Transoral robotic surgery (TORS) for head and neck cancer of unknown primary, oropharyngeal cancer and supraglottic laryngeal cancer

What is an evidence note?

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

Key points

Head and neck cancer of unknown primary

- In small single-arm case series, tumour detection rates for transoral robotic surgery (TORS) tongue base mucosectomy or lingual tonsillectomy in patients with head and neck cancer of unknown primary ranged from 51% to 54%. The extent of prior investigation that defined head and neck cancer of unknown primary varied between studies. No studies were identified that directly compared detection rates from different diagnostic strategies.

- No cost effectiveness studies were identified that compared TORS tongue base mucosectomy or lingual tonsillectomy with blind biopsy in patients with head and neck cancer of unknown primary.

Oropharyngeal cancer

- Small non-randomised observational studies comparing TORS with (chemo)radiotherapy reported no statistically significant differences in overall or disease-free survival in patients with oropharyngeal cancer. These studies were retrospective and at risk of bias, particularly relating to patient selection.
Evidence on survival in small non-randomised studies that compared TORS with conventional transoral or open surgery in patients with oropharyngeal cancer was inconsistent, involved different patient populations, and was at risk of selection bias.

In oropharyngeal cancer patients, swallowing-related quality of life was statistically significantly better in patients treated with TORS compared with (chemo) radiotherapy at varying follow-up points up to 12 months post-treatment.

The evidence on whether TORS is cost-effective at UK willingness-to-pay thresholds in patients with oropharyngeal cancer was unclear and results may not be applicable to the UK setting.

Supraglottic laryngeal cancer

No studies were identified that directly compared TORS with radiotherapy in patients with supraglottic laryngeal cancer. The evidence base consists of single-arm case series. No conclusions could therefore be reached on the clinical or cost-effectiveness of TORS in this patient group.

Patient and social aspects

No studies explored patient experiences or preferences relating to TORS. Evidence from two qualitative studies suggests that treatment of head and neck cancer with open surgery or (chemo)radiotherapy can have a significant impact on the physical and psychosocial functioning of patients. A narrative systematic review found that head and neck cancer patients rated survival, cure, pain and swallowing outcomes as important.

Learning curve and volume-outcome

In a retrospective cohort study the TORS surgical learning curve for oropharyngeal cancer varied by surgeon (n=3). Competence was potentially reached after 15–40 cases depending on the outcome measured.

In a recent retrospective analysis hospitals with high TORS volume were associated with statistically significantly lower positive margin rates compared with low volume hospitals: 8.2% versus 16.7%, p=0.001.

Definitions

**Tongue base mucosectomy:** surgical removal of part of the mucous membrane at the base of the tongue.

**Mandibulotomy:** surgical division of the lower lip and jawbone (mandible) to allow access to the oral cavity and oropharynx.

**Gastrostomy:** surgical creation of an opening into the stomach through the abdominal wall.

**Squamous cells:** thin, flat cells that are found in tissues that form the surface of the skin, the lining of hollow organs of the body, and the lining of the respiratory and digestive tracts.
Literature search

A systematic search of the secondary literature was carried out between 13 and 20 June 2017 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Medline in process, Embase, Web of Science and Cochrane databases were searched for systematic reviews and meta-analyses.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

Medline, Medline in process, Embase, and Cochrane databases were searched to identify primary studies on the use of transoral robotic surgery in patients with head and neck cancer of unknown primary and patients with supraglottic laryngeal cancer. Only studies published since the date of the literature search in the most recent systematic review (2014) were sought.

A search was carried out between 18 and 20 July 2017 to identify literature on patient experiences and preferences relating to treatment of head and neck cancer. Key websites and the Medline, Medline in process, and PsychInfo databases were searched. Only studies published in the last two years (2016–2017) were selected due to the volume of literature. This literature search was not restricted to transoral robotic surgery.

A search was carried out between 9 and 10 October 2017 to identify literature on surgical learning curves and volume-outcome studies. The Medline, Medline in process, and Embase databases were searched.

All results were limited to English language.

Concepts used in all searches included: head and neck cancer/tumour/neoplasm/carcinoma, oropharyngeal cancer, supraglottic laryngeal cancer, transoral robotic surgery (TORS), da Vinci robotic assisted surgery. A full list of resources searched and terms used are available on request.

Introduction

The most common sites of cancers in the head and neck include the oral cavity, oropharynx and larynx. Most head and neck cancers are squamous cell carcinomas which may spread to lymph nodes in the neck (cervical lymph nodes) but usually do not spread to more distant sites.

Head and neck cancer of unknown primary is characterised by malignant metastases in the cervical lymph nodes and insufficient information from non-invasive diagnostic investigations to determine the precise location of the primary tumour. Identifying the primary tumour is important for controlling the cancer, improving patient survival, reducing patient distress over undetected disease, and minimising treatment-related toxicity from broad spectrum adjuvant therapies.

Oropharyngeal cancers develop in the tissues of the oropharynx: the soft palate, tonsils, pharyngeal wall, or base of the tongue (Figure 1). Approximately 90% of oropharyngeal cancers are squamous cell carcinomas. Key risk factors for oropharyngeal cancer include smoking, heavy alcohol consumption, human papillomavirus (HPV) infection and male gender.

Supraglottic laryngeal cancer (supraglottic cancer) is the second most common type of laryngeal cancer (Figure 1). This cancer occurs more frequently in men than women and is almost exclusively a squamous cell carcinoma. Supraglottic cancer tends to spread from the larynx to surrounding lymph nodes and the oropharynx.
There is currently no international consensus on which diagnostic tests to use to locate tumours in patients with head and neck cancer of unknown primary. When the primary tumour remains undetected following non-invasive diagnostic investigations current practice in the UK is to perform a bilateral palatine tonsillectomy and take blind biopsies from several mucosal sites at the base of the tongue. Investigations recommended by the National Institute for Health and Care Excellence (NICE) for patients with head and neck cancer of unknown primary in England and Wales are listed in Box 1.

**Box 1: NICE recommendations on investigation of head and neck cancer of unknown primary**

- Consider an 18F-fluorodeoxyglucose (FDG) positron emission tomography – computed tomography (PET-CT) scan as the first investigation
- Consider imaging endoscopy if FDG PET-CT is contraindicated or has failed to locate the primary tumour
- Offer a biopsy to confirm a possible primary site
- If FDG PET-CT does not identify the primary tumour site, offer a surgical diagnostic assessment which may include guided biopsies, tonsillectomy or tongue base mucosectomy

Treatment options for oropharyngeal cancer include open surgery, transoral surgery, chemoradiotherapy, radiotherapy, or open surgery followed by adjuvant chemoradiotherapy/radiotherapy. Conventional open surgery for oropharyngeal cancer is associated with long-term or permanent impairment of speech and swallowing, facial disfigurement, severe pain and prolonged recovery. Consequently open surgery is no longer considered to be the standard of care for this condition.
in the UK (V Paleri, Consultant Head and Neck and Thyroid Surgeon, Royal Marsden Hospital. Personal communication, 22 September 2017).

For early supraglottic laryngeal cancer, treatment options include radiotherapy or surgery (transoral or open) to remove the tumour while preserving the function of the larynx (speech)\textsuperscript{10, 14}. Open surgery for supraglottic cancer carries similar risks to open surgery for oropharyngeal cancer and is therefore rarely used to treat this condition in the UK (V Paleri, Consultant Head and Neck and Thyroid Surgeon, Royal Marsden Hospital. Personal communication, 22 September 2017).

Transoral robotic surgery (TORS) has been proposed as an alternative to manual palatine tonsillectomy and blind mucosal biopsy in patients with head and neck cancer of unknown primary\textsuperscript{7}, and as a less invasive surgical approach to treating oropharyngeal and supraglottic laryngeal cancers\textsuperscript{9}. Transoral laser microsurgery, another minimally invasive surgical approach to the removal of oropharyngeal and supraglottic laryngeal cancers, was excluded from this rapid review to facilitate a meaningful comparison between TORS and the treatments most commonly offered to patients with these tumours in NHSScotland - radiotherapy and chemoradiotherapy (S Robertson, Consultant ENT Head and Neck Surgeon, NHS Greater Glasgow & Clyde. Personal communication, 7 November 2017).

This Evidence Note addresses the following three questions:

- Is bilateral palatine tonsillectomy plus tongue-base mucosectomy using TORS clinically and cost-effective compared with conventional bilateral palatine tonsillectomy and blind biopsy for assisting with the diagnosis of head and neck cancer of unknown primary?
- Is TORS clinically and cost-effective compared with radiotherapy or open surgery in patients with oropharyngeal cancer?
- Is TORS clinically and cost-effective compared with radiotherapy in patients with supraglottic laryngeal cancer?

**Health technology description**

The technology for TORS comprises a surgeon console, computerised control system, and patient-side cart that houses robotic arms which hold a dual telescope and surgical instruments. The surgeon operates the robotic arms by remote control from the console while viewing the magnified 3D surgical field on the monitor. The da Vinci\textsuperscript{®} System (Intuitive Surgical Inc., California)\textsuperscript{15} is available with three or four robotic arms. Products include the da Vinci\textsuperscript{®} Xi, the da Vinci\textsuperscript{®} Si and the da Vinci\textsuperscript{®} Si-e.

TORS involves inserting one or more arms of the robotic surgical device through the oral cavity to take mucosal biopsies for diagnostic purposes or to remove primary tumours from the oropharynx or supraglottis\textsuperscript{6, 7}.

Da Vinci\textsuperscript{®} robotic systems are installed in three centres in Scotland - Edinburgh, Glasgow and Aberdeen - and are presently used to provide a robot assisted laparoscopic prostatectomy service. Da Vinci robotic systems are currently used in England and Wales to perform TORS in selected head and neck cancer patients (S Robertson, Consultant ENT Head and Neck Surgeon, NHS Greater Glasgow and Clyde. Personal communication, 8 September 2017). An NHS England commissioning policy on TORS concluded that there is currently insufficient evidence to support routinely referring patients with oropharyngeal or laryngeal cancer for TORS\textsuperscript{16}.
Epidemiology

Incidence estimates for head and neck cancer of unknown primary are highly variable due to difficulties in defining an ‘unknown primary’. Cervical lymph node metastases from an unknown primary tumour are estimated to account for 2-5% of all head and neck squamous cell carcinomas. Based on the incidence of head and neck cancer in Scotland in 2015 (n=1,283) a prevalence of 2-5% equates to 26–64 people in Scotland developing cervical metastases from an unknown primary head and neck tumour in that year. Other estimates suggest up to 160 cases of head and neck cancer of unknown primary are investigated in Scotland each year (S Robertson, Consultant ENT Head and Neck Surgeon, NHS Greater Glasgow and Clyde. Personal communication, 8 November 2017). The location of over 50% of head and neck cancers of unknown primary remains undiscovered. Failure to locate the primary tumour can impact on disease control, result in patients receiving large volume head and neck mucosal irradiation with associated treatment toxicities and may be stressful for patients who are left with the uncertainty of undiagnosed disease.

Oropharyngeal cancer incidence has increased in the last decade due to the rising prevalence of HPV infection. Patients with HPV-associated oropharyngeal cancer are often younger (aged 40 to 60 years) and have a better long-term prognosis than patients who have HPV-negative oropharyngeal cancer. In 2015 there were 348 new diagnoses of oropharyngeal cancer in Scotland, which represents a European age standardised rate of 6.6 new oropharyngeal cancer diagnoses per 100,000 person-years at risk (95% confidence interval (CI) 5.9 to 7.3). In the same year 103 deaths from oropharyngeal cancer were recorded in Scotland.

Scottish epidemiological data is not reported for supraglottic cancer specifically, although data is available for laryngeal cancer. In 2015 there were 293 new cases of laryngeal cancer in Scotland. This represents a European age standardised rate of 5.9 new diagnoses per 100,000 person-years at risk (95% CI 5.3 to 6.6). In the same year 127 deaths from laryngeal cancer were recorded in Scotland. The proportion of laryngeal cancers that originate in the supraglottis varies between countries.

Clinical effectiveness

Head and neck cancer of unknown primary

Evidence on the use of TORS in patients with head and neck cancer of unknown primary was limited to small single-arm case series. Three case series were excluded from this Evidence Note as they did not focus on detection rates, had overlapping patient populations or had fewer than ten participants. Patient characteristics and primary tumour detection rates reported in the remaining case series are summarised in Table 1. Primary tumour detection rates ranged from 51% (95% CI 39% to 62%) to 54% (95% CI 42% to 65%) for patients undergoing TORS lingual tonsillectomy or tongue base mucosectomy for the diagnosis of head and neck cancer of unknown primary. The basis on which cancer of unknown primary was defined varied between studies, as did the TORS procedure used, which may have influenced detection rates.

A systematic review incorporated five small case series and a case report from the US. Preliminary diagnostic investigations performed prior to TORS varied between included studies which may indicate heterogeneity in the patient populations. It was not clear if studies in the systematic review included palatine tonsillectomy in the TORS procedure. Primary tumour detection rates were high, both in patients who had abnormal results from initial diagnostic tests (physical examination, computed
tomography/magnetic resonance imaging (MRI), or PET-CT) and in patients who did not have abnormal findings from these investigations.

One small prospective case series from three centres in the UK (London, Oxford, Newcastle) was published after the systematic review\(^7\). The participating centres used slightly different robotic devices and followed local protocols, which may have introduced variation in surgical practices.

A small retrospective case series from Denmark reported post-operative changes in patient treatment for all patients where the primary tumour site was identified following TORS lingual tonsillectomy\(^{19}\).

**Table 1: participant characteristics and tumour detection rates for TORS in patients with head and neck cancer of unknown primary**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Basis of CUP classification</th>
<th>N</th>
<th>Mean age in years (range)</th>
<th>% Male</th>
<th>% HPV/ p16 positive</th>
<th>Detection rate (TBM/ lingual tonsillectomy)</th>
<th>TNM stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter (2017)(^7)</td>
<td>Case series</td>
<td>Clinical examination, PET-CT, palatine tonsillectomy</td>
<td>32</td>
<td>57 (41 to 74)</td>
<td>84</td>
<td>72 (p16)</td>
<td>53% 95% CI 36% to 71% (TBM)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Fu (2016)(^6)</td>
<td>Systematic review: 5 case series, 1 case study</td>
<td>Some or all of: clinical examination, CT, MRI, PET-CT, panendoscopic examination under anaesthesia</td>
<td>85</td>
<td>57.3 (44 to 78)</td>
<td>88</td>
<td>82 (p16)</td>
<td>51% 95% CI 39% to 62% (tonsillectomy)</td>
<td>N1–N3</td>
</tr>
<tr>
<td>Channir (2015)(^19)</td>
<td>Case series</td>
<td>Clinical examination, flexible fibre optic laryngoscopy, PET-CT, bilateral tonsillectomy, random BOT biopsies</td>
<td>13</td>
<td>60 (50 to 79)</td>
<td>69</td>
<td>54 (HPV)</td>
<td>54% 95% CI 42% to 65% (tonsillectomy)</td>
<td>Tx, T1, T2, N1, N2</td>
</tr>
</tbody>
</table>

*Detection rate: proportion of patients (incident cases) where the primary tumour was located.*


**Oropharyngeal cancer**

No studies were identified that directly compared TORS with radiotherapy alone in patients with oropharyngeal cancer. A systematic review and two small retrospective cohort studies compared TORS, with or without adjuvant therapy, with (chemo)radiotherapy\(^9,22,23\). Three non-randomised observational studies compared TORS with conventional surgery (transoral or open)\(^{24,26}\). One case-control study compared TORS with open surgery in patients with recurrent oropharyngeal cancer\(^{27}\).
**TORS versus (chemo)radiotherapy**

A systematic review reported results from two small non-randomised controlled studies (Genden et al 2011 and More et al 2013) comparing TORS plus adjuvant chemoradiotherapy with chemoradiotherapy alone9. Individual study results were not combined in the systematic review, therefore the studies are described separately below. The study by Genden et al (2011) was a small retrospective case-control study (n=56) in patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. The majority of participants had oropharyngeal cancer (89%, n=50). The chemoradiotherapy group was recruited prospectively “using a separate protocol”, which is not explained in the systematic review, and had more advanced oropharyngeal cancer at baseline compared with the TORS group. More et al (2013) enrolled participants with advanced stage III-IVa oropharyngeal (n=37) or supraglottic (n=3) carcinoma in a prospective non-randomised trial. Participants self-selected their treatment which may have introduced selection bias to this study. Some participants in both TORS study groups received adjuvant chemoradiotherapy, which makes it difficult to separate the effect of TORS from the effect of adjuvant chemoradiotherapy.

The study by Genden et al (2011) reported no statistically significant difference in 18-month Kaplan-Meier estimated overall or disease-free survival between the TORS and chemoradiotherapy groups (Table 2). There were no statistically significant differences in gastrostomy rate between TORS and chemoradiotherapy groups in either study (Genden et al 2011 or More et al 2013) at 12 months follow-up. More et al (2013) reported a statistically significant difference in gastrostomy rate favouring TORS at six months follow-up (0% versus 60%, p<0.0001). The two studies reported differing results for swallowing-related quality of life. In Genden et al (2011), aspects of swallowing-related quality of life (eating in public and consuming a normal diet) were statistically significantly better in the TORS group compared with the chemoradiotherapy group two weeks after treatment (p=0.008 and p=0.01, respectively). There were no statistically significant differences in swallowing-related quality of life at three, six or 12 months follow-up. More et al (2013) reported that swallowing-related quality of life, measured with a different instrument, was statistically significantly better in the TORS group compared with the chemoradiotherapy group at six and 12 months follow-up (p=0.004 and p=0.006, respectively).

A retrospective cohort study compared TORS, with or without adjuvant therapy, with chemoradiotherapy alone in 138 patients with histologically confirmed T0-T2, N0-N2 oropharyngeal cancer23. In this study 57% of the TORS group received adjuvant therapy which allowed comparisons to be made between TORS alone, TORS plus adjuvant therapy, and chemoradiotherapy alone. Participants in the chemoradiotherapy group had significantly higher N classification at baseline compared with the TORS group, which may have biased study results in favour of TORS. Quality of life scores were not available for all participants at all follow-up points (one, six, 12 and 24 months). No quality of life assessment was conducted prior to treatment which limits the conclusions that can be drawn from the study. There was no statistically significant difference in actuarial two-year overall, disease-free, or disease-specific survival between the TORS and chemoradiotherapy treatment groups (Table 2).

Compared with chemoradiotherapy alone, TORS alone resulted in statistically significantly better saliva-related quality of life at all four follow-up points (p<0.001, p=0.025, p=0.017 and p=0.011, respectively). Mean saliva-related quality of life was statistically significantly worse in the TORS plus adjuvant therapy group compared with chemoradiotherapy alone at one month follow-up (p=0.006). There were no statistically significant differences in saliva-related quality of life at six, 12 or 24 months follow-up in comparisons of TORS plus adjuvant therapy and chemoradiotherapy alone. A multivariable linear regression analysis concluded that treatment strategy (TORS or chemoradiotherapy) and N classification were statistically significant predictors of saliva-related quality of life at six months follow-up (p=0.043 and p=0.027, respectively).
TORS alone and TORS plus adjuvant therapy both resulted in statistically significantly better chewing-related quality of life at 12 months follow-up compared with chemoradiotherapy alone (p=0.029 and p=0.034, respectively).

A retrospective matched cohort study compared TORS with radiotherapy or chemoradiotherapy in 127 patients with T1-T3, N0-N3 oropharyngeal cancer. Thirty-nine TORS patients were matched with 88 patients receiving radiotherapy (6.8%) or chemoradiotherapy (93.2%). Despite matching, a smaller proportion of patients in the TORS group had comorbidities or a history of smoking at baseline. Gastrostomy prevalence was used as a surrogate measure of swallowing function. Based on estimated prevalence of gastrostomy in oropharyngeal cancer patients the study sample size provided adequate statistical power for the analysis. The majority of patients in the TORS group (89.7%) received adjuvant therapy, although at a lower dose than in the comparator group. This complicates separating the effects of TORS from the effects of (chemo)radiotherapy. In a multivariable Cox proportional hazards model there was no statistically significant difference in disease-free survival between TORS and (chemo)radiotherapy during a median 18 months follow-up (hazard ratio (HR) 0.22, 95% CI 0.04 to 1.36, p=0.10). The relative risk (RR) of having a gastrostomy tube fitted was statistically significantly lower in the TORS group compared with the (chemo)radiotherapy group at three months follow-up (RR 0.26, 95% CI 0.09 to 0.79, p=0.02) and six months follow-up (RR 0.12, 95% CI 0.02 to 0.92, p=0.04), but not at 12 months follow-up (RR 0.24, 95% CI 0.03 to 1.68, p=0.15). The study authors noted that presence of a gastrostomy tube does not necessarily indicate gastrostomy dependence or an inability to swallow.

In summary, no studies comparing TORS with (chemo)radiotherapy reported a statistically significant difference in survival. Statistically significant differences in swallowing-related quality of life were reported in comparisons of TORS with (chemo)radiotherapy at various points up to 12 months after treatment.

Table 2: overall and disease-free survival following TORS for oropharyngeal cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Patient group</th>
<th>Follow-up (months)</th>
<th>2-year overall survival</th>
<th>2-year disease-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TORS vs. non-surgical</td>
<td></td>
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<tr>
<td>Ling (2016)</td>
<td>TORS ± adjuvant therapy vs. chemoradiotherapy</td>
<td>n=138 Oropharyngeal cancer T0-2, N0-2</td>
<td>Median 22.1 (range 0.33 to 83.4)</td>
<td>97.1% vs. 92.3% p=0.22</td>
<td>91.6% vs. 90.3% p=0.90</td>
</tr>
<tr>
<td>Sharma (2016)</td>
<td>TORS ± adjuvant therapy vs. (chemo)radiotherapy</td>
<td>n=127 Oropharyngeal cancer T1-3, N1-3</td>
<td>TORS Median 24 (IQR 18 to 27) (Chemo)radiotherapy Median 18 (IQR 12 to 24)</td>
<td>Not reported</td>
<td>HR 0.22 95% CI 0.04 to 1.36 p=0.10</td>
</tr>
<tr>
<td>More (2013)</td>
<td>TORS plus adjuvant therapy vs. chemoradiotherapy</td>
<td>n=40 Oropharyngeal (n=37) or supraglottic (n=3) cancer T1-3, N0-2</td>
<td>Median 14 (range 12 to 16)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Genden (2011)</td>
<td>TORS plus adjuvant therapy vs. chemoradiotherapy</td>
<td>n=56 Cancer of the oropharynx</td>
<td>TORS Median 20.4 (range 12.9 to 39.2)</td>
<td>*90% vs. 100% p=0.41</td>
<td>*77.8% vs. 87.8% p=0.36</td>
</tr>
</tbody>
</table>

* Statistically significant difference compared to TORS group.
### TORS vs. conventional surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparisons</th>
<th>Patients</th>
<th>Tumour Stage</th>
<th>Surgery Type</th>
<th>Recurrence</th>
<th>Survival</th>
<th>Voice Status</th>
<th>Length of Hospital Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biron (2017)</td>
<td>TORS vs. lip-splitting mandibulotomy</td>
<td>n=47</td>
<td>Oropharyngeal cancer T1-3, N0-3</td>
<td>Unclear</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ford (2014)</td>
<td>TORS vs. transoral or open surgery</td>
<td>n=130</td>
<td>Oropharyngeal cancer T1-4, N0-3</td>
<td>Unclear</td>
<td>Not reported</td>
<td>91% vs. 75% p=0.035</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee (2014)</td>
<td>TORS vs. transoral surgery or mandibulotomy</td>
<td>n=57</td>
<td>Tonsillar carcinoma T1-3</td>
<td>Mean 20.3</td>
<td>100% vs. 96.7% p=0.352</td>
<td>95.7% vs. 91.6% p=0.733</td>
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</table>

### TORS vs. conventional surgery: recurrent cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparisons</th>
<th>Patients</th>
<th>Tumour Stage</th>
<th>Surgery Type</th>
<th>Recurrence</th>
<th>Survival</th>
<th>Voice Status</th>
<th>Length of Hospital Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>White (2013)</td>
<td>TORS vs. open surgery</td>
<td>n=128</td>
<td>Recurrent oropharyngeal cancer T1-4, N0-3</td>
<td>Unclear</td>
<td>74% vs. 43% p=0.02</td>
<td>74% vs. 43% p=0.01</td>
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</table>

*18-month Kaplan Meier estimated. IQR = inter-quartile range.

**TORS versus conventional surgery (transoral or open)**

One prospective non-randomised study compared TORS with conventional transoral surgery or mandibulotomy in 57 patients with T1-3 tonsillar cancer. A greater proportion of patients in the mandibulotomy group had advanced T stage cancer at baseline. TORS and conventional surgeries were performed by different surgeons and not all participants received adjuvant therapy, which may have introduced bias to this study. There was no statistically significant difference in Kaplan Meier two-year overall or disease-free survival between the TORS and conventional surgery groups (Table 2). There was a statistically significant difference between treatment groups in time to return to an oral diet: TORS 6.5 ± 4.2 days, transoral radical tonsillectomy 7.0 ± 7.9 days, mandibulotomy 16.7 ± 5.3 days, p<0.001. Swallowing-related quality of life was statistically significantly better in the TORS and transoral tonsillectomy groups compared with the mandibulotomy group at 12 months follow-up (p=0.034). There was no statistically significant difference in voice status between groups at 12 months follow-up (p=0.342). There was a statistically significant difference between groups in length of hospital stay: TORS 14.6 ± 4 days, transoral radical tonsillectomy 14.0 ± 6.4 days, mandibulotomy 24.6 ± 5.9 days, p=0.001.

A matched case-control study compared TORS with conventional transoral or open surgery in patients with oropharyngeal cancer (n=130). The conventional surgery group was retrospectively matched with TORS patients based on TNM stage and adjuvant therapy regimen. Despite matching, tumours within the tongue base were statistically significantly more common in the TORS group, which may indicate that conventional surgery patients had more complex tumours. There was a statistically significant difference in recurrence-free survival that favoured the TORS group at one year (94% versus 85%), two years (91% versus 75%) and three years (89% versus 73%) post-surgery (p=0.035). There was no statistically significant difference in recurrence-free survival between study groups when only patients with HPV-
positive oropharyngeal cancer (n=95) were included. The difference in recurrence-free survival was statistically significant and favoured the TORS group in an analysis involving only patients with HPV-negative cancer (n=24).

A matched case-control study in patients with advanced oropharyngeal cancer compared TORS (n=18) with a historical control group (n=29) who underwent lip-splitting mandibulotomy\textsuperscript{24}. Length of hospital stay was statistically significantly shorter in the TORS group compared with the lip-splitting mandibulotomy group: 14.4 days versus 19.7 days, p=0.03. There were no statistically significant differences between groups in length of stay in the intensive care unit, time to tracheostomy removal, or gastrostomy tube dependence.

In summary, evidence on recurrence-free survival was conflicting in two studies comparing TORS with conventional surgeries for oropharyngeal cancer. Swallowing-related quality of life was statistically significantly better in one study comparing TORS with conventional transoral surgery or mandibulotomy in patients with tonsillar cancer. In two studies reporting length of hospital stay following surgery, patients undergoing TORS were discharged earlier than conventional surgery patients.

**TORS versus open surgery in patients with recurrent oropharyngeal cancer**

One study was identified that compared TORS with open surgery in patients who had recurrent oropharyngeal cancer\textsuperscript{27}. Patients with recurrent oropharyngeal cancer have a poor prognosis and treatment options may be limited to surgery if the patient received (chemo)radiotherapy as part of previous treatment regimes\textsuperscript{28}.

A retrospective matched case-control study compared TORS with undefined open surgery in 128 patients with recurrent oropharyngeal cancer\textsuperscript{27}. A greater proportion of patients in the open surgery group had undergone previous surgery compared with the TORS group (69% versus 19%, p<0.001). Two-year overall and recurrence-free survival was statistically significantly greater in the TORS group compared with the open surgery group, although this may be at least partially due to selection bias (Table 2). Mean length of hospital stay was statistically significantly longer in patients undergoing open surgery compared with patients receiving TORS: 8.0 days versus 3.8 days, p<0.001. Presence of a gastric feeding tube was used as an indicator of swallowing difficulties. At baseline (peri-operatively) 23/64 (35%) TORS patients and 48/64 (75%) open surgery patients were given a percutaneous gastric feeding tube. At one year follow-up 2/64 (3%) TORS patients and 20/64 (31%) open surgery patients still required feeding tube support.

**Supraglottic laryngeal cancer**

No studies were identified that directly compared TORS with radiotherapy in patients with supraglottic laryngeal cancer. Evidence on TORS in patients with supraglottic cancer was limited to small single-arm case series.

A narrative systematic review\textsuperscript{29} incorporated four small prospective, and two small retrospective, case series on TORS in a total of 76 patients with supraglottic squamous cell carcinoma (stage T1-3). Kaplan Meier two-year overall survival estimates ranged from 66.7% to 100% in the four case series reporting this outcome (n=50). A single prospective case series (n=16) reported favourable post-operative swallowing function in 95% (n=15) of participants. In another prospective case series a third of patients (n=3) reported normal post-operative speech, while the remainder (n=6) had mild to moderate dysphonia. Another prospective case series reported participant voice-specific quality of life scores of 0/100 to 40/100 on the Voice Handicap Index (low scores indicate less handicap).
A small prospective case series (n=13) in patients with supraglottic carcinoma (T1-2, N0) was identified that was not included in the narrative review\(^\text{14}\). Patients self-selected to receive TORS, which may have introduced selection bias to this study. Results from this case series were consistent with the systematic review findings.

**Ongoing studies**

A protocol was identified for a phase II randomised trial comparing TORS ± adjuvant therapy with (chemo)radiotherapy in patients with early stage (T1-2, N0-2) oropharyngeal cancer (ORATOR; [NCT01590355])\(^\text{30}\). This was the only randomised study identified in the published or ongoing literature. The protocol provides minimal detail on randomisation methods and the trial is almost certainly unblinded. The primary endpoint of the trial will be quality of life one year after treatment. Secondary outcomes include overall and disease-free survival, toxicity, and swallowing function. The trial is expected to be complete in 2021.

Table 3 provides a summary of ongoing non-comparative studies on TORS in patients with oropharyngeal cancer, supraglottic laryngeal cancer, or head and neck cancer of unknown primary.

**Table 3: ongoing studies on TORS in patients with head and neck cancer**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Patient group</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02159703</td>
<td>HPV positive oropharyngeal cancer</td>
<td>TORS plus radiotherapy</td>
<td>Adverse events&lt;br&gt;2-year follow-up&lt;br&gt;5-year follow-up</td>
<td>Feb 2018</td>
</tr>
<tr>
<td>NCT01819480</td>
<td>Oropharyngeal or supraglottic carcinomas</td>
<td>TORS</td>
<td>Overall, progression-free and disease-specific survival&lt;br&gt;Functional quality of life&lt;br&gt;Adverse events&lt;br&gt;3-year follow-up</td>
<td>Sept 2019</td>
</tr>
<tr>
<td>NCT02225496</td>
<td>HPV positive oropharyngeal carcinoma</td>
<td>TORS plus adjuvant therapy</td>
<td>Time to loco-regional recurrence&lt;br&gt;6-month follow-up</td>
<td>Sept 2019</td>
</tr>
<tr>
<td>NCT01473784</td>
<td>Benign and/or malignant diseases of the oral cavity or laryngopharynx</td>
<td>TORS</td>
<td>TORS feasibility&lt;br&gt;Intra-operative outcomes (blood loss, operative time, complications)&lt;br&gt;Learning curve&lt;br&gt;Quality of life&lt;br&gt;8-year follow-up</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT03281499</td>
<td>Head and neck squamous cell carcinoma</td>
<td>TORS</td>
<td>Rate of out-of-field failures&lt;br&gt;Adverse events&lt;br&gt;Proportion of occult cancers identified, patients with complete resection of primary tumour, suitable for de-intensification of radiotherapy&lt;br&gt;Swallowing function&lt;br&gt;Neck or speech impairment&lt;br&gt;Survival rates</td>
<td>Aug 2021</td>
</tr>
</tbody>
</table>
Patient and social aspects

No studies were identified that reported on patient or social aspects relating to the use of TORS in patients with head and neck cancer. This section describes patient experiences and preferences in relation to open surgery or (chemo)radiotherapy for head and neck cancer.

Patient experiences

Three recent studies were selected that explored patients’ experiences during and after treatment for head and neck cancer. Study characteristics are presented in Table 4.

A qualitative study in patients with head and neck cancer (n=56) explored how everyday life was affected by treatment. All participants underwent radiotherapy, with or without open surgery or chemotherapy. Fifteen patients reported having regained their ability to lead a normal life two years after treatment, nine patients were of the opinion that difficulties experienced were not directly related to their condition or cancer treatment and 12 patients reported both negative experiences and a positive change in attitudes to life. However, 20 patients reflected that life was worse, with the key challenges being the physical (lost ability to smell or taste, pain) and psychological (altered self-image, fear about the future) effects of their condition. Due to heterogeneity in participants’ diagnoses and treatment it is unclear whether it is the type of treatment, tumour site or tumour stage, which affects the way that head and neck cancer impacts patients’ everyday life.

A qualitative study explored the experiences of patients who underwent open surgery and adjuvant (chemo)radiotherapy for head and neck cancer that resulted in alterations in their appearance (n=9). Patients reported experiences of trauma, terror and distress as a result of their diagnosis and subsequent treatment. Distress was perceived by some participants as a catalyst for new life interpretations. Participants experienced an identity struggle due to changes in their facial appearance following open surgery, which led to embarrassment and distancing themselves from existing social circles. Changes in the physical self, however, also led participants to seek social contacts with other stigmatised groups. This resulted in the development of an empathetic understanding and altruism for others with cancer.

Evidence from the two primary studies discussed above suggests that treatment of head and neck cancer can have a significant impact on the physical and psychosocial functioning of patients. These studies identified issues related to communication difficulties, altered sense of self and treatment side effects. Head and neck cancer was also associated with some positive patient experiences, such as developing empathy towards other cancer patients, seeking new social contacts and new life interpretations.
## Table 4: patient experience study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N, cancer type, treatment type, follow-up)</th>
<th>Mean age (years)</th>
<th>Participant recruitment method</th>
<th>Data collection and analysis methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isaksson (2016)31</td>
<td>n=56 Histologically confirmed head and neck cancer Radiotherapy (single or combined modality) 24 months follow-up</td>
<td>59</td>
<td>Received primary treatment at a tertiary referral hospital in Sweden</td>
<td>Face-to-face, semi-structured interviews</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data categorised by two researchers and reviewed by a third</td>
</tr>
<tr>
<td>Threader (2016)32</td>
<td>n=9 History of head and neck cancer Open surgery resulting in altered facial appearance 1-14 months follow-up</td>
<td>59.5</td>
<td>Referred by nurse coordinators at a teaching hospital in Australia</td>
<td>Semi-structured interviews</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interpretative phenomenological analysis by two researchers</td>
</tr>
</tbody>
</table>

### Patient preferences

Results from thirteen cross-sectional studies involving patients with head and neck cancer were extracted from a narrative systematic review investigating patient, carer, spouse, healthy subject and healthcare professional preferences and priorities regarding treatment outcomes in head and neck cancer34.

Three studies suggested that (chemo)radiotherapy was preferred over open surgery in patients with mixed head and neck cancers. Another study (n=59) found that 69% of oropharyngeal cancer patients would not trade chemoradiotherapy for radiotherapy if the risk of death was greater than 5%.

Three studies reported that head and neck cancer patients ranked being cured and living longer as top priorities, followed by items related to pain, energy, swallowing, voice, and appearance. One study found that priority outcomes for head and neck cancer patients (n=35) were social function and pain, followed by physical appearance, eating and speech problems. Similar findings were reported in a second study (n=300) where 58% of patients interviewed ranked survival as the top priority, followed by expenses for cancer treatment (ranked by 51%) and being able to perform all daily life tasks well (ranked by 50%). Four studies in patients with mainly hypopharyngeal cancer found that patients were willing to compromise on survival in favour of laryngeal preservation.

One study comparing outcome preferences between head and neck cancer patients (n=49) and healthcare professionals (n=50) concluded that preferences were similar for head and neck cancer specific outcomes such as appearance, eating, speech and breathing, but were not similar for more general outcomes such as pain and work/social function. A second study reported that there was agreement between patients, spouses and multidisciplinary team members regarding treatment outcome priorities: being cured/living longer items were uniformly ranked first and pain or swallowing items ranked next, but with varying scores.
Four studies included patients with oropharyngeal cancer who had experienced toxicity. Ratings on the importance of toxicity varied widely between studies. Participants tended to focus on toxicity related to oropharyngeal disease, such as issues with speech, chewing, swallowing, or bone necrosis. One study in patients who received open surgery for cancer of the oral cavity or oropharynx (n=48) reported that speech, chewing and swallowing tended to be rated as important.

Overall, the importance to patients of survival appears to vary depending on the type of head and neck cancer. A small number of studies suggest that patients may prefer (chemo)radiotherapy to open surgery for treatment of head and neck cancer. Ratings and rankings of outcomes varied widely between studies and cancer types. Pain and swallowing related functions were however frequently ranked as high priorities after survival and cure.

Safety

There was substantial variation between TORS study groups in the proportion of patients experiencing an adverse event: range 8% to 65% (Table 5). Some of this variation may be due to differences in patient populations and TORS procedures.

No studies were identified that provided comparative adverse event rates in patients with head and neck cancer of unknown primary or supraglottic laryngeal cancer. Table 5 reports adverse event rates from single-arm case series on TORS in these patient groups\textsuperscript{6, 7, 14, 19, 29}.

Four studies provided comparative adverse event or complication rates in patients with oropharyngeal cancer treated with TORS, (chemo)radiotherapy or open surgery (Table 5)\textsuperscript{9, 24, 27}. Studies comparing TORS with (chemo)radiotherapy reported no adverse events in the (chemo)radiotherapy group. It is unclear if this was due to a lack of adverse events in the (chemo)radiotherapy groups or if relevant adverse events for (chemo)radiotherapy were not included in the analysis.

Adverse events described in individual studies varied. The most commonly reported adverse events were bleeding and respiratory problems including breathing difficulties, pneumonia, and airway oedema. It should be noted that these adverse events relate to surgical treatments only. Different adverse events may be expected to occur in TORS, conventional surgery, and (chemo)radiotherapy patients.

\textbf{Table 5: adverse events reported in study participants undergoing TORS}

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of cancer</th>
<th>TORS adverse event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter (2017)\textsuperscript{7} Cases series</td>
<td>Unknown primary</td>
<td>3/32 (9%)</td>
</tr>
<tr>
<td></td>
<td>Chest infection, n=1</td>
<td>Postoperative bleeding, n=2</td>
</tr>
<tr>
<td>Fu (2016)\textsuperscript{6} Systematic review</td>
<td>Unknown primary</td>
<td>7/85 (8%)</td>
</tr>
<tr>
<td></td>
<td>Haemorrhage, n=4</td>
<td>Gastrostomy, n=1</td>
</tr>
<tr>
<td></td>
<td>No return to oral diet, n=1</td>
<td>Tongue swelling, n=1</td>
</tr>
<tr>
<td>Channir (2015)\textsuperscript{19} Case series</td>
<td>Unknown primary</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td></td>
<td>Temporary impaired tongue sensitivity, n=1</td>
<td>Breathing difficulties, n=1</td>
</tr>
</tbody>
</table>
Fourteen deaths and eleven injuries that occurred during any robot assisted head and neck surgery were reported in the USA between 2009 and 2015. All but one occurred during TORS. The majority of these deaths (86%) and injuries (73%) were reported between 2009 and 2012, the first three years of robot assisted head and neck surgery. The most common cause of death was post-operative bleeding (79%) and the most frequent injury was intra-operative thermal and/or mechanical injury to the lip or oral cavity. It was concluded in all cases that the robotic device had performed as expected during the surgery.
No incidents attributable to any da Vinci robot assisted surgery have been recorded by the NHSScotland Incident Reporting and Investigation Centre (IRIC) database (C Campbell, IRIC. Personal communication, 30 August 2017). One incident relating to dismantling the robotic system was recorded on the NHS Greater Glasgow and Clyde risk management system (C Campbell, IRIC. Personal communication, 20 September 2017).

The NHS England National Reporting and Learning System (NRLS) recorded 104 incidents relating to the da Vinci robotic device/equipment between 2007 and 2017. Of these incidents, 95 were categorised as no harm, eight as low harm and one as moderate harm (P Salter, Oversight and Business Support Officer, NRLS. Personal communication, 10 October 2017).

A total of 10,624 (0.6%) adverse events associated with any da Vinci robot assisted surgery (n=1,745,000) were reported in the USA between 2000 and 2013. These adverse events included 144 deaths (1.4%), 1,391 injuries (13.1%), and 8,061 da Vinci robotic device malfunctions (75.9%). Complex surgeries, such as head and neck surgery, had a higher rate of injuries, deaths and conversions to open surgery per procedure compared with surgical specialties, such as urology, that used robotic surgery more extensively.

**Learning curve**

The learning curve for any procedure can be conceptualised as the number of procedures required for an individual to reach a defined measure of adequacy or competence. Comparison of the learning curve for a surgical procedure requires consideration of potential confounding factors such as skill, previous experience and training of the surgeon(s)/surgical assistant(s)/surgical team, extent of supervision, and patient factors such as tumour complexity and comorbidities.

Three studies were identified that reported on aspects of the surgical learning curve for TORS in patients with head and neck cancer. Studies varied in the number of cases examined, the measure of adequacy/competence used, type of cancer, and method of learning curve assessment. The studies did not specify a pre-defined competency level but instead sought to identify plateaus or changes over time in selected metrics.

A retrospective cohort study (n=160) assessed the learning curve for three surgeons performing TORS for oropharyngeal cancer at a tertiary care centre. Supervised surgeries were excluded. The surgeons were described as having several years’ experience of open surgery. Each surgeon’s TORS performance was assessed against their overall average performance using both surgical process measures (surgical margin status and time to resection) and patient outcome measures (duotube placement rate, length of hospital stay, and 30-day readmission rate). Patients assigned to one surgeon, who appeared to have less prior experience, had a lower mean age compared with patients assigned to the other surgeons. The learning curves for positive final margins peaked at 27 cases, 25 cases and >37 cases. For positive initial margins, learning curves peaked at 15 cases and 22 cases (no peak occurred for one surgeon). Margin status was agreed in collaboration with the surgeon(s) and the positive margin rate was higher than in other published studies, which may have affected study conclusions. Peaks in the learning curves for time to resection occurred after 40 cases, 30 cases, and 27 cases. There was no consistent evidence of a learning curve for any of the patient measures considered. The study concluded that the surgical learning curve for TORS in oropharyngeal cancer patients varied by surgeon and ranged from 15 to 40 cases depending on the metric used.

A prospective cohort study (n=168) reported four years’ experience of TORS for head and neck tumours at a tertiary care centre. Ninety-five percent of patients had malignant tumours; 66% were
oropharyngeal. The number and previous experience of surgeons are not described. The cohort was divided into four equal groups of 42 patients based on date of surgery. The learning curve is described as the change in each outcome measure between groups (over time). Both surgical process and patient outcome measures were used: operative time, total intubation time, number of post-operative tracheostomies/feeding tubes, length of hospital stay, margin status, and rate of complications. There was no statistically significant change over time in positive margin rate, number of salvage cases or number of tracheostomies/feeding tubes. There was a statistically significant decrease in mean operative time from 3 hours 3 minutes (range 24 minutes to 6 hours 7 minutes) in group one, to 1 hour 26 minutes (range 32 minutes to 3 hours 23 minutes) in group four, p<0.001. The wide range in operative times, however, suggests high variability in case complexity which limits the validity of these results. The study reported an 87% reduction in mean intubation time from 12.9 hours (range 1 to 72 hours) to 1.7 hours (range 1 to 2 hours), p=0.001. This result is likely misleading due to distant outliers for intubation time that artificially increase the mean in groups one to three. If these outliers were removed it is likely that the change in intubation time would not be statistically significant.

A small prospective study (n=24) described eighteen months’ experience of TORS in patients with supraglottic, pharyngeal or oral cancer at one hospital. Patients were divided into two groups of 12 based on surgery date. The number of surgeons is not reported. The authors state that participating surgeons had extensive prior experience with transoral laser surgery and access to TORS-specific training. Two surgeons appear to be present during some surgeries. There was a statistically significant reduction in overall procedure time between the first (117 ± 64 minutes) and second (66 ± 33 minutes) group, p=0.014. Procedure time may have been affected by the location, type and size of tumour being removed. There was a statistically significant inverse correlation between the sequential order of cases and overall procedure time (r=-0.59, p=0.002). The authors suggest the learning curve for TORS in surgeons familiar with transoral laser surgery may be relatively short.

Volume-outcome

Three studies were identified that explored volume-outcome relationships for TORS in patients with head and neck cancer. Two studies reported on the relationship between hospital TORS case volume and outcomes in patients with oropharyngeal cancer. Both studies were retrospective analyses of data from the US National Cancer Database and consequently are subject to the same potential coding bias. There is overlap in the patient sample in the two studies due to the data years analysed: 2010-2011 and 2010-2013. The older study reported more patient outcomes and the most recent study covered a larger sample of patients.

The most recent analysis used data from 3,071 patients who received primary surgery for the treatment of oropharyngeal cancer. Hospitals were divided into quartiles based on volume of oropharyngeal cancer cases treated with a primary surgical approach between 2010 and 2013 inclusive: 1 to 4 cases, 5 to 15 cases, 16 to 32 cases, and 34 to 155 cases. Approximately a quarter of patients in the sample were treated with TORS (27.6%, n=846). In multivariate analysis, high volume hospitals (34 to 155 cases) were statistically significantly more likely to use TORS compared with low volume hospitals (1 to 4 cases): odds ratio (OR) 9.07, 95% CI 3.19 to 25.79, p<0.001. This relationship was also statistically significant when comparing each of the middle two quartiles (5 to 15 cases and 16 to 32 cases) with the lowest volume hospitals. Positive margin rates were statistically significantly lower in high volume hospitals (34 to 155 cases) compared with low volume hospitals (1 to 4 cases): 8.2% versus 16.7%, p=0.001. There was therefore an inverse association between number of TORS procedures and positive margin rate.
In the older analysis hospitals were divided into two categories: high volume centres with more than ten TORS cases and low volume centres with ten TORS cases or less\(^40\). The study included 877 patients with oropharyngeal cancer who received TORS. Positive margin rate was statistically significantly lower in high volume TORS centres compared with low volume centres: 15.8% versus 26.1%, \(p<0.001\). There was no statistically significant difference in length of hospital stay following TORS between low and high volume centres (4.4 versus 4.8 days, \(p=0.36\)). Low volume centres did however have a statistically significantly higher rate of unplanned readmissions following TORS compared with high volume centres: 6.1% versus 3.1%, \(p=0.03\).

One additional study reported on the relationship between surgeon case volume and post-operative complication rates\(^41\). This was a voluntary Internet based survey of TORS surgeons who were identified through a database held by the da Vinci robot manufacturer (Intuitive Surgical Inc.). This may have introduced bias to the study as 39/45 respondents were industry sponsored. Recall bias may have been introduced by the study design. Patients were heterogeneous, including both benign and malignant disease. A total of 2,015 TORS procedures were reported by respondents, with a median of 25 procedures per surgeon (range 4–750). Surgeon case volume was divided into three categories: <25 cases (25 surgeons), 26-50 cases (16 surgeons), >50 cases (4 surgeons). Overall complication rates were statistically significantly lower for surgeons performing more than 50 TORS procedures compared with surgeons performing less than 50 procedures: OR 2.4, 95% CI 1.6 to 3.4, \(p<0.0001\). Note however, that two surgeons contributed almost half of the total TORS procedures reported and had lower complication rates than other surgeons. Only four surgeons performed more than 50 TORS procedures.

**Cost effectiveness**

**Head and neck cancer of unknown primary**

Only one study was identified that provided evidence on the relative costs and effectiveness of TORS for localising the primary tumour in patients with head and neck cancer of unknown primary\(^43\). The key limitation with this study is that the comparator in the study (lingual tonsillectomy) is not the comparator used in this Evidence Note (blind biopsy). As such, the study was not included in the clinical effectiveness section and is only described here to illustrate the potential cost and effectiveness implications of TORS.

The study was a small retrospective chart review (n=25) from a hospital in the US. Three procedures were compared in the analysis: transoral robotic tongue base mucosectomy (TORS) followed by traditional exam under anaesthesia (EUA) with lingual tonsillectomy (hereafter referred to as ‘sequential EUA/TORS’); simultaneous TORS with EUA lingual tonsillectomy (‘simultaneous EUA/TORS’); and traditional exam under anaesthesia with lingual tonsillectomy (EUA).

The study concluded that the use of TORS may lead to an improved tumour detection rate. A 30% detection rate was assumed for the EUA group based on published literature. Of the eleven patients undergoing sequential EUA/TORS, the tumour was correctly identified in nine patients (87%). There was an identification rate of 100% in the six patients who underwent simultaneous EUA/TORS. These detection rates were higher than those reported in the studies described in the clinical effectiveness section of this evidence note.

Comparative costs and detection rates for the three interventions are presented in Table 6. EUA was much less costly than the EUA/TORS options, but also had a lower detection rate.
Table 6: costs* and effectiveness (detection rate) for each of the three treatment groups

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Hospital costs</th>
<th>Physician costs</th>
<th>Total costs</th>
<th>Detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUA</td>
<td>£641</td>
<td>£407</td>
<td>£1,048</td>
<td>30%</td>
</tr>
<tr>
<td>Sequential EUA/TORS</td>
<td>£4,098</td>
<td>£735</td>
<td>£4,833</td>
<td>87%</td>
</tr>
<tr>
<td>Simultaneous EUA/TORS</td>
<td>£4,652</td>
<td>£760</td>
<td>£5,412</td>
<td>100%</td>
</tr>
</tbody>
</table>

*All costs have been converted from US dollars (USD) to Great Britain pounds (GBP)

Other important limitations of this study include:

- The study was performed from a third-party payer perspective which excluded hospital fixed costs. Hence the cost of purchase, amortization and maintenance of the da Vinci® robot system have not been taken into account. Further, the US healthcare costing approach is likely to mean the costs presented are not generalisable to the UK setting.
- The effectiveness of each intervention has been expressed as the proportion of primary tumours detected. Data surrounding impact on clinical decision-making and subsequent outcome data are required in order to more fully assess the effectiveness of the interventions.
- The study is based on a small sample and is retrospective. Patients have not been randomised to the intervention groups and participant characteristics for each group have not been provided meaning there is a high risk of bias.
- The 100% tumour localisation in the simultaneous EUA/TORS group is likely to be artificially high due to the small sample size. The authors suggest a more likely identification rate of between the overall rate of 86.4% in this study and the highest published rate of 94%.

Oropharyngeal cancer

The cost-effectiveness evidence for oropharyngeal cancer comes from four studies comparing TORS with radiotherapy (RT) or chemoradiotherapy (CRT) in patients with early stage oropharyngeal cancer. All studies are from the US, therefore the costs reported here have been converted from USD to GBP.

**Rodin et al (2017)**

Rodin et al (2017) developed a state-transition model to compare TORS with RT alone in patients with oropharyngeal cancer (T1-2, N0-1). The model was based on a lifetime time horizon and assumed a discount rate of 3%. Data to inform the model were drawn from the literature.

Clinical parameters for the RT arm of the model were based on a single arm study that sought to address the feasibility of RT for oropharyngeal cancer. Model inputs for TORS were based on systematic reviews or the best available evidence source. Key health states within the model included overall survival and disease-free survival, both of which were assumed to be improved with TORS versus RT alone.

Cost data incorporated direct medical costs including surgery, RT, adjuvant therapy and support therapy. The analysis included non-medical costs such as patient transportation and patient time. Capital costs associated with the robot were not included.
The results of the model showed that RT had an overall cost of $123,410 (£94,101) and generated 10.43 quality-adjusted life years (QALYs). TORS had an overall cost of $178,480 (£136,086) and generated 11.10 QALYS. As such, TORS was associated with an increase in cost of $58,070 (£44,276) and 0.67 additional QALYs, resulting in an incremental cost effectiveness ratio (ICER) of $82,190 (£62,667) per QALY. The probabilistic sensitivity analysis indicated that at a willingness-to-pay threshold of $50,000 (£37,520) the probability of TORS being cost-effective is 40%.

There are some key limitations to this study. The analysis assumes that TORS is associated with an improvement in overall and disease-free survival which does not reflect the clinical effectiveness evidence. Furthermore US cost data may not be generalisable to the UK and the study includes two key assumptions that favour the intervention arm (inclusion of non-medical costs and omission of robot costs).

Overall, the findings of this analysis suggest that TORS is not cost-effective compared to RT. Furthermore, study limitations undermine the applicability of the findings to the UK setting.


Rudmik et al (2015)\textsuperscript{46} carried out an analysis using a decision tree and Markov model to compare the cost-effectiveness of TORS and intensity-modulated radiotherapy (IMRT) for patients with early stage oropharyngeal cancer (T1-2, N0). The model was from a US third party payer perspective, assumed a five year time horizon and used a discount rate of 3.5%.

Clinical data to inform the probabilities within the model were drawn from the literature, with the model assuming a small advantage in disease-specific survival in the IMRT arm. There was assumed to be a reduced likelihood of TORS related morbidity compared to IMRT related morbidity. For example, xerostomia and osteoradionecrosis were fairly common events within the IMRT arm.

Utility values were applied to each of the health states using validated utilities from other cost-effectiveness analyses. Cost data included healthcare costs only.

Over the five year time horizon the TORS strategy cost $30,992 (£23,621) and generated 4.81 QALYs. The IMRT strategy cost $26,033 (£19,842) and generated 4.78 QALYs. The ICER for TORS was therefore $165,300 (£125,991) per QALY, which exceeds commonly applied willingness-to-pay thresholds.

The studies by Rodin et al (2017) and Rudmik et al (2015) differed in the time horizon, payer perspective, assumptions about need for adjuvant therapy following TORS and discount rate. These methodological differences, in addition to the clinical data on disease-specific survival that favours TORS in Rodin et al (2017) but not in Rudmik et al (2015), may explain the difference in ICERs between the two studies.

de Almeida et al (2014)

A US cost-utility analysis assessed the cost effectiveness of TORS compared with (chemo)radiotherapy (CRT) for the treatment of oropharyngeal cancer with any N stage\textsuperscript{44}. A decision tree and Markov model were used based on a ten year time horizon. A societal perspective was adopted.

The methods used to conduct the analysis were similar to the aforementioned cost-effectiveness studies. Model parameters were determined from published systematic reviews, duration of time in each health state was based on published expert opinion and cost data were drawn from a single US institution. Treatment costs did not include robot costs but did include patient costs and lost wages.
The results of the analysis showed that the cost of TORS was $50,408 (£38,403) compared with CRT which cost $51,778 (£39,441). TORS generated 7.11 QALYs compared to 6.86 with CRT. As such TORS was found to offer cost savings ($1,366 (£1,040)) and increased benefits (0.25 QALYs). Base case results were sensitive to variations in adjuvant therapy but even if 100% of patients received adjuvant therapy following TORS the ICER only increased to $50,000 (£38,087).

Patient differences in this study may explain why the results seem to contradict more recent studies. In de Almeida et al (2014) a quarter of the patients had more advanced oropharyngeal cancer than in the other studies which affected the RT outcome data used. The proportion of patients needing adjuvant therapy following TORS was lower in this study than in Rodin et al (2017) and a proportion of patients in the comparator arm received chemotherapy as well as radiotherapy which increased costs in the comparison arm. Moreover, the probability of distant metastases seemed to favour TORS more than in other studies and the non-medical savings associated with TORS were higher than in Rodin et al (2017).

Sher et al. (2015)

Another US study compared the cost-effectiveness of TORS and chemoradiotherapy in patients with HPV-positive oropharyngeal cancer. The methods used were similar to the studies above. However in this study the base case analysis showed that CRT was associated with a mean total cost of $50,100 (£38,162) and 7.31 QALYs compared to $62,200 (£47,381) and 7.29 QALYs for TORS. This makes CRT the dominant strategy as it results in decreased costs and increased QALYs. It is worth noting that most of the increased cost and QALY decrement following TORS was attributed to adjuvant CRT. Hence, in the hypothetical scenario that no patients require adjuvant CRT, the total mean cost and quality-adjusted life expectancy for patients receiving post-operative RT alone would be $51,000 (£38,850) and 7.35 QALYs. This would make TORS the likely cost-effective alternative at an ICER of $23,000 (£17,520) per QALY. A sensitivity analysis showed that in the case of a large relative improvement in locoregional recurrence and associated utilities following surgery TORS would become the higher value treatment.

Based on the four cost-effectiveness studies discussed above, there seems to be considerable uncertainty around the cost-effectiveness of TORS compared to RT/CRT in patients with oropharyngeal cancer. Cost-effectiveness in this population seems to vary with the use of adjuvant therapy, post-surgical disease recurrence and type of costs used. Based on US data the balance of evidence suggests that TORS may not be cost-effective in patients with oropharyngeal cancer. However the results presented need to be considered in the context of available funding and local priorities. Long-term randomised studies are still needed to establish the potential health-related outcomes for TORS which would help to inform cost effectiveness analyses that are applicable to the UK setting.

Supraglottic cancer

No cost-effectiveness evidence was identified on the use of TORS in patients with supraglottic cancer.
Conclusion

It was difficult to determine the impact on quality of life and survival attributable to TORS in published studies due to a lack of properly controlled prospective comparisons and the use of adjuvant therapy in a proportion of patients receiving TORS. None of the studies identified reported long-term oncological outcomes.

Detection rates of approximately 50% were reported for TORS mucosectomy/lingual tonsillectomy in small case series in patients with head and neck cancer of unknown primary. Heterogeneity in prior investigations received by patients in the studies identified, lack of prospective comparative studies and uncertainty about the impact of locating the primary tumour on treatment and patient outcomes, limits the conclusions that can be drawn on the clinical effectiveness of TORS in this patient population. No conclusions could be drawn on the cost-effectiveness of TORS in patients with head and neck cancer of unknown primary.

Based on a small number of non-randomised comparative studies, there was no statistically significant difference in survival between patients with oropharyngeal cancer treated with TORS and those treated with (chemo)radiotherapy. Swallowing-related quality of life was statistically significantly better in patients treated with TORS compared with (chemo)radiotherapy. Conflicting evidence on the cost-effectiveness of TORS compared with (chemo)radiotherapy in patients with oropharyngeal cancer prevented any conclusions being reached on whether TORS was cost-effective in this patient group.

Results from studies comparing TORS with conventional surgery were limited and inconsistent. This prevented conclusions being drawn about quality of life or survival outcomes in these comparisons. No studies were identified that evaluated cost-effectiveness of TORS compared with conventional surgery.

No conclusions could be drawn on the clinical effectiveness of TORS in patients with supraglottic laryngeal cancer due to a lack of prospective comparative studies in this patient population. Cost-effectiveness of TORS in this patient group could not be assessed due to a lack of published economic evaluations.

Adverse event rates for TORS were highly variable. This variation may be the result of several factors including variation in study sample sizes, heterogeneity of patient populations, different levels of surgeon experience, heterogeneity in baseline disease severity, or differences in adverse event definitions.

Studies assessing the surgical learning curve for TORS in patients with head and neck cancer included varied patient groups and did not pre-define surgical competence. Only one study reported number of cases required to achieve competence and this varied between the three surgeons assessed. Therefore it was not possible to reach a robust conclusion on the number of cases required for TORS competence.

Two retrospective studies, with overlapping patient samples, concluded that hospitals with high volumes of TORS oropharyngeal cancer procedures had lower positive margin rates compared with low volume hospitals. The different definitions of high volume used in these studies suggests there is uncertainty about the volume of TORS cases required for optimal patient outcomes.

Identified research gaps

Based on the IDEAL framework for assessment of surgical interventions44, TORS appears to be at an early stage of evidence development. Most studies are non-comparative case series aimed at increasing
technical (surgical) skills and experience of the procedure (stage 2a development). Therefore future research should focus on:

- Randomised controlled trials (RCTs) or prospective comparative observational studies that compare TORS mucosectomy or lingual tonsillectomy with blind biopsy in the diagnosis of head and neck cancer of unknown primary. Studies should focus on diagnostic accuracy, quality of life, survival, and cost-effectiveness.
- RCTs with long-term follow-up to establish the health-related outcomes of TORS in patients with oropharyngeal cancer to help inform cost-effectiveness analyses that are applicable to the UK setting.
- RCTs or prospective comparative observational studies that compare TORS with radiotherapy in patients with supraglottic laryngeal cancer. Studies should focus on survival, quality of life and cost-effectiveness.

**Equality and diversity**

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on [www.healthcareimprovementscotland.org](http://www.healthcareimprovementscotland.org).

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A glossary of commonly used terms in Health Technology Assessment is available from [htaglossary.net](http://htaglossary.net).

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References


