLS.	**Follow-up issues**: • 8 patients had less than 2 years' follow-up. Those lost to follow-up after recurrences were considered disease deaths. **Study design issues**: • 2 tertiary care centres • Patients with base of tongue tumour predominated in the group that declined RT. • 9 patients with N0 necks were only observed. 6 had ND at 21 and 30 days after TLS. • Swallowing function before and after TLS was assessed on a clinically relevant functional outcome swallow scale (baseline data not reported). **Study population issues**: • Contraindications include patient or tumour factors that might result in inadequate endoscopic access or tumour exposure. • Patients with contraindication to lengthy periods of GA, neck surgery were staged 3-4 weeks after TLS.

	Patients not indicated for AT n=44	Patients declined AT n=25*
5-year overall survival	86%	49 % (for stage IV)
Stage I & II; III & IV	79%, 86%	
Disease-specific survival stage I& II; III & IV	88%; 86%	72%

Adverse events	n
Death within 30 days (1 due to myocardial infarction in a CVD patient 2 days after surgery, 1 suicide 2 weeks, other 2 reasons not reported).	4
Acute aspiration after TLS (T2 tonsil, T3 tongue base tumours, both had tracheostomy tubes at surgery, recovered with normal swallow function at last follow-up).	2
Minor postoperative bleeding (after 14 days in a T3 tongue base tumour, needed no intervention).	1
Minor complications related to neck surgery	4

Abbreviations used: AJCC, American Joint Committee of Cancer; AT, Adjuvant Therapy; CO_2, Carbon dioxide; CRT, Chemoradiotherapy; FOSS, Functional Outcome Swallowing Scale; HPV ISH, Human PapillomaVirus in situ hybridization; HR, hazard ratio; NA, Not Applicable; NED, No Evidence of Disease; ND, Neck Dissection; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; TLS, Transoral Laser Surgery; UICC, Union Internationale Contre le Cancer; W, watts.

Study details

Steiner W (2003)[6]

Germany

Retrospective case series (single centre)

Recruitment period: 1986-1997

Study population: previously untreated histologically confirmed patients with SCC of the base of the tongue.

n=48

UICC/AJCC TNM staging:

T1, 1; T2, 12; T3, 7; T4, 28

N0, 15; N1, 9; N2, 24. 73% (34/48) were T3 and T4 tumours. 94% (45/48) were advanced stages III and IVa.

Age: mean 57years

Sex: 81% (39/48) male

Patient selection criteria:

Technique: TLS ± selective ND ± postoperative RT/ CRT with curative intent. A single laser incision perpendicular to one another that cross in the middle of the tumour was done in small lesions; in extended tumours more cuts into manageable pieces were performed. A second resection was done for positive margins. Unilateral or bilateral selective NDs were performed in 90% (43/48) patients and 48% (23/48) had adjuvant RT, 52% (12/23) had CRT.

Follow-up: median 47 months

Conflict of interest/source of funding: none reported.

Key efficacy findings

Number of patients analysed: **48**

Oncologic results of TLS + ND vs TLS + ND + postoperative RT (with/without chemotherapy)

	Local recurrences % (n)	Locoregional recurrences % (n)	Distant metastases % (n)	TNM-related recurrent disease % (n)
All patients				
Surgery alone (TLS + ND) (n=25)	20	28	0	28
Combined therapy (n=23)	9 (2/23)	17	13 (3/23)	26
T4				
Surgery alone (TLS +ND) (n=15)	27	33	0	33
Combined therapy (n=13)	8	23	23	38
Stage IVa				
Surgery alone (TLS +ND) (n=20)	20	25	0	25
Combined therapy (n=21)	10	19	14	29

Key safety findings

Postoperative complications

Adverse event	% (n)
Bleeding (within 7 days). Vessel localised at base of tongue in 1, lateral orpharyngeal wall in 1, aryepiglottis fold in 1, from wound cavity in 2 (managed by microparyngopharyngoscopy with electrocoagulation).	10 (5/48)
Gastric ulcer (treatment not reported).	1
Bilateral lung embolism to femoral vein thrombosis 1 day after SND (treated with heparin).	1
Severe dysphagia and recurrent aspiration (due to extended tumour resection including adjacent sites and structures) required gastrostomy tube.	6 (3/48)

83% (40/48) patients needed nasogastric tube feeding.

Comments

Study design issues:

- 79% of tumours (38/48) were moderately differentiated and 21% (10/48) were poorly differentiated.
- T4 tumours included extension to adjacent sites, subsites and structures.
- Tumours infiltrating the soft tissues of the neck were not treated transorally with curative intent.

Study population issues:

- Patients who underwent radiotherapy or chemotherapy alone, previous treatments, advanced unresectable disease, simultaneous distant metastases or second primary tumour were excluded.

Other issues:

- Local control, 5-year recurrence free and overall survival rates and performance status scores for normalcy of diet and understandability of speech are not reported as they are presented for all patients.

Abbreviations used: AJCC, American Joint Committee of Cancer; AT, Adjuvant Therapy; CO_2, Carbon dioxide; CRT, Chemoradiotherapy; FOSS, Functional Outcome Swallowing Scale; HPV ISH, Human PapillomaVirus in situ hybridization; HR, hazard ratio; NA, Not Applicable; NED, No Evidence of Disease; ND, Neck Dissection; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; TLS, Transoral Laser Surgery; UICC, Union Internationale Contre le Cancer; W, watts.

Study details	Key efficacy findings	Key safety findings	Comments
Deasi SC (2008)[7] **Prospective case series (pilot study)** USA Recruitment period: not reported Study population: patients with tumours of the upper aerodigestive tract (oropharynx and supraglottic larynx). n = **8** (with base of the tongue (2), palate (2), supraglottic (2) and tonsil (2); T1 and T2 lesions) Age: mean 60 years Sex: 86% (7/8) male Patient selection criteria: not reported Technique: transoral robotic surgery with the carbon dioxide (CO_2) flexible laser (Omniguide, 200μm spot-size, 10-14 W continuous mode). Robotic bipolar forceps was used (da vinci robot). Flexible CO_2 laser was placed on the tip of the robotic arm to allow 360^o manipulation. Follow-up: **mean 4.0 months** Conflict of interest/source of funding: not reported.	Number of patients analysed: **8** Seven patients successfully underwent transoral robotic tumour resection. In 1 patient access to the supraglottic larynx site could not be gained and converted into a standard CO_2 laser procedure for tumour resection. Final pathology revealed 7 patients with squamous cell carcinoma and 1 patient with adenocystic carcinoma. **Tumour clearance** Negative frozen section margins were confirmed in all 7 patients. **Recurrence** No evidence of recurrence in any of the 6 patients with tumours of the oropharynx. All 6 patients with tumours of the oropharynx were able to tolerate a clear or soft diet on postoperative day 1 while the supraglottic laryngeal cancer patient tolerated a clear diet on postoperative day 3.	No patients experienced airway problems or signs of aspiration. No intraoperative or postoperative complications. Tracheostomy was performed in 1 patient with a supraglottic laryngeal cancer.	**Study population issues**: • Limited patients. Of these 2 patients had tumours in the supraglottic larynx (not the indication for present review) • Neck dissections and reconstructions were performed in 71% (5/7) and 86% (6/7) patients.

Efficacy

Survival

A prospective case series of 204 patients (of whom 203 were analysed) with stage III and IV oropharyngeal cancers treated by transoral carbon dioxide laser surgery (TLS) ± neck dissection (ND) alone (53 patients) or by TLS±ND and combined adjuvant treatment (150 patients: 117 radiotherapy alone, 33 chemoradiotherapy) reported that 5-year overall survival, disease-specific survival and disease-free survival were 78%, 84% and 74% respectively across all groups. TLS combined with postoperative adjuvant radiotherapy (in 117/204 patients) reduced the risk of death by >50% (hazard ratio [HR] 0.33–0.48) relative to receiving TLS±ND alone (in 53/204 patients). Patients with adjuvant radiotherapy had a reduction of 62% in the risk of recurrence or death relative to those with no adjuvant therapy (HR=0.38; CI 0.20 to 0.73). The addition of chemotherapy to radiotherapy had no further risk reduction[1].

A prospective case series of 117 patients (with 53 oropharyngeal squamous cell carcinoma [SCC] patients) treated by TLS ± ND combined with radiotherapy reported that tumour-related 5-year survival is 86% for stage I and II disease of the oropharynx and 65% for stage III disease of the oropharynx[3].

A retrospective comparative case series of 223 patients with T1 oropharyngeal carcinoma treated by TLS ± ND (n=53) or electrocautery (n=170) reported that 5-year disease-specific survival was 89% for TLS ± ND and 87% respectively, for electrocautery (p value not significant)[4].

The retrospective case series of 69 patients treated by TLS + ND reported that the 5-year overall survival was 86% in patients without an indication for adjuvant radiotherapy (n=44). The 5-year overall survival for stage I and II and stage III and IV were 79% and 86%. Disease-specific survival for stage 1 and II and stage III and IV were 88% and 86% respectively. The 5-year overall survival rate for stage IV patients with an indication for radiotherapy but declined (n=21) was 49% and the 5-year disease-specific survival was 72%[5].

Local control

The retrospective comparative case series of 223 patients with T1 oropharyngeal carcinoma treated by TLS ± ND (n=53) or electrocautery (n=170) reported that 5-year local control rate was 95% for TLS ± ND and 91% for electrocautery (p value not significant) [4].

The retrospective case series of 69 patients with previously untreated SCC (T1 to T3, N0 to N2) of the oropharynx treated by TLS ± ND reported that 96% (66/69) patients had no recurrence at primary site at a mean follow-up of 44 months. The overall 5-year local control rate was 94%[5].

Tumour clearance

The retrospective case series of 69 patients with previously untreated SCC (T1 to T3, N0 to N2) of the oropharynx treated by TLS ± ND reported that tumour clearance was achieved in 96% (66/69) patients at a mean follow-up of 44 months[5].

Recurrence

The retrospective case series of 69 patients with previously untreated SCC (T1 to T3, N0 to N2) of the oropharynx treated by TLS ± ND reported that 4% (3/69) patients had disease recurrence at the primary site at a mean follow-up of 44 months. The overall 5-year locoregional control rate in patients without an indication for adjuvant therapy was 82%. The 5-year local regional control in patients who declined adjuvant therapy was 74%. There was no statistical significant difference in locoregional control between groups[5].

A prospective case series of 59 patients with SCC of the base of the tongue treated by TLS + ND (in 83% patients) + radiotherapy (in 47% patients) reported that the incidence of local recurrence appeared to be lower (4%, 1/28) in the TLS + adjuvant therapy group than in the TLS + ND group (10%, 3/31) at a mean follow-up of 31 months. Overall 7 patients presented with disease recurrence and distant metastasis was reported in 2 patients with stage IVa disease. Regional recurrence was reported in 1 patient who had TLS with no ND[2].

A retrospective comparative case series of 48 previously untreated patients with SCC of the base of the tongue treated by TLS ± ND (in 43 patients) + radiotherapy with or without chemotherapy (in 23 patients) reported that the incidence of disease recurrence (local and locoregional) was less (local recurrence 9%, locoregional recurrence 17%) in the combined therapy group (n=23) than with TLS + ND group (local control 20%, locoregional control 18%) (n=25) at a median follow-up of 47 months. Distant metastases occurred in 13% (3/23) patients in the combined therapy group but did not occur in the patients who had TLS ± ND[6].

Functional results (swallowing and speech)

A prospective case series of 204 patients with stage III and IV oropharyngeal cancers treated by TLS ± ND and combined adjuvant treatment reported that functional outcome swallowing scale (FOSS) scores were 0 to 2 (either normal swallowing or mild dysphagia, without weight loss or aspiration) in 87% (176/203) patients and 3 to 5 (either dysphagia, aspiration or gastrostomy tube dependent) in 13% (26/203) patients at a mean follow-up of 48 months. The proportion of patients with FOSS score 0 to 2 was highest in those receiving no adjuvant treatment (90%, 47/176), followed by those treated with radiotherapy alone (88%, 103/176) and chemoradiotherapy (78.7%, 26/176). Significant differences in median FOSS score were reported between different treatments (p=0.0006) – that is, between patients with no adjuvant treatment and adjuvant radiotherapy alone (p=0.012) and between no adjuvant treatment and chemoradiotherapy (p=0.0006)[1].

The prospective case series of 59 patients with SCC of the base of the tongue treated by TLS + ND (in 83% patients) + radiotherapy (in 47% patients) reported that the median preoperative functional outcome swallowing scale (FOSS) score was 0, (normal function) and at 1 year or more after treatment changed to 1 (normal function with episodic or daily symptoms of dysphagia) in 41 patients. Combined therapy resulted in greater change in swallow score than TLS ± ND. The median preoperative speech stage on a communication scale was 0 (normal speech) and at 1 year or more after surgery remained 0[2].

The retrospective case series of 69 patients with previously untreated SCC (T1 to T3, N0 to N2) of the oropharynx treated by TLS ± ND assessed swallowing function (on a functional outcome swallow scale) in 71% (49/69) patients without any disease recurrence. The study reported that 97% (48/49) patients had stage 0 or 1(normal or near normal) swallow function and one patient had stage 2 swallow function (stable with a modified diet only) at a mean follow-up of 44 months[5].

Safety

Haemorrhage

Bleeding within the first 7days after the procedure was reported in 10% (5/48) of patients in the retrospective case series of 48 patients with SCC of the base of the tongue treated by TLS ± ND ± adjuvant radiotherapy. The bleeding was from a vessel at the base of the tongue in 1 patient, at the lateral oropharyngeal wall in 1 patient, at the aryepiglottic fold in 1 patient, and from the wound cavity in 2 patients (no further details given). All complications were managed by micropharyngoscopy with electrocoagulation[6].

Dysphagia and aspiration

Severe dysphagia and recurrent aspiration were reported in 6% (3/48) of patients in the retrospective case series of 48 patients, as a result of extended tumour resection including ‘resection in adjacent sites and structures’. All 3 patients needed gastrostomy tubes[6].

Acute aspiration after TLS was reported in 2 patients (with T2 tonsil, T3 tongue base tumours) in the retrospective case series of 69 patients. Both had tracheostomy tubes at surgery, but had recovered with normal swallow function at last follow-up[5].

Loss of airway

Airway loss (needing surgical cricothyroidotomy) was reported in 1 patient in the prospective case series of 204 patients; this occurred during reoperative resection of a tumour-positive margin[1].

Tracheostomies (permanent or temporary) were needed in 11% (6/53) of patients in theTLS group and 5% (9/170) of patients in the electrocautery group in the retrospective comparative case series of 223 patients (no significance test reported)[4].Permanent tracheotomy was needed in 1 patient in the prospective case

series of 59 patients with T1 oropharyngeal carcinoma and temporary tracheostomies were needed in 37% (22/59) of patients [5].

Fistula formation

Fistula formation was reported in 1 patient in the TLS group (n=53) and 2 patients in the electrocautery group (n=170) in the retrospective comparative case series of 223 patients with T1 oropharyngeal carcinoma at a mean follow-up of 65 months. Further details were not reported[4].

Other

Gastric ulceration was reported in 1 patient in the retrospective case series of 48 patients treated by TLS ± ND ± adjuvant radiotherapy. Further details were not reported[6].

Bilateral hypoglossal nerve paresis (due to 'stretch-related complication' of the endoscopic approach to the pharynx) was reported in 1 patient in the prospective case series of 204 patients with stage III and IV oropharyngeal carcinomas. Postoperative 'velopharyngeal incompetence' (not severe enough to prevent oral intake or good speech) was also reported in 11 patients. Further details were not reported[1].

Validity and generalisability of the studies

- No prospective randomised controlled trials evaluating TLS alone for oropharyngeal tumour resection.
- Very few prospective studies evaluating outcomes after treatment with TLS plus neck dissection.
- Only 1 retrospective study comparing transoral laser surgery with electrocautery for oropharyngeal tumours particularly in terms of survival and local and regional control.
- Evaluating the evidence supporting efficacy of TLS as a single treatment over other treatments is complicated by different combination treatment approaches.
- Many papers on multimodal treatment approaches for advanced stage oropharyngeal cancers are presented in appendix A.
- Studies mainly evaluated survival according to TNM classification but not according to localisation of primary tumour.
- None of the studies reported quality of life outcomes.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Tonsillectomy using laser. NICE interventional procedure guidance IPG186 (2006). Available from www.nice.org.uk/guidance/IPG186
- Tonsillectomy using ultrasonic scalpel. NICE interventional procedure guidance IPG178 (2006). Available from www.nice.org.uk/guidance/IPG178
- Electrosurgery (diathermy and coblation) for tonsillectomy. NICE interventional procedure guidance IPG150 (2005). Available from www.nice.org.uk/guidance/IPG150
- Coblation tonsillectomy. NICE interventional procedure guidance 9 (2003) Available from www.nice.org.uk/guidance/IPG9

Clinical guidelines

- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005) (last modified April 2011) Available from www.nice.org.uk/guidance/CG27
- Improving outcomes in head and neck cancers: the manual. NICE cancer service guidance (2004) Available from www.nice.org.uk/guidance/CSGHN

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Mr Ceri Hughes, Mr Cyrus Kerawala (British Association of Head and Neck Oncologists); Mr Michael Bater, Mr Michael Fardy (British Association of Oral and Maxillofacial Surgeons); Mr Colin Hopper (British Medical Laser Association)

- Two specialist advisers perform this procedure regularly; 1 has performed it at least once and 2 have not performed this procedure before but have taken part in patient selection or referral.
- All advisers considered it as an established procedure and no longer new.

- The main comparators for this procedure are chemoradiotherapy, open surgery (via oral route or lip split mandibulotomy), diathermy or transoral robotic surgery.
- Four advisers stated that 10-50% of specialists are engaged in this work. One adviser stated that more than 50% specialists are involved in this work.
- The use of the carbon dioxide laser with robotic surgery is thought to be the most recent development.
- Theoretical adverse events listed include collateral damage from lasers to surrounding tissue or staff, damage to oral cavity or teeth via access retraction and inadequate surgical margins
- Key efficacy outcomes listed include survival, local control, margin control, local recurrence, functional outcomes (swallowing and voice) and quality of life.
- One specialist adviser stated there is insufficient evidence to show that transoral lasers are preferable than radiotherapy. Other uncertainties listed include adequate surgical clearance, disease free survival and long term survival.
- Four advisers stated that specific training is required in head and neck cancer surgery and the safety of lasers. One adviser stated that laser safety officers are needed for institutions performing this procedure and one of these advisers stated that proper theatre facilities and equipment are needed.
- The procedure is likely to be performed in regional head and neck units and satellite units as part of a cancer network, with agreed clinicians in most district general hospitals. The procedure is already in wide spread use in ENT departments and likely impact on NHS resources in thought to be moderate. One adviser stated that there is a possibility that it may increase the numbers of patients treated if it became available to oral and maxillofacial surgery departments generally across the UK.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- Ongoing trials:
  - NCT01355926; Flexible Fiber-based **CO_2 Laser** Versus Monopolar Cautery for Resection of Benign, Pre-malignant And Malignant Oral Cavity Lesions: A Single Center Randomized Controlled Trial Assessing Pain and Quality of Life Following Surgery; estimated enrolment: 68; location: USA; estimated completion date: May 2014.
  - NCT01276418; ENT FiberLase **CO_2** Study (other device name: Acupulse WG **CO_2 Laser)**; study type: open label single group assignment (treatment is performed transorally (through the mouth) for oral or laryngeal indications in the field of Ear, Nose and Throat (ENT); location: Belgium, Italy; estimated enrolment: 50; completion date March 2012. Not recruiting participants.

References

1. Haughey BH, Hinni ML et al (2011). Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. Head & Neck 33 (12) 1683-1694.

2. Grant DG, Hinni ML et al (2009). Oropharyngeal cancer: a case for single modality treatment with transoral laser microsurgery. Archives of Otolaryngology Head & Neck Surgery 135 (12) 1225-1230.

3. Grant DG, Salassa, JR et al (2006). Carcinoma of the tongue base treated by transoral laser microsurgery, part one: Untreated tumors, a prospective analysis of oncologic and functional outcomes. Laryngoscope 116 (12) 2150-2155.

4**.** Steiner W, Fierek O et al (2003).Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. Archives of Otolaryngology -- Head & Neck Surgery 129 (1) 36-43.

5. Karatzanis AD, Psychogios G et al (2012). Surgical management of T1 oropharyngeal carcinoma. Head and Neck.34 (9) 1277-1282.

6. Eckel HE, Volling P et al (1995). Transoral laser resection with staged discontinuous neck dissection for oral cavity and oropharynx squamous cell carcinoma. Laryngoscope 105 (1) 53-60.

7. Desai SC, Sung CK et al (2008). Transoral robotic surgery using a carbon dioxide flexible laser for tumors of the upper aerodigestive tract. Laryngoscope.118 (12) 2187-2189.

8. Sobin LH, Wittekind C, editors. TNM Classification of Malignant Tumours. 6th Edition ed. Hoboken, NJ: Wiley; 2002.

Appendix A: Additional papers on transoral carbon dioxide laser surgery for primary treatment of oropharyngeal malignancy

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Canis M et al (2012) Impact of elective neck dissection vs observation on regional recurrence and survival in cN0-staged patients with squamous cell carcinomas of the upper aerodigestive tract. Archives of Otolaryngology -- Head & Neck Surgery 138 (7) 650-55.	n=202 Retrospective case series Patients with previously untreated squamous cell carcinoma of the upper aerodigestive tract (T1-T4). Transoral laser surgery and selective neck dissection (SND) vs observation (with curative intent). Follow-up: 5 years	In the SND group, 15% of occult metastases were found. In pN0 necks we found 4 late metastases (4%), and in pN+ necks, 1 recurrent neck metastasis (7%) (pT1-pT2) (n = 109). In pT3-pT4 tumors (n = 93), 5 late neck metastases (5%) were observed. The wait-and-see group comprised 7 late metastases (4%) in patients with pT1-pT2 tumors (n = 171) and 9 late metastases (17%) in patients with pT3-pT4 tumors (n = 52). In early-stage T1-T2 tumors, the 5-year recurrence-free survival rate was 95% in the neck dissection group and 96% in the wait-and-see group. Advanced stages T3 to T4 presented rate of 90% in the neck dissection group and 75% in the wait-and-see group. In early-stage T1-T2 tumors, the 5-year overall survival rate was 83% in the neck dissection group and 72% in the wait-and-see group. Advanced T3-T4 categories showed rates of 58% in the neck dissection group and 60% in the wait-and-see group	Different tumour sites included (oral cavity, oropharynx, hypopharynx, larynx subglottic, larynx glottis). Only oropharynx tumours (n=41) are relevant to this review but the subgroup analysis was presented separately for oropharynx primary tumours.
Canis M et al (2013) Oncologic and functional results after transoral laser microsurgery of tongue base carcinoma. European Archives of Oto-Rhino-Laryngology.270 (3) 1075-83.	n=82 Retrospective case series Previously untreated SCC of base of tongue. TLS only (6) +ND (75) +adjuvant therapy (45) Follow-up: median 51 months	The results were Kaplan-Meier 5-year local control rate for all patients was 84 %. T-stage-related local control rate after 5 years was 94 % for stage I-II, 78 % for stage III and 81 % for stage IV. 5-year overall survival and recurrence-free survival were 59 and 69 %, respectively. UICC stage-related overall survival and recurrence-free survival were 70 and 86 % for stage I-II, 44 and 54 % for stage III and 58 and 69 % for stage IV. Postoperative bleeding at the primary tumor site occurred in 9 patients (11 %). Gastrostomy tubes remained in place permanently in 5 patients (6	Combined treatment approach. Results not reported separately for TLS only/ND patients.

		%).	
Canis M et al (2013) Results of transoral laser microsurgery in 102 patients with squamous cell carcinoma of the tonsil. European Archives of Oto-Rhino-Laryngology 270 (8) 2299-2306.	n=102 Retrospective case series patients with SCC of the tonsil TLS +ND (95%) and postoperative radiotherapy (66%) Follow-up: median 63 months	5-year Kaplan-Meier local and loco-regional control was 78% for pT1 and pT2 and 75% for pT3 and pT4a tumors. 5-year Kaplan-Meier disease-free survival, recurrence-free survival, and overall survival and was 74, 64 and 59% for stage I and II, 68, 60 and 56% for stage III and IVa, respectively. Our data supports the conclusion, that TLS should be considered as a therapeutic option for the treatment of cancer of the tonsil. The oncological and functional results are comparable to any other treatment regimen, while the morbidity and complications tend to be lower.	Combined treatment approach. Results not reported separately for TLS only/ND patients. Only 3 patients with TLS alone.
Camp AA et al (2009) Functional and oncologic results following transoral laser microsurgical excision of base of tongue carcinoma. Otolaryngology - Head & Neck Surgery 141 (1) 66-69.	n=71 Base of tongue carcinoma Retrospective case series TLS in all +ND +Adjuvant therapy in 68 Follow-up: 24 months	Of the 71 patients treated, one (1.4%), nine (12.7%), seven (9.9%), and 54 (76.1%) were stage I, II, III, and IV, respectively, at diagnosis. At 24 months, overall survival was 90 percent; disease-specific survival was 94 percent. Locoregional recurrence occurred in 10 percent. Given the low number of deaths, no significance was detectable between survival and gender, overall stage, tumor size, nodal status, or adjuvant therapy. Quality-of-life data, obtained for 46 patients, revealed the majority of patients had mild or no pain, minimally impaired to normal swallowing, and normal speech.	Combined treatment approach. Results not reported separately for TLS only/ND patients.
Carney AS et al (2008) Radiofrequency coblation for the resection of head and neck malignancies. Otolaryngology - Head & Neck Surgery 138 (1) 81-85.	Retrospective case series n=40 SCC of head and neck (of these only 10 oropharynx tumours) 20 radiofrequency coblation vs 20 co2 laser resection Follow-up: postoperative	Coblation proved to be an effective method for resection of selected head and neck malignancies. It allows for much faster resection times than the CO(2) laser (P = 0.017) especially in the oropharynx (P = 0.007), but the large probes currently available can cause problems in assessment of adequate resection margins.	Only median resection times reported each type of tumours according to type of resection.

Cengiz M et al (2006) In regards to: Adjuvant radiotherapy after transoral laser microsurgery for advanced squamous cell carcinoma of the head and neck by Pradier et al. (Int J Radiat Oncol Biol Phys 2005; 63:1368-1377). International Journal of Radiation Oncology, Biology, Physics 65 (3) 955-56.	n=208 Retrospective case series Patients with advanced NHSCC (stage III or IV) Postoperative adjuvant radiotherapy after transoral laser resection of primary tumours (oral cavity 38, oropharynx 88, larynx 36, hypopharynx 46).		Letter and reply on an article by Pradier et al (2005) on combined treatment for different types of HNSCC.
Christiansen H et al (2006). Long-term follow-up after transoral laser microsurgery and adjuvant radiotherapy for advanced recurrent squamous cell carcinoma of the head and neck. International Journal of Radiation Oncology, Biology, Physics 65 (4) 1067-1074.	n=37 Patients with advanced local recurrent head and neck squamous cell carcinoma (HNSCC) without distant metastases Transoral co2 laser microsurgery followed by adjuvant radiotherapy after (with curative intent). Follow-up: median 124 months	The 5-year overall survival rate was 21.3%, the loco-regional control rate 48.3%, respectively. In multivariate analysis, stage of original primary tumor (Stage I/II vs. Stage III/IV), and patient age (<58 years vs. >or=58 years) showed statistically significant impact on prognosis. In laryngeal cancer, larynx preservation rate after treatment for recurrent tumor was 50% during follow-up	Combined treatment for different types of HNSCC. Primary sites (oral cavity in 3, oropharynx 13, hypopharynx 5, larynx 16).
Eckel HE (1995). Transoral laser surgery for oral carcinoma. Advances in Oto-Rhino-Laryngology 49 185-190.	n=117 Case series Oral and oropharynx tumours Transoral laser surgery of primary tumour and staged discontinuous neck dissection (ND) Postoperative radiotherapy in stage III and IV patients Follow-up: min 3 years.	The cure rates of these combined procedures is comparable to those after radical extraoral surgery. These 2 minor interventions cause less morbidity and excellent functional results.	Combined treatment approach.
O Flynn P (2010) The first UK report of the applications of flexible CO laser in head and neck surgery: how we do it. Clinical Otolaryngology 35 (2) 139-42.	Case series n=9 (only 3 base of tongue and vallecula tumours: 2 SCC, 1 adenocarcinoma are relevant to this review) Patients with tumours in 3 different sites within the head and neck (the glottis and supraglottis (5), base of the tongue (3) and postnasal space (1)).	All tumours were completely excised with adequate safety margins and minimal repositioning of the tongue and laryngoscope. The visibility was better due to the use of telescope. All 3 patients had postoperative radiotherapy to the neck and base of tongue. No recurrence at 9 months follow-up. No patients experienced airway	Only 3 patients. Larger studies included in table 2. 5 other patients had laryngeal tumours and 1 had a tumour in the postnasal space (not the indications for present review).

	Transoral flexible CO2 laser for local resection with an angulated telescope (Hopkins telescope).	problems or signs of aspiration. No intraoperative or postoperative complications. Tracheostomy was performed in 1 patient with a supraglottic laryngeal cancer.	
Haughey BH and Sinha P (2012). Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer. Laryngoscope 122 Suppl-33.	Retrospective case series n=171 Patients with oropharynx cancer (base of tongue, tonsil) TML for untreated primary tumour with neck dissection (n=165) and adjuvant therapy (n=142) Follow-up: median 47 months	The 3- and 5-year Kaplan-Meier estimates for disease free survival (DFS) were 91% and 88%, respectively, whereas for disease specific survival (DSS) they were 95.5% and 94.4%, respectively. A total of 12 (7%) recurrences occurred: two local, four regional, and six distant. Of all T-stage categories, pT4 tumors were strongest predictors of poorer DFS. cT4 tonsil primaries, ever smoking status, three or more metastatic nodes, pN2b+ stage, and radiation-based adjuvant therapy were other prognosticators for DFS. Angioinvasion and T3-T4 tumors were prognostic for reduced DSS, although smoking parameters were not. Extracapsular spread, N stage, and margins were nonprognosticators. Recursive partitioning analysis defined high- and low-risk groupings of prognosticators. Downstaging of clinical T stage was observed for 31% of tumors on application of pathological classification.	Combined treatment approach (transoral co2 laser surgery + neck dissection+ adjuvant therapy)
Haughey B et al (2012). Reply, Comparison of transoral laser microsurgery and nonsurgical approaches for management of oropharyngeal cancer. Head and Neck.34 (8) (pp 1199-1202), 2012.Date of Publication: August 2012. (8) 1199-1202.2012.			Reply to a letter on an article (Haughey et al 2011).

Holsinger FC et al (2006). Use of the photonic band gap fiber assembly CO2 laser system in head and neck surgical oncology. Laryngoscope 116 (7) 1288-90.	Case reports USA n = 3 (only 1 base of tongue tumour is relevant to this review) Technique: mucosal biopsy performed in the base of tongue using transoral suspension micropharyngoscopy with Omniguide flexible CO_2 laser (photonic band gap fiber) in a 57 year man. Laser was used in both superpulsed and continuous modes. Output ranged from 2-8W.	Aspiration biopsy revealed metastatic SCC. However, no primary tumour was found on previous examinations (direct biopsies, CT or clinical). A small lesion of the glossopharyngeal sculus was found by palpitation and microscopic visualization. A large biopsy specimen was obtained in this area which difficult to visualise with minimal bleeding. The patient completed radiotherapy and was free of disease 3 months after treatment.	Larger studies included in table 2. 2 patients had laryngeal tumours (not the indication for present review).
Jackel MC (2006). Platysma myofascial flap for reconstruction of oropharyngeal defects after transoral laser microsurgery of locally advanced carcinomas. Journal of Laryngology & Otology 120 (12) 1055-58.	n=6 Patients with locally advanced carcinomas of the lateral oropharynx (tonsillar cancers) neck dissection followed by transoral co2 laser surgery with flap reconstruction. All patients had adjuvant radiotherapy. Follow-up: mean 24.8 months	All tumours were completely resected. Intra- and post-operative bleeding complications requiring blood transfusion or surgical revision did not occur. None of the patients developed a cervical fistula., no local and/or regional recurrence was observed. The described approach is oncologically safe and seems to ensure reliable protection of neck vessels during and after transoral laser resection of locally advanced oropharyngeal carcinomas, as well as to prevent fistula formation.	Combination of co2 laser surgery with flap reconstruction.
Kutter J et al (2007). Transoral laser surgery for pharyngeal and pharyngolaryngeal carcinomas. Archives of Otolaryngology -- Head & Neck Surgery 133 (2) 139-44.	n=55 Case series Pharyngeal and pharyngolaryngeal SCC tumours Transoral Co2 laser microsurgery (TOLS) +neck dissection (n=43)+ adjuvant radiotherapy (n=18). second TOLS in 15 patients. Follow-up: median 24 months	Local control rate was 90% and overall survival rate was 78%. There were 16 early postoperative complications: recurrent aspiration pneumonia (n = 7); laryngeal obstruction, which required tracheotomy (n = 3); severe postoperative hemorrhage (n = 2); and cervical emphysema, which resolved spontaneously (n = 4). Feeding tubes were necessary in 37 patients. removed after a median 7 days. The median pain score was 4 of 10 during the first postoperative week and 0 of 10 after 4 weeks. The median hospital stay was 13	Combined treatment approach and also location of tumours in different sites (epiglottis, laryngeal rim, piriform sinus and oropharynx). Only 15 patients had tumours in the oropharynx. Results not reported separately.

		days (15 days for patients with neck dissection).	
Luna-Ortiz K et al (2013). Soft palate preservation after tumor resection with transoral laser microsurgery. Medicina Oral, Patologia Oral y Cirugia Bucal.18 (3) e445-e448.	n=3 Case series patients with minor salivary gland tumours (>3cm) Transoral Co2 laser microsurgery. Follow-up: 12-18 months	Soft palate function was preserved and reconstruction performed with primary closure. Patients began oral feeding and discharged same day. All patients were alive and disease free at 12, 14 and 18 months and no functional impairment. One patient had adjuvant radiotherapy due to tumour grade.	Limited cases. no new safety events
Lippert BM et al (2003). Wound healing after laser treatment of oral and oropharyngeal cancer. Lasers in Medical Science.18 (1) 36-42.	n=24 Patients with oral or oropharynx cancer Laser surgery (co2 and ND Yag laser)	The histological findings showed that the beginning of wound healing was delayed after laser surgery. The duration of wound healing after laser surgical tumour resection revealed a clear dependence on the size of the initial defect. The average duration of wound healing after CO₂ laser surgery (32.8 +/- 9.2 days) was significantly shorter than after Nd:YAG laser surgery (40.4 +/- 9.2). Due to the more pronounced zone of necrosis at the base of the wound ground this effect is more evident using the Nd:YAG laser. However, the different course of wound healing with both laser systems does not seem to have a negative influence on functional results.	Course of wound healing assessed.
Magill JC et al (2010). Inflammatory myofibroblastic tumour of the tonsil: case report and literature review. Journal of Laryngology & Otology 124 (10) 1123-25.	n=1 Case report Pregnant woman with inflammatory myofibroblastic tumour of the tonsil (grade 2) Co2 laser excision. Follow-up: 13 months	Histologically clear margins obtained. No complications of surgery, uneventful pregnancy. Free of disease at 13 months.	Case report No new safety events.
Market Velker BA et al (2012). Adenocarcinoma not otherwise specified on dorsum of tongue: case report and literature review. Current Oncology 19 (5) e358-e363.	n=1 Adenocarcinoma of the base of the tongue, minor salivary gland origin. Laser excision + radiotherapy	No evidence of recurrence at 1 month and no evidence of disease at 6 years follow-up.	Larger studies included in table 2.

	Follow-up: 6 years		
McGrew RN and Graham SS (1981). Clinical applications of the CO2 laser in neoplastic lesions of the aerodigestive tract. Southern Medical Journal 74 (7) 802-4.	n=14 Case series Neoplastic lesions in aerodigestive tract. Co2 laser resection (primary mode) in combination with irradiation and chemotherapy Follow-up: 2-24 months	Local control of the neoplasms achieved. Vascular tissue of the tongue proved to be an excellent receptor for laser treatment.	Variety of lesions in different sites (oral cavity, pharynx and larynx). Only 2 primary tumour resections with no irradiation (no evidence of disease at 13 and months).
Mejia-Hernandez IJ et al (2013). Malignant myoepithelioma of the soft palate. Larynx 40 (2) 231-34.	n=1 Case report Patient with malignant myoepithelioma of the soft palate Transoral resection with a microscope and co2 laser.	Soft palate function was preserved intact. No complications and patient discharged on same day. Excellent postoperative evolution with no alternations of phonation or swallowing.	Case report No new safety events.
Ossoff RH et al (1983) CO2 laser in otolaryngology-head and neck surgery: A retrospective analysis of complications. Laryngoscope.93 (10) 1287-89.	n=204 Retrospective review co2 laser surgery in patients with head and neck cancers (oral cavity, 47, pharynx 8)	4 complications related to tongue excisions. These included enamel burn in 1 patient, postoperative airway obstruction in 2 and lip burn in 1 patient. All resolved after reintubation or antibiotic treatment.	No new safety issues.
Panje WR et al (1989) Transoral carbon dioxide laser ablation for cancer, tumors, and other diseases. Archives of Otolaryngology -- Head & Neck Surgery 115 (6) 681-88.	n=71 Patients with oral cavity or oropharyngeal cancers (premalignant-11, benign-14, malignant-32, other-11, palliation-3, leukoplakia 6) co2 laser excision Follow-up: 2 years	The use of this modality for treatment of these conditions is highly successful, with excellent preservation of oral and pharyngeal function and minimal patient morbidity. Deep excisions of tumors that could lead to restricted motion of the tongue and/or jaw tended to have an adverse effect on both speech and swallowing.	Variety of lesions included. Multimodal treatment approach in some patients (28 had radiation therapy before or after co2 laser excision. 6 had neck dissections). Results not reported separately for each modality.
Pradier O et al (2005). Adjuvant radiotherapy after transoral laser microsurgery for advanced squamous carcinoma of the head and neck. International Journal of Radiation Oncology, Biology, Physics 63 (5) 1368-77.	n=208 Retrospective case series Patients with advanced NHSCC (stage III or IV) Postoperative adjuvant radiotherapy (conventional radiotherapy vs split course radiotherapy) after transoral laser	Patients had 5-year locoregional control and disease-specific survival (DSS) rates of 68% and 48%, respectively. The 5-year DSS was 70% and 44% for Stages III and IV, respectively (p = 0.00127). Patients treated with a hemoglobin level greater or equal to 13.5 g/dL before radiotherapy had a 5-year DSS of 55% as compared with 39% for patients	Combined treatment approach for different types of HNSCC.

	resection of primary tumours (oral cavity 38, oropharynx 88, larynx 36, hypopharynx 46).	treated with a hemoglobin level greater than 13.5 g/dL (p = 0.0054)	
Remacle M et al (2012). Combining a new CO2 laser wave guide with transoral robotic surgery: a feasibility study on four patients with malignant tumors. European Archives of Oto-Rhino-Laryngology 269 (7) 1833-37.	n = 4 (with T1 base of the tongue (1), T1 palatine tonsil tumour (2), supraglottic tumours T1, T2 (2) Prospective case series Study population: patients with tumours of the upper aerodigestive tract (oropharynx and supraglottic larynx). Technique: transoral robotic surgery with the carbon dioxide laser wave guide (CO_2, LWG) (Lumenis Fiberlase). Follow-up: mean 9 months	Average overall operative time was 94 minutes. Mean coagulation time was 200μm. Mean hospital stay was 6 days. Oral feeding resumed at 3 days under speech control therapy. In all cases, histological examination confirmed that negative resection margins were achieved. No recurrences were reported. No intraoperative or postoperative complications (airway obstruction, bleeding) due to robot or CO2 LWG. None required tracheostomy. Healing seemed faster than observed with the use of electrocautery.	Larger studies included in table 2.
Rich JT et al (2009). Transoral laser microsurgery (TLM) +/- adjuvant therapy for advanced stage oropharyngeal Cancer: Outcomes and prognostic factors. Laryngoscope.119 (9) 1709-19.	n=84 Prospective case series Patients with advanced stage oropharyngeal cancer (base of tongue, tonsil and soft palate). Transoral laser microsurgery of primary tumour with adjuvant therapy (ND in all, adjuvant radiotherapy in 55, adjuvant chemotherapy in 28) Follow-up: mean 52.6 months	Overall survival at 2 and 5 years was 94% and 88%, respectively. Disease-specific survival at 2 and 5 years was 96% and 92%, respectively. Six patients recurred (7%): locally (one), regionally (four), and distant (five). T stage, positive margins, and p16 status significantly impacted survival. The addition of adjuvant chemotherapy in high-risk patients did not significantly impact survival. Five patients (6%) had major surgical complications, but without mortality. Eighty-one percent of patients had acceptable swallowing function at last follow-up. Immediately postoperatively, 17% required G-tubes, which dropped to 3.4% of living patients at 3 years. In this population, our findings validate TLM +/- adjuvant therapy as a highly effective strategy for survival, locoregional control, and swallowing recovery in	Combined treatment approach (transoral co2 laser surgery + neck dissections + adjuvant therapy).

		AJCC stage III and IV oropharyngeal cancer. Our finding also show that p16 positivity improves survival	
Rich JT et al (2011). Swallowing function after transoral laser microsurgery (TLM) +/- adjuvant therapy for advanced-stage oropharyngeal cancer. Laryngoscope.121 (11) 2381-90.	n=118 Retrospective analysis of longitudinal descriptive study. Patients with advanced stage oropharyngeal cancer (stage 3 to 4, base of tongue, tonsil). Transoral laser microsurgery of primary tumour with adjuvant therapy (ND in all, adjuvant radiotherapy in 47%, adjuvant chemotherapy in 41%) Follow-up: mean 53.9 months	Patients tolerated TLM well with 82% enjoying good swallowing at 1 month after surgery. During adjuvant therapy, at 3 months, good swallowing dropped to 55%. At 1 and 2 years after TLM, 89% and 88% of patients had good swallowing function, respectively. At 2 years, 9 patients had persistently poor swallowing function. 93% of patients with T1 through T3 enjoyed good swallowing at 2 years. T4 base of tongue disease was associated with persistently poor swallowing function in multivariate analyses (P = 0.0023), with 40% having good swallowing at 2 years. Preexisting comorbidities and conversion to an open procedure were associated with delayed return of swallowing function, but not with persistently poor swallowing. Seven patients developed late-onset swallowing dysfunction. Treatment of advanced stage OPC with TLM +/- adjuvant therapy results in excellent swallowing outcomes for patients with either T1 to T3 tonsil or T1 to T3 base of tongue resections.	Combined treatment approach (transoral co2 laser surgery + neck dissections + adjuvant therapy).
Salassa JR et al (2008) Postoperative bleeding in transoral laser microsurgery for upper aerodigestive tract tumors. Otolaryngology - Head & Neck Surgery 139 (3) 453-59.	n= 701 Prospective case series Patients with upper aero digestive tract tumours. Follow-up: postoperative	Ten patients (1.4%) experienced postoperative bleeding between 0 and 17 days after surgery. Five patients had previously untreated tumors, and five patients had salvage surgery. Two patients (0.3%) had minor bleeding and required observation only. Five patients (0.7%) experienced major bleeding requiring exploration under general anesthesia. Three patients (0.4%) had catastrophic life-threatening bleeds, two of whom died.	No new safety issues. 4/10 cases are relevant, 3 had base of tongue tumours and 1 had a tumour in the tonsil. Larger studies included in table 2.
Sinha P et al (2012).	n=152	The presence of ECS was	Patients received

Extracapsular spread and adjuvant therapy in human papillomavirus-related, p16-positive oropharyngeal carcinoma. Cancer 118 (14) 3519-30.	Matched analysis Patients with HPV related p16-positive primary Oropharyngeal SCC and pathologically positive necks. Primary TLS resection and neck dissection with or without adjuvant therapy Follow-up: median 43 months	not associated with poorer DFS in multivariate analyses (ECS(report): hazard ratio [HR], 3.42; 95% confidence interval [CI], 0.45-25.88; P = .23; ECS(graded): HR, 2.54; 95% CI, 0.88-7.34; P = .09). T-stage and high-grade ECS, ie soft tissue metastasis (STM(graded)) were prognostic. Overall and in the presence of ECS or even STM, adjuvant CRT was not associated with better DFS over radiotherapy alone (HR, 0.25; 95% CI, 0.06-1.13; P = .07). In addition, matched analyses demonstrated no significant reduction in DFS for the presence of ECS versus the absence of ECS or reduced DFS for the administration of adjuvant radiotherapy alone versus CRT in ECS-positive patients.	adjuvant therapy either RT or CRT and were evaluated for extracapsular grading and its impact on survival.
Sutter R and Grossenbacher R (1990). Resection of palatal tumours with the CO2 laser. Journal of Laryngology & Otology 104 (1) 20-23.	n=20 Retrospective case series Patients with palatal tumours (12 benign, 8 malignant SCC) Co2 laser resection Follow-up: 5 months to 4 years.	CO2 laser resection of palatal tumours has proved to be a good alternative to conventional surgical resection. The CO2 laser permits precise resection, with only slight intra-operative bleeding. Wound healing is good and little post-operative pain. In 2 patients a small perforation in the soft palate occurred but spontaneously closed within a short time. 2 patients with extensive resection had eating problems because of velo-pharyngeal deficiency and improved with obturator prosthesis. Only 1 patient had tumour recurrence and 2 treated palliatively for persistent tumours.	Benign and malignant lesions. Results not reported separately.
Timmermans AJ et al (2013). Cervical osteomyelitis after carbon dioxide laser excision of recurrent carcinoma of the posterior pharyngeal wall. Annals of Otology, Rhinology & Laryngology 122 (4)	n=2 Case reports Recurrent carcinoma of the posterior pharyngeal wall after previous treatment with chemoradiotherapy or hyperbaric oxygen therapy.	Patient presented with neck pain due to cervical osteomyelitis. In one patient this led to cervical spine instability, for which a haloframe was applied. Our working hypothesis was that cervical osteomyelitis was caused by an infected wound bed induced by CO2	Previously irradiated patients with recurrent tumours treated by co2 excision.

273-76.	Co2 laser excision	laser excision of the tumor in the already vascular-compromised area of the irradiated posterior pharyngeal wall. Prophylaxis antibiotic treatment was given.	
Villarreal Renedo PM, Monje Gil F et al (2004). Treatment of oral and oropharyngeal epidermoid carcinomas by means of CO2 laser. Medicina Oral 9 (2) 172-175.168.	n=70 prospective comparative case series 35 co2 laser resection vs 35 conventional surgery. Follow-up: not reported	A smaller painful degree and postoperative cicartical retraction was reported in the CO2 laser group. It minimises the functional speech and swallowing sequels.	Mix of small oral and oropharyngeal epidermoid carcinomas. Results not reported separately for different tumour sites.
Veit JA et al (2009). Signet ring cell adenocarcinoma of the oropharynx: Presentation of a rare case and review of the literature. Auris Nasus Larynx.36 (6) 717-20.	n=1 (signet ring cell carcinoma of the oropharynx) case report Transoral co2 laser resection + bilateral neck dissection + adjuvant radiotherapy for bilateral lymph node metastases and extracapsular spread. Follow-up: 12 months	Complete remission with no signs of tumour manifestation.	Larger studies included in table 2.

Appendix B: Related NICE guidance for transoral carbon dioxide laser surgery for primary treatment of oropharyngeal malignancy

Guidance	Recommendations
Interventional procedures	**Coblation tonsillectomy. NICE interventional procedure guidance IPG9 (2003). Available from www.nice.org.uk/guidance/IPG9** This guidance was superceded by IPG150 (see below). **Electrosurgery (diathermy and coblation) for tonsillectomy. NICE interventional procedure guidance IPG150 (2005) Available from www.nice.org.uk/guidance/IPG150** 1.1 Current evidence on the safety and efficacy of electrosurgery (diathermy and coblation) for tonsillectomy appears adequate to support the use of these techniques, provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 Surgeons should avoid excessive use of diathermy during tonsillectomy. Surgeons using diathermy in tonsillectomy for dissection and/or haemostasis should be fully trained in its use and should understand the potential complications. 1.3 Use of coblation for tonsillectomy can result in higher rates of haemorrhage than other techniques and clinicians wishing to use coblation should be specifically trained. The British Association of Otorhinolaryngologists – Head and Neck Surgeons has agreed to produce standards for training. 1.4 Surgeons should ensure that patients or their parents/carers understand the risk of haemorrhage after tonsillectomy using these techniques. In addition, use of the Institute's information for the public is recommended. 1.5 Surgeons should audit and review the rates of haemorrhage complicating tonsillectomy in their own practices and in the context of the techniques they use. Publication of further information about the influence of different techniques and other factors (such as age) on the incidence of haemorrhage after tonsillectomy would be useful in guiding future practice. **Tonsillectomy using ultrasonic scalpel. NICE interventional procedure guidance IPG178 (2006) Available from www.nice.org.uk/guidance/IPG178** 1.1 Current evidence on the safety and efficacy of tonsillectomy using

	ultrasonic scalpel appears adequate to support the use of this technique provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 The use of ultrasonic scalpel for tonsillectomy may result in higher rates of secondary haemorrhage than some other techniques, and clinicians wishing to use ultrasound scalpel should be specifically trained. The British Association of Otorhinolaryngologists – Head and Neck Surgeons has agreed to produce standards for training. 1.3 Surgeons should ensure that patients or their parents/carers understand the risk of haemorrhage after tonsillectomy using ultrasonic scalpel. In addition, use of the Institute's information for the public is recommended. 1.4 Surgeons should audit and review rates of haemorrhage following tonsillectomy in their own practices and in the context of the techniques they use. Publication of further information about the influence of different techniques and other factors (such as age) on the incidence of haemorrhage after tonsillectomy would be useful in guiding future practice. **Tonsillectomy using laser. NICE interventional procedure guidance IPG186 (2006) Available from www.nice.org.uk/guidance/IPG186** 1.1 Current evidence on the safety and efficacy of tonsillectomy using laser appears adequate to support the use of this technique provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 Use of laser for tonsillectomy may result in higher rates of haemorrhage than some other techniques, and clinicians wishing to use lasers should be specifically trained in their use. The British Association of Otorhinolaryngologists – Head and Neck Surgeons has agreed to produce standards for training. 1.3 Surgeons should ensure that patients or their parents/carers understand the risk of haemorrhage after tonsillectomy using laser. In addition, use of the Institute's information for patients is recommended. 1.4 Surgeons should audit and review the rates of haemorrhage complicating tonsillectomy in their own practices and in the context of the techniques they use. Publication of further information about the influence of different techniques and other factors (such as age) on the incidence of haemorrhage after tonsillectomy would be useful in guiding future practice.

Clinical guidelines	**Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005) (last modified April 2011) Available from www.nice.org.uk/guidance/CG27** 1.11 Head and neck cancer including thyroid cancer General recommendations 1.11.1 A patient who presents with symptoms suggestive of head and neck or thyroid cancer should be referred to an appropriate specialist or the neck lump clinic, depending on local arrangements. 1.11.2 Any patient with persistent symptoms or signs related to the oral cavity in whom a definitive diagnosis of a benign lesion cannot be made should be referred or followed up until the symptoms and signs disappear. If the symptoms and signs have not disappeared after 6 weeks, an urgent referral should be made. 1.11.3 Primary healthcare professionals should advise all patients, including those with dentures, to have regular dental checkups. Specific recommendations 1.11.4 In a patient who presents with unexplained red and white patches (including suspected lichen planus) of the oral mucosa that are: • painful, or • swollen, or • bleeding an urgent referral should be made. A non-urgent referral should be made in the absence of these features. If oral lichen planus is confirmed, the patient should be monitored for oral cancer as part of routine dental examination[1]. [1] See Dental recall: recall interval between routine dental examinations. NICE clinical guideline 19 (2004) 1.11.5 In patients with unexplained ulceration of the oral mucosa or mass persisting for more than 3 weeks, an urgent referral should be made. 1.11.6 In adult patients with unexplained tooth mobility persisting for more than 3 weeks, an urgent referral to a dentist should be made. 1.11.7 In any patient with hoarseness persisting for more than 3 weeks, particularly smokers aged 50 years and older and heavy drinkers, an urgent referral for a chest X-ray should be made. Patients with positive

	findings should be referred urgently to a team specialising in the management of lung cancer. Patients with a negative finding should be urgently referred to a team specialising in head and neck cancer. 1.11.8 In patients with an unexplained lump in the neck which has recently appeared or a lump which has not been diagnosed before that has changed over a period of 3 to 6 weeks, an urgent referral should be made. 1.11.9 In patients with an unexplained persistent swelling in the parotid or submandibular gland, an urgent referral should be made. 1.11.10 In patients with unexplained persistent sore or painful throat, an urgent referral should be made. 1.11.11 In patients with unilateral unexplained pain in the head and neck area for more than 4 weeks, associated with otalgia (ear ache) but with normal otoscopy, an urgent referral should be made. <u>Investigations</u> 1.11.12 With the exception of persistent hoarseness (see recommendation 1.11.7), investigations for head and neck cancer in primary care are not recommended as they can delay referral.
NICE Cancer service guidance	**Service guidance on improving outcomes in head and neck cancers. Cancer service guidance Head and neck (CSGHN) (2004)** The key recommendations are: • Cancer networks should decide which hospitals will diagnose, treat and care for patients. • Multidisciplinary teams should be responsible for every patient. • Clear systems should be in place for patients to be seen quickly by specialists. • Support services should be available to all patients who need them. • Local support teams should provide long-term support in the community. • Information should be collected. • More research should be done.

Evidence Updates (NHS Evidence)	Improving outcomes in head and neck cancers: a summary of new evidence relevant to NICE cancer service guidance (May 2012)

Treatment	Effect on guidance: Potential change	No change
Radiotherapy		
• Altered fractionated radiotherapy may be associated with better patient outcomes than conventional radiotherapy.	✓	
• Swallowing outcomes do not appear to be reported consistently in clinical trials of intensity-modulated radiation therapy.		✓
Surgery		
• Current evidence seems insufficient to guide the choice of elective or therapeutic neck dissection for people with oral and pharyngeal cancers. However, elective neck dissection for node-negative disease may be associated with a lower risk of disease-specific death than therapeutic neck dissection.		✓
• Placing dental implants at the same time as radical surgery in head and neck cancer may be effective but current evidence is not consistent.		✓
• Open partial laryngectomy might be an effective, organ-sparing treatment alternative to total laryngectomy in people with early laryngeal carcinoma that recurs after radiotherapy.	✓	
Surgery versus radiotherapy		
• • CO2 endolaryngeal laser excision may be more cost effective than standard-	✓	

	fractionation radiotherapy for the treatment of early-stage glottic cancer.		
	• Current evidence suggests no difference between radiotherapy and transoral laser surgery for early glottic cancer.		✓
	Mixed treatment comparisons		
	• Altered fractionated radiotherapy with concurrent chemotherapy is possibly associated with better outcomes than other strategies for treating head and neck cancer.	✓	
	Biological treatments		
	• Cetuximab in combination with platinum-based chemotherapy seems to be associated with an increase in response over platinum-based chemotherapy plus placebo.		✓
	• Hypomagnesaemia may be seen in around a third of people treated with cetuximab		✓
	Alternative therapies		
	• Acupuncture does not appear to have any objective benefit for patients with radiation-induced xerostomia.		✓
	Nutritional support		
	• Evidence is insufficient to guide the choice of nasogastric feeding or percutaneous endoscopic gastrostomy for nutrition support in people with head and neck cancer undergoing radiotherapy or chemotherapy.		✓

Appendix C: Literature search for transoral carbon dioxide laser surgery for primary treatment of oropharyngeal malignancy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	23/07/2013	Issue 6 of 12, June 2013
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	23/07/2013	Issue 2 of 4, April 2013
HTA database (Cochrane Library)	23/07/2013	Issue 2 of 4, April 2013
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	23/07/2013	Issue 6 of 12, June 2013
MEDLINE (Ovid)	23/07/2013	1946 to July Week 2 2013
MEDLINE In-Process (Ovid)	23/07/2013	July 23, 2013
EMBASE (Ovid)	23/07/2013	1974 to 2013 Week 29
CINAHL (NLH Search 2.0 or EBSCOhost)	23/07/2013	n/a
BLIC (Dialog DataStar)	23/07/2013	

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1	"Head and Neck Neoplasms"/
2	Tongue Neoplasms/
3	Palatal Neoplasms/
4	Pharyngeal Neoplasms/
5	Tonsillar Neoplasms/
6	Oropharyngeal Neoplasms/
7	((head or neck or tongue or oropharyn* or oro-pharyn* or pharyn* or throat or palat* or tonsil*) adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metastas* or lesion*)).tw.
8	or/1-7

9	Lasers, Gas/
10	(omniguide* or omni-guide*).tw.
11	(((carbon adj2 dioxide) or CO2 or CO?2*) adj4 flexible adj4 laser*).tw.
12	(((carbon adj2 dioxide) or CO2 or CO?2*) adj4 laser*).tw.
13	((transoral or trans-oral) adj4 laser*).tw.
14	or/9-13
15	8 and 14
16	animals/ not humans/
17	15 not 16