NHS England

Evidence Review:

Robotic assisted trans-oral surgery for throat and voice box cancers

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Contents

1. Introduction

Transoral Robotic Surgery (TORS) is a relatively new surgical technique that permits removal of throat and voice box cancers through the mouth. TORS enables the surgeon to resect squamous and non-squamous cancers without disrupting the external muscles of the throat. While Transoral Laser Microsurgery (TLM) has been widely used for Head and Neck Cancer treatment, TORS is seen by some as a progression on the existing techniques using a sophisticated, computer-enhanced system to guide the surgical tools, giving better access to tumours in otherwise hard to reach areas in this region. TLM and TORS are both procedures that permit natural orifice surgery with some differences in the technique used to remove the cancers.

TORS requires expensive equipment, which represents a capital cost as well as the cost of consumables. Currently providers are reimbursed for the TORS procedure through national tariff, with separate additional payment for the cost of the robotic consumables, which is a specific tariff exclusion.

2. Summary of results

The research questions to inform the evidence review sought to determine whether there is sufficient evidence of clinical and cost effectiveness for Transoral Robotic Surgery (TORS) as a surgical option for patients with head and neck cancers compared to existing surgical techniques. Comparator interventions included open surgery, chemotherapy and radiotherapy and Transoral Laser Microsurgery (TLM).

Clinical effectiveness is assessed in terms of oncological outcome (survival and disease-free survival), functional outcomes, quality of life and adverse effects. Secondary outcomes are those associated with perioperative outcomes e.g. length of stay, complications etc.

The overall grade of evidence for this clinical evidence review is Grade D, reflecting the reliance on case series in the systematic reviews and the complete absence of randomisation in any of the studies, therefore introducing a high risk of bias. There was one recently published study on cost effectiveness of TORS. All studies were on adult patients. None of the studies were specifically designed to analyse outcome of TORS by disease stage. In the studies where tumour staging was specified, the majority of patients included had early oropharyngeal carcinoma (listed as early stage or T1/2, with N0/1 staging specified only in Choby et al 2015). Some studies included patients across all tumour stages (Hutcheson et al 2015, Weinstein et al 2012, Richmon JD et al 2014). Genden et al 2011 included 73% patients in Stage III-IV patients in the thirty patient case series.

Overall the literature review identified 5 systematic reviews all graded as having a high risk of bias (1-) due to the reliance on non-randomised case series studies as the primary source of data. The literature review identified 3 cohort studies directly comparing 2 or more interventions and one cohort study looked at survival outcome for TORS cases. Nine case series studies (excluding those reported in the systematic reviews) were identified and excluded as lower grade evidence sources and no further action was taken with them in the review.

Oncological outcomes:

Three systematic review papers (Yeh et al 2015, Kelly et al 2014 and de Almeida 2014) were identified that described oncological outcomes in terms of survival and disease-free survival of cancers of the oropharynx. All three papers describe the findings from primary research papers with limited follow up (less than 2 years). Two of the reviews (Yeh et al 2015 and de Almeida et al 2014) are comparisons to Intensity Modulated Radiotherapy and concluded that there was no advantage in terms of survival. The final paper (Kelly et al 2014) did not include comparisons to other interventions.With regards to locoregional control the review authors conclude that TORS is equivalent to comparator interventions (IMRT or chemoradiation) in control of disease.

A cohort study of 410 patients treated across 11 centres treated with TORS with or without chemotherapy or radiotherapy (de Almeida 2015) found that the 2- year locoregional control rate was 91.8% (95%CI, 87.6%-94.7%), disease-specific survival was 94.5% (95%CI, 90.6%-96.8%), and overall survival was 91%(95%CI, 86.5-94.0%).

Functional outcomes and Quality of Life (QoL) measures:

The consensus across the systematic review literature (Yeh et al 2015, Hutcheson et al 2015) is that TORS has

improved functional outcomes, with lower rates of feeding tube usage, and better quality of life outcomes around swallowing and oral feeding than in comparators. When comparing between TORS and radical open surgery (Park et al 2013) and CRT (Genden et al 2011), the authors found in unmatched case cohort studies more favourable outcomes for TORS in terms of functional and QoL measures.
Adverse events:

Comparison of adverse events is problematic for a large part of the literature where comparators treatments are not both surgical, and there is some cross over with reporting of functional outcomes.

Perioperative outcomes:

One systematic review (Chan et al 2015) summarised perioperative outcomes for TORS but without comparison to another therapeutic modality. A single study of 9601 patients undergoing treatment for head and neck cancers (Richmon et al 2014) found that TORS (n=116) was associated with significantly shorter lengths of stay in hospital.

Safety and learning curve:

The clinical evidence review was asked to address the question of the impact of the surgeon or centre volume on outcomes. Largely the literature is weighted towards a small number of centres or surgeons who have been pioneering the use of TORS, and therefore impact of the surgeon or centre volume is difficult to assess. The evidence review identified 5 case series (evidence level 3) that described experiences of the authors in the first cases of use of TORS. Findings were comparable between the papers, identifying good clinical perioperative and post functional outcomes across the time series. Two reports found no evidence of a learning curve measureable in terms of shortening operative times (Richmon et al 2011 and Vergez et al 2012), and this was explained by either the preparatory programme of work prior to the first surgery, or the inclusion of senior experienced surgeons as a part of the surgical team. Across the 3 remaining reports (Lawson et al 2011, Hans et al 2012, and White et al 2013) reductions in operative and total surgical times were observed. In the first two reports, a significant reduction was observed between the first half of the case series and the second (split at the 10-12 case). The latter report described a 4 year time series during which there was constant improvement in operative times, total surgical times and hospitalisation time. Even within this longer time series, rapid improvements in time metrics were observed in the first 10-20 cases. In all cases, the patients were not randomised in whether they received TORS but were subject to rigorous selection processes.

Cost effectiveness:

Comparative cost effectiveness modelling of TORS based on systematic review (De Almeida JR et al, 2014) found that over a 10-year time horizon, without taking capital cost into account, the cost of TORS compared to the cost of (chemo) radiotherapy is expected to result in a cost savings to the society of $1366 USD [£871 based on the exchange rate reported on XE.com on 26/10/15] per patient treated and incremental effectiveness of 0.25 QALY/ patient. The cost effectiveness reduces progressively as adjunct therapy is added to the treatment plan. The costing data is based on a US single centre clinical costs and US societal value estimates, limiting the direct application of the study in UK context.

3. Research questions

What evidence is available on the clinical effectiveness of transoral robot-assisted surgery compared to existing conventional surgical techniques and transoral laser microsurgery, primary (chemo)radiation therapy?

What evidence is available on the cost effectiveness of transoral robot-assisted surgery compared to existing conventional surgical techniques and transoral laser microsurgery, primary (chemo)radiation therapy?

What is the impact of surgeon or centre volume on the clinical and cost effectiveness of transoral robot-assisted surgery?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Level	Study design and			Outcomes							Reference	Other		
Level of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Study Endpoint	Study Endpoint Result	Reference	Complications noted	Benefits noted	Comments
3	Case series	34	TORS	Clinical effectiveness of the intervention	Quality of Life	The University of Washington Quality of Life, version 4, questionnaire was completed by patients preoperatively and at 1-, 6-, 12-, and 24-month intervals after TORS. Demographic, clinicopathologic, and follow-up data were collected. RESULTS: Mean follow-up time was 14 months (May 1, 2010, to April 30, 2014). Most patients had T1 (20 [59%]) or T2 (13 [38%]) and N0 (13 [38%]) or N1 (16 [47%]) disease. Statistically significant improvement in QOL outcomes was noted in the following postoperative domains: chewing from 1 month (median, 50 [IQR, 50-100]) to 12 months (100 [IQR, 100-100]; P = .048), swallowing from 1 month (70 [IQR, 30-85]) to 6 months (100 [IQR, 70-100]; P = .047) and 1 to 24 months (100 [IQR, 70-100]; P = .048), pain from 1 month (38 [IQR, 25-75]) to 6 months (88 [IQR, 75-100]; P = .006) and 1 to 12 months after surgery (100 [IQR, 75-100]; P = .01), and activity from 1 month (63 [IQR, 50-88]) to 24 months (100 [IQR, 75-100]; P = .03). Two participants (6%) died during the follow-up period: 1 because of disease and 1 because of a myocardial infarction. Two patients (6%) required temporary gastrostomy tube placement, but none required tracheostomy. CONCLUSIONS AND RELEVANCE: Appropriately selected patients who undergo TORS alone for oropharyngeal squamous cell carcinoma experience acceptable short- and long-term QOL outcomes.	NA	NA	NA	NA	Choby, Garret W.; Kim, Jeehong; Ling, Diane C.; Abberbock, Shira; Mandal, Rajarsi; Kim, Seungwon; Ferris, Robert L.; Duvvuri, Umamaheswar. Transoral robotic surgery alone for oropharyngeal cancer: quality-of-life outcomes. JAMA Otolaryngol Head Neck Surg 2015;74(3):124-128.	NA	Acceptable functional and QOL outcomes under TORS	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series with low numbers.
3	Case series	13	-	-	Perioperative outcomes	Thirteen of 126 patients underwent TORS supraglottic laryngectomy for laryngeal cancer. Average robotic operative time and estimated blood loss were 25.3 minutes and 15.4 mL, respectively. Negative surgical margins were achieved in all patients. Eleven patients were started on an oral diet within 24 hours of surgery with no evidence of immediate airway compromise. Two patients (15.4%) received adjuvant radiation therapy based on pathology.	NA	NA	NA	NA	Ozer, Enver; Alvarez, Bianca; Kakarala, Kiran; Durmus, Kasim; Teknos, Theodoros N.; Carrau, Ricardo L.. Clinical outcomes of transoral robotic supraglottic laryngectomy. Head Neck 2013;36(8):1138-1145.	NA	Safe procedure with good outcomes	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series with low numbers.
2-	Cohort	56 - 30 TORS and 26 open	TORS	Clinical effectiveness of the intervention compared to existing interventions	Oncological Outcomes, Functional outcomes and QOL outcomes	Oncological outcomes: There was no significant difference between the overall and disease-free survival times between the groups. TORS: The 3-year overall survival and disease-free survival rates were 85% and 81%, respectively. Radical open surgery group: The 3-year overall survival and disease-free survival rates of the radical open surgery group were 78% and 76%, respectively. Functional outcomes: shorter requirement for feeding tubes in TORS group - full swallowing ability by 8.4 days on average (2-14 days) cf. open surgery - full swallowing ability by 20.6 days on average (11-56 days). The average hospital stay for the TORS and radical open surgery groups were 26.1 days and 43.4 days, respectively. There were significant differences in swallowing function, time to de cannulation, and length of hospital stay between the groups ($p < 0.001$, $p < 0.001$, and $p = 0.045$, respectively) Quality of Life - using the University of Washington QOL score, TORS came out favourably for pain ($p = 0.013$), appearance ($p = 0.005$), activity ($p = 0.009$), recreation ($p = 0.005$), swallowing ($p = 0.03$), speech ($p < 0.001$), taste ($p = 0.039$), and anxiety ($p = 0.004$) between the two groups.	NA	NA	NA	NA	Park, Young Min; Byeon, Hyung Kwon; Chung, Hyun Pil; Choi, Eun Chang; Kim, Se-Heon. Comparison study of transoral robotic surgery and radical open surgery for hypopharyngeal cancer. Acta Otolaryngol. 2013;124(9):2089-2095.	NA	The oncologic outcome of TORS was comparable to that of conventional surgery. Benefits include the ability to save the larynx: "all patients in the TORS group could preserve their larynx, the larynges of only four patients (15.3%) in the radical open surgery group could be saved". Strong benefits in quality of life	Retrospective study. Not randomised and with the potential biases noted. Cohorts were comparable in terms of patient characteristics and tumour state.

3	Case series	22	TORS	Clinical effectiveness of the intervention	Quality of Life	The mean follow-up time was 19.8 months. There were overall declines in all quality of life scores during treatment period, which was followed by a continuous recovery. The scores immediately after transoral robotic surgery (3 weeks) were significantly higher than the scores after conclusion of adjuvant therapy (3 months) in multiple domains (P < .05) and the 6-month scores in speech (P = .02) and eating (P = .008) domains. All scores, except for eating (P = .01) returned to pre-treatment levels at 1 year. Patients with detected primaries displayed similar quality-of-life scores compared to patients with occult primaries. Human papillomavirus status and type of adjuvant treatment had no significant impact on quality of life.	NA	NA	NA	NA	Durmus, Kasim; Patwa, Hafiz S.; Gokozan, Hamza N.; Kucur, Cuneyt; Teknos, Theodoros N.; Agrawal, Amit; Old, Matthew O.; Ozer, Enver. Functional and quality-of-life outcomes of transoral robotic surgery for carcinoma of unknown primary. Laryngoscope 2014;124(8):1836-1842.	NA	NA	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series.
3	Case series	39	TORS	Clinical effectiveness of the intervention	Oncological and Functional outcomes	Thirty-seven patients (95%) had histologically clear margins of resection. Overall survival at 2 years was 96% and disease-free survival 92%. An oral diet was tolerable after a mean of 6 (range 1-18) days. No serious swallowing difficulties were seen on the videopharyngogram. Thirty-six of 38 patients could swallow well (97%) with FOSS scores ranging from 0 to 2 (1 patient had a poor score but was able to take an oral diet after postural training). Voices were maintained close to the normal range on the acoustic waveform analysis.	NA	NA	NA	NA	Park, Young Min; Kim, Won Shik; Byeon, Hyung Kwon; Lee, Sei Young; Kim, Se-Heon. Oncological and functional outcomes of transoral robotic surgery for oropharyngeal cancer. Br J Oral Maxillofac Surg 2013;145(2):248-253.	NA	Oncological and functional outcome acceptable for treatment of head and neck cancers	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series.
3	Case series	64	TORS	Clinical effectiveness of the intervention	QOL and Functional outcomes	Sixty-four patients who underwent TORS were enrolled. A total of 113 TORS procedures were performed. The mean follow-up time was 16.3 ± 7.49 months. The HRQOL was assessed at 3 weeks and at 3, 6, and 12 months, with a response rate of 78%, 44%, 41%, and 28%, respectively. TORS was performed most frequently for squamous cell carcinoma (88%). There was a decrease from baseline in the speech, eating, aesthetic, social, and overall QOL domains immediately after treatment. At the 1-year follow-up, the HRQOL scores in the aesthetic, social, and overall QOL domains were in the high domain. Patients with malignant lesions had significantly lower postoperative HRQOL scores in the speech, eating, social, and overall QOL domains (P < .05). Patients who underwent adjuvant radiation therapy or chemotherapy and radiation therapy had lower postoperative scores in the eating, social, and overall QOL domains (P < .05).	NA	NA	NA	NA	Hurtuk, Agnes M.; Marcinow, Anna; Agrawal, Amit; Old, Matthew; Teknos, Theodoros N.; Ozer, Enver. Quality-of-life outcomes in transoral robotic surgery. Otolaryngol Head Neck Surg 2012;139(8):773-778.	NA	NA	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series.
3	Case series	16	TORS	Clinical effectiveness of the intervention	QOL, Functional and Oncological Outcomes	A negative margin was reported in 88% patients. During the follow-up period, distant metastasis occurred in one patient at 6 months. The Kaplan-Meier disease-free survival at 1 year was 91%. Patients exhibited complete recovery of swallowing ability after an average of 8.3 days. Videopharyngogram study showed aspiration in one patient. The cannula could be removed at an average 11.2 days. The average hospital stay was 13.5 days. Concerning the results of the functional outcome swallowing scale and Voice Handicap Index 10, most patients (90.9%) subjectively reported favourable swallowing and voice function.	NA	NA	NA	NA	Park, Young Min; Kim, Won Shik; Byeon, Hyung Kwon; Lee, Sei Young; Kim, Se-Heon. Surgical techniques and treatment outcomes of transoral robotic supraglottic partial laryngectomy. Laryngoscope 2013;124(1):165-171.	NA	NA	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series.

2-	Cohort	9601 TORS n= 116	TORS	Clinical effectiveness of the intervention compared to existing interventions	perioperative outcomes	TORS procedures were not associated with significant differences in acute postoperative morbidity or mortality. The use of TORS was associated with significantly decreased length of hospitalization (21.5 days) and hospital-related costs (-$4,285).	NA	NA	NA	NA	Richmon, Jeremy D.; Quon, Harry; Gourin, Christine G.. The effect of transoral robotic surgery on short-term outcomes and cost of care after oropharyngeal cancer surgery. Laryngoscope 2014;137(2):151-156.	NA	The authors conclude that "National data demonstrates that TORS is associated with a lower incidence of perioperative gastrostomy and tracheostomy tube placement, with significantly decreased length of hospitalization and hospital-related costs compared to other surgical techniques. TORS appears to be a safer and more generalizable surgical technique for oropharyngeal cancer treatment."	Large study. No follow up data on outcomes beyond 30 days so no oncological outcomes. Comparator group is all other ablative procedures. No control is made for prior chemo or radio therapy.
2-	Cohort	56 - 30 TORS, 26 Concomitant Chemoradiotherapy	TORS	Clinical effectiveness of the intervention compared to existing interventions	Oncological outcomes Quality of Life outcomes	TORS group: Kaplan-Meier estimates of 18-month loco regional control, distant control, disease-free survival, and overall survival rates were 91%, 93%, 78%, and 90%, respectively (Fig. 2). Specifically, the 18-month local control and neck control rates were 91% and 100%, respectively. CRT group: The 18-month loco regional control, distant control, disease-free survival, and overall survival rates were 94%, 92%, 88%, and 100%, respectively. No significant differences between the two groups. QOL outcomes: Performance Status Scale for Head and Neck Patients (PSS-HN) and the Functional Oral Intake Score (FOIS). PSS-HN is a validated questionnaire method for evaluation of subjective swallowing function. It has eating in public, understand ability of speech, and normalcy of diet domains. The FOIS is an ordinal scale designed to assess the current status and functional change in the oral intake of patients with dysphagia. At 2 weeks after treatment TORS patients demonstrated significantly better eating and diet scores in PSS-HN and FOIS compared to CRT. By 3, 6, 9, and 12 months after treatment, there were no significant differences in eating, speech, diet, or FOIS between the two groups. In the TORS group, PSS-HN and FOIS returned to baseline within 9 months of surgery. In contrast, in the CRT group, diet and FOIS remained lower than baseline at 12 months after treatment.	Perioperative	LoS mean 2 days (1-7 days).	NA	NA	Genden, Eric M.; Kotz, Tamar; Tong, Charles C. L.; Smith, Claris; Sikora, Andrew G.; Teng, Marita S.; Packer, Stuart H.; Lawson, William L.; Kao, Johnny. Transoral robotic resection and reconstruction for head and neck cancer. Laryngoscope 2011;37(1):125-126.	NA	Comparable disease control outcomes between interventions, but favourable quality of life outcomes for the TORS group with better functional outcomes shortly after treatment.	Relatively small sized groups. Short follow up (18 months survival reported).
3	Case series	177	TORS	Clinical effectiveness of the intervention	Perioperative outcomes	There was no intraoperative mortality or death in the immediate postoperative period. Average estimated blood loss was 83 mL; no patient required transfusion. The rate of positive margins was 4.3%. Twenty-nine patients (16%) experienced 34 serious adverse events that required hospitalization or intervention (grade 3) or were considered life threatening (grade 4, 2.3%). Tracheostomy was performed in 12.4% of all patients (22/177), but only 2.3% had a tracheostomy at last follow-up. For all patients undergoing TORS without previous therapy, the percutaneous endoscopic gastrostomy dependency rate was 5.0%. The average hospital stay was 4.2 days.	NA	NA	NA	NA	Weinstein, Gregory S.; O'Malley, Bert W.; Magnuson, J. Scott; Carroll, William R.; Olsen, Kerry D.; Daio, Lixia; Moore, Eric J.; Holsinger, F. Christopher. Transoral robotic surgery: a multicenter study to assess feasibility, safety, and surgical margins. Laryngoscope 2012;48(6):560-566.	NA	Safe and feasible procedure	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series.

3	Case series	23	TORS	Clinical effectiveness of the intervention	functional outcomes	Overall survival at 3 years was 89% and disease-free survival was 84%. On the VEF study, serious aspiration or delay of swallowing was not observed during the pharyngeal stage of the swallowing process. Overall, 96% of the patients showed favourable swallowing abilities with an FOSS score ranging from 0 to 2. The fundamental frequency variation (vF0) and jitter were increased upon acoustic waveform analysis (vF0=2.71 ± 0.063, Jitter=2.01 ± 0.034), but the harmonic-to-noise ratio (HNR) and shimmer were maintained close to the normal range (HNR=1.28 ± 0.001, Shim=1.74 ± 0.036). The oncologic and functional results of TORS were quite acceptable for the treatment of hypopharyngeal cancer.	NA	NA	NA	NA	Park, Young Min; Kim, Won Shik; De Virgilio, Armando; Lee, So Yoon; Seol, Jeong Hun; Kim, Se-Heon. Transoral robotic surgery for hypopharyngeal squamous cell carcinoma: 3-year oncologic and functional analysis. Oral Oncol. 2012;139(11):1099-1108.	NA	Safe and feasible procedure	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series.
3	Case series	10	TORS	Clinical effectiveness of the intervention	oncological outcomes	All cancers treated were either T1 (40%) or T2 (60%). Negative margins were achieved in all patients. Four patients received adjuvant radiation therapy (40%). No patients experienced surgical complications and all had excellent functional outcomes. Mean follow-up was 24 months (range, 2-60 months) with loco regional and distant control achieved in 8 patients (80%) and 9 patients (90%), respectively.	NA	NA	NA	NA	Villanueva, Nathaniel L.; de Almeida, John R.; Sikora, Andrew G.; Miles, Brett A.; Genden, Eric M.. Transoral robotic surgery for the management of oropharyngeal minor salivary gland tumors. Head Neck 2014;19(1):60-66.	NA	Safe and feasible procedure	Paper considered, but not subject to detailed review due to the low grade of the evidence - case series.
1-	Systematic	0	TORS	Clinical effectiveness of the intervention compared to existing interventions	Oncological - survival and disease free survival Complications/Adverse Effects - Toxicity Functional Outcomes Quality of life	Oncological: Disease-free or disease-specific survival was reported in 14 papers following IMRT and 6 papers following TORS. Patients with higher T classification and overall TNM stage demonstrated worse overall survival, disease-free survival and loco regional control in patients undergoing IMRT. Overall survival was improved in the HPV-positive population. Disease-free survival was improved in all studies but one. Uncontrolled TORS studies have reported overall survival ranging from 81% to 100% and disease-free survival rates of 85.7% to 96%. Uncontrolled IMRT studies have reported overall survival rates of 69% to 100% and disease-free survival of 64% to 96%. Complications/Adverse Effects: Complications and toxicities are difficult to directly compare between the two treatment groups because different measures used. Fourteen IMRT studies and eight TORS studies reported on complications or toxicities in the management of oropharyngeal squamous cell carcinoma (OPSCC). In the IMRT studies, the major toxicities consistently reported were the rates of skin and mucosal toxicity. For the surgical approach, complications included fistula formation, postoperative haemorrhage and hematoma formation, as well as surgical site infections and pneumonias. Functional outcomes: Many of the TORS studies have demonstrated low rates of percutaneous feeding-tube and tracheostomy dependence—these rates compare favourably to those achieved with IMRT. The reports suggest lower long-term feeding-tube dependence with TORS (0%-20.7%) compared to IMRT (0%-18%). Five of the thirteen TORS studies reported none of their patients requiring a feeding-tube at one-year follow-up. All but one IMRT study demonstrated at least one patient feeding-tube dependent in long-term follow-up and this series included only early T-stage disease. Quality of Life metrics: Quality of life (QoL) analysis was included in four IMRT and three TORS studies; two additional studies included a comparison between TORS and IMRT. In the first of the comparison studies the researchers found that TORS patients had better QOL scores 6 and 12 months postoperative (no difference pre or 3 months post op). In the second study there was no significant difference between surgical and chemoradiation groups with the exception of the swallowing score. At 1 year 74% of the surgical patients reported, “swallowing as well as ever” versus only 32% of the patients who underwent chemoradiotherapy.	Cost Effectiveness	When compared to open surgical approaches to the oropharynx, studies have shown that TORS compares favourably. More challenging to make the comparison to IMRT. de Almeida et al. performed an extensive cost-analysis comparing the cost of TORS versus that of primary RT for the management of early T-classification oropharyngeal cancer. Their study accounted for variations in adjuvant therapy, costs, utilities, complications and recurrence rates. TORS demonstrated a cost savings of $1366 in addition to an increase of 0.25 QALYs. Not surprisingly, the subsequent sensitivity analysis demonstrated that with increasing rates of adjuvant treatment with TORS, and decreasing rates of concurrent chemotherapy with primary radiotherapy, TORS was less cost-effective.	NA	NA	Yeh DH, Tam S, Fung K, MacNeil SD, Yoo J, Winquist E, Palma DA, Nichols AC. Transoral Robotic Surgery vs. Radiotherapy for Management of Oropharyngeal Squamous Cell Carcinoma – A systematic review of the literature. European Journal of Surgical Oncology 2015;124(9):2096-2102.	NA	Based on the current literature, TORS appears to yield similar oncologic outcomes but better functional	Robust systematic review, which reports it's limitations and potential confounders. The methodology for identifying studies for inclusion was strong. The authors note that there are a few confounders/limitations: 1) most studies come out of a small number of high volume centres, 2) use of adjuvant therapies will confound the findings on QOL and outcomes, 3) none of the studies are RCT, and there is potential bias in patient selection.

1-	Systematic	Eight studies with 1,337 patients (1,010 patients with T1 or T2 tumours) investigated the role of IMRT. Twelve studies including 772 patients (502 patients with T1 or T2 tumours; 185 patients did not have stage indicated) investigated TORS.	TORS	Clinical effectiveness of the intervention compared to existing interventions	Oncological - survival and disease free survival Complications/Adverse Effects - Toxicity	Oncological: The present study suggests that there is no survival advantage of surgery over radiation. Both modalities confer excellent survival and loco regional control. The lack of individual patient level data, however, precludes a summary estimate comparing the two treatment modalities. IMRT: Four studies reported a 2-year overall survival ranging from 84% to 95.5%. TORS Two studies reported 2-year overall survival ranging from 82% to 94%. Note only 2 year survival. Adverse Event: different complications arise from the different treatment modalities. However the study suggests a lower rate of gastrostomy tubes in patients who have adjuvant treatment compared to those treated definitively and a markedly lower rate of gastrostomy tubes in patients having surgery alone. The authors suggest that these findings may translate to an improvement in quality of life and perhaps a cost saving.	NA	NA	NA	NA	de Almeida, John R.; Byrd, James K.; Wu, Rebecca; Stucken, Chaz L.; Duvvuri, Uma; Goldstein, David P.; Miles, Brett A.; Teng, Marita S.; Gupta, Vishal; Genden, Eric M.. A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: a systematic review. Laryngoscope 2014;272(2):463-471.	NA	The authors conclude that "Survival seems comparable, and differences between the two treatments are likely based on the specifics of their toxicity and complication profiles. Further comparative studies are needed to better elucidate these differences."	Clear methodology and exclusion/inclusion criteria. Study is limited to early stage oropharynx cancers. Query - the authors are unable to distinguish between tumours with an HPV background that are prognostically more favourable, and this presents a confounder. Systematic review of case series, so subject to potential sources of bias in the original research. No meta-analysis or comparisons possible.
1-	Systematic	441	TORS	Clinical effectiveness of the intervention	Functional Outcomes	Functional outcomes Feeding tube: Feeding tube rates were reported in all 12 studies. Excluding studies that restricted inclusion to early-stage disease and those that routinely prophylactically placed PEG tubes, 18–39 % of patients required PEG tubes in TORS series compared with 29–60 % of patients in definitive IMRT series Oral Intake: Measures of oral intake or dietary outcomes were reported in 8 studies. Time to oral intake varies by tumour stage. Early stage cancers oral intake began in 96% of patients on point of discharge. Mean time to oral intake was 2 days after TORS for T1–T3 OPC tumours. Swallowing related quality of life: MD Anderson Dysphagia Inventory (MDADI); 19-item composite summary scores were calculated per Chen et al. [28]. Composite MDADI scores reported among 89 patients in 3 studies at a mean follow-up of 12–13 months ranged from 65.2 to 78. c.f. compared with 73.6 to 74.1 in published series of OPC patients treated with nonsurgical chemoradiation approach. Small number of studies being compared so low quality evidence. The paper reports a comparative study: "No significant differences were observed in MDADI scores at 3 months, but patients treated with TORS have significantly better scores at 6 and 12 months, suggesting better long-term recovery after primary TORS compared with chemoradiation. Trends of better swallowing-related QOL in the TORS group were maintained when stratified by T-stage or oropharyngeal tumour subsite. Likewise, gastrostomy duration was shorter in the TORS (+adjuvant therapy) group compared with the primary chemoradiation group (mean duration gastrostomy: 3 months versus 6 months, respectively)". Findings from two case–control studies favour better long-term swallowing recovery with upfront transoral surgery (robotic or laser) and adjuvant radiation at postoperative doses. Long term functional follow-up: Long-term gastrostomy tube rates were reported in 426 patients from 11 studies and ranged from 0 to 7 %, with mean follow-up in most studies between 1 and 2 years. Paucity of data on swallowing. Favourable outcomes on diet, and long term airway and speech functioning. 2 patients out of 411 pooled were permanently tracheostomy dependent, and both were in series that included advanced-stage tumours.	NA	NA	NA	NA	Hutcheson, Katherine A.; Holsinger, F. Christopher; Kupferman, Michael E.; Lewin, Jan S.. Functional outcomes after TORS for oropharyngeal cancer: a systematic review. Eur Arch Otorhinolaryngol 2015;50(8):696-703.	NA	Conclusions ambiguous. Some benefits noted - promising swallowing outcomes and favourable gastrostomy utilization - lower in primary TORS series than in published IMRT benchmarks. Some gaps - inconsistency in the reporting of instrumental swallowing assessments and long term outcomes	All case series studies. No stratification in the primary research of HPV status. No randomisation in source research. How the published benchmarks for the gastrostomy in IMRT were identified is not made clear in the paper.

1-	Systematic	190	TORS	Clinical effectiveness of the intervention	Oncological - local control	Seven out of 11 studies reported recurrence rates: the aggregate rates of local, regional, and distant disease control were 96.2% (I-squared = 0.0, p = 0.94), 91% (I-squared = 0.0, p = 0.54) and 100% respectively (no statistical analysis performed for uniform results). The authors argue that this performance is favourable when compared to rates published for chemoradiation therapy.	Oncological - survival rates Functional outcomes	Oncological outcomes - survival: Seven out of the 11 studies reported survival rates. Disease-free survival was seen in 90% (I-squared = 0.0, p = 0.65), with an overall survival rate of 95% (I-squared = 0.0, p = 0.68). Follow-up ranged from 1 to 51 months with a mean of 19.9 months. Functional outcomes: The authors conclude that "In this review, only 5% of patients at 12 months remained GT-dependent following TORS; however, they did not control for CRT administration, dose or field. It is possible that with the potential for reduction or elimination of adjuvant CRT following primary TORS for early OPSCC, we may see an even greater reduction in post-treatment dysphagia and GT dependence." This low rate of Gastric Tube dependency is compared favourably to published literature on other treatment modalities.	NA	NA	Kelly, Kate; Johnson-Obaseki, Stephanie; Lumingu, Julie; Corsten, Martin. Oncologic, functional and surgical outcomes of primary Transoral Robotic Surgery for early squamous cell cancer of the oropharynx: a systematic review. Oral Oncol. 2014;138(7):628-634.	NA	Data suggest good treatment outcomes in terms of disease control, survival and function. However lack of comparative analysis to match cohorts limits the ability to make a definitive recommendation	Systematic review of case series. No direct comparison with other treatment modalities possible, and risk of publication bias in the reporting of comparators in the paper. Study design clear and well described.

1-	Systematic	44	TORS	Clinical effectiveness of the intervention	Perioperative outcomes	Mean robot time (n534) 68.8 min Mean total operating time (n=27) 157.0 min Mean estimated blood loss (n=40) 58.2 mL Mean follow-up (n=41) 18.5 mo Mean time to oral diets (n=22) 1.0 d Mean length of stay (n=32) 3.0 d High rate of unintended capsule violation of pleomorphic adenomas in this series at 24%, a rate much higher than with open approaches. With an average follow-up of 18.5 months in the cohort, there were no recorded recurrences of the primary neoplasms, but the follow up time isn't really sufficient	NA	NA	NA	NA	Chan, Jason Y. K.; Tsang, Raymond K.; Eisele, David W.; Richmon, Jeremy D.. Transoral robotic surgery of the parapharyngeal space: a case series and systematic review. Head Neck 2015;151(4):606-611.	NA	The authors are equivocal on the benefits of TORs. "TORS resection of PPS neoplasms seems to be a safe and feasible technique with minimal complications when compared to traditional transcervical techniques. Caution should be taken with pleomorphic adenomas given the relatively high likelihood of capsular violation and insufficient long-term data on recurrence rates." Transcervical routes to PPS can have higher rates of complications. The authors question whether TORS for PPS is truly minimally invasive and less morbid than transcervical approaches because of the surgical approach requiring division of membranes latterly associated with pain and in the absence of comparative data no conclusion can be reached.	Systematic review of case series data with the limitations that implies. Follow up periods were short - median less than 2 yrs, so efficacy of the intervention can not be judged.
3	Case series	20	TORS	Safety of the intervention	Learning Curve	The paper describes case series of the first 20 patients at the hospital to undergo TORS for head and neck cancers. The papers describes the perioperative outcomes associated with that learning curve. Average LoS 1.3 days. No patients required readmission and no long-term surgical complications were detected. No patient required a tracheotomy and no procedure was aborted secondary to inability to expose the tumour . Negative margins obtained in all ablative cases. Room set up averaged 24+/- 12 mins. Anaesthesia time averaged 22 +/-10 minutes. Patient positioning 38+/- 13 minutes. Operative time 71 +/- 54 minutes. Total time 242+/- 84 minutes. There were no significant differences (all P values >.5) in any of the time measurements above between the initial and subsequent 10 cases or the first 15 and last 5 cases although there was a trend toward shorter OT and TTR with greater experience.	NA	NA	NA	NA	Richmon, Jeremy D.; Agrawal, Nishant; Pattani, Kavita M.. Implementation of a TORS program in an academic medical center. Laryngoscope 2011;147(3):475-481.	NA	Prior to first surgery the authors had invested time in preparation of the TORS programme, and they point to this as reason why there wasn't a significant shortening of times involved in the procedure. Operative success as defined by negative margins and functional outcomes was noted as 'excellent'.	It isn't clear from the paper whether this is a case series for 1 surgeon or a full surgical team where variability between surgical practice can have impact on timing. Only perioperative outcomes with no evaluation of longer term oncological rates. One criticism of the 20 case series is whether the lack of significant difference between early and late times can be causally linked to their preparation as they conclude, or whether 20 cases is sufficient learning curve. However the outcomes they report, are compared favourably to the literature.

3	Case series	130	TORS	Safety of the intervention	Learning Curve	Study design: 130 patients across 7 surgical teams in 7 institutions. 4 patients identified as not suitable for TORS 116 out of 126 procedures were en bloc resections. Lack of surgical exposure resulted in 6 conversions to open surgery. Surgical exposure was rated as optimal in 74% of cases. Exposure challenges in the other 33 were multifactorial - anatomical, oncological or difficulty in accessing the tumour site. Average set up time 53+/- 46 minutes with surgical time of 90 +/- 92 minutes. Surgeon reported improvement in setup, exposure and dissection abilities but no significant decrease in times observed. Postoperative course simple for 84% of patients. 19 patients received tracheostomies - 2 performed as emergencies. 3 deaths due to medical diseases. Cost of additional experienced surgeon noted as a drawback but the authors report findings from the literature that indicates that this has lead to significant improvements in operative times.	NA	NA	NA	NA	Vergez, Sebastien; Lallemant, Benjamin; Ceruse, Philippe; Moriniere, Sylvain; Aubry, Karine; De Mones, Erwan; Benlyazid, Adil; Mallet, Yann. Initial multi-institutional experience with transoral robotic surgery. Otolaryngol Head Neck Surg 2012;139(6):564-567.	NA	Benefits of TORS in terms of postoperative course noted to be tied in with a preoperative selection process. TORS allows avoided a tracheostomy in a significant majority of cases. The authors note that with optimal instrumentation and a pair of trained senior surgeons, rapid progression on the TORS learning curve is seen for setup, surgical exposure, dissection, and patient selection.	The patient selection process is a large part of the study, and TORS was only approved following a pre visualisation by a multidisciplinary board. This could lead to some bias in the case complexity and therefore not generalisable to all head and neck cancers requiring surgical intervention. No randomisation of the procedure to cohorts of patients.
3	Case series	168	TORS	Safety of the intervention	Learning Curve	168 patients divided into 4 consecutive equally sized groups based on time. 31 deemed unsuitable for TORS. There was no statistically significant difference over time in initial positive margin status (2-5 per group), number of salvage cases performed (7-9 per group), number of tracheostomies required (2-4 per group), or feeding tubes required (22-25 per group) (P .99 for all). The frequency of TORS cases performed varied from month to month but increasing as experience increased. Total operative time showed a significant decrease with experience. Group 4 mean operative time was 86 mins which was significantly lower than the mean 183 minutes observed in group 1. Mean intubation time in group 4 was 1.7hrs compared to 12.9 hours in group 1. Length of stage decreased from 3 to 1.4 days (p <0.001). No significant difference in the number of patients requiring tracheostomy or feeding tubes.	NA	NA	NA	NA	White, Hilliary N.; Frederick, John; Zimmerman, Terence; Carroll, William R.; Magnuson, J. Scott. Learning curve for transoral robotic surgery: a 4-year analysis. JAMA Otolaryngol Head Neck Surg 2013;269(8):1979-1984.	NA	The authors state that they "demonstrated particular areas of expected improvement as case number increased in the following end points: (1) decrease in operative time, (2) decrease in postoperative intubation time, (3) decrease in hospital stay, and (4) decrease in overall TORS-related complications." The evidence they present from their time series shows a sharp reduction in operative times and constant improvement in LoS, but no evidence of it achieving steady state even after 150 cases.	Uncontrolled or unassessed variability between surgical teams. Groups comparable in terms of disease burden.

3	Case series	23	TORS	Safety of the intervention	Learning Curve	23 patients but 25 TORS procedures on 25 tumour sites. Learning curve noted in robotic set up time. The mean robotic set-up time was 25 min (range: 15– 100 min) and mean TORS operating time was 70 min (range: 20–150 min). The TORS operating time essentially depends on the site and size of the tumour. Set-up and operating times presented a learning curve (Fig. 1). Starting with the tenth patient, the mean robotic set-up time was 25 min (range: 15–60 min). No postoperative complication was observed. No tracheotomy was performed. Oral feeding resumed between the 1 to 3rd day post survey. Mean LoS was 6.4 days (range 4-19 days). Positive resection margin in one patient. 11 patients has multiple positive metastatic lymph nodes (n=7) and or extracapsular spread (n=4). Mean follow up was 20 months - no death or local or metastatic failure observed.	NA	NA	NA	NA	Hans, Stéphane; Badoual, Cécile; Gorphe, Philippe; Brasnu, Daniel. Transoral robotic surgery for head and neck carcinomas. Eur Arch Otorhinolaryngol 2012;268(12):1795-1801.	NA	Safe process with value. Benefits in post operative outcomes with faster swallowing recovery and shorter hospital stay. Presence of a learning curve but with no compromise in terms of patient safety as measures by complications.	Non randomised prospective case series reviewed in retrospective. Follow-up short and no reporting of oncological outcomes, bar the lack of recurrence.
3	Case series	24	TORS	Safety of the intervention	Learning Curve	First procedures performed by two senior surgeons. Latterly one senior surgeon at the console and one fellow or senior resident as a helping hand. The surgeon at the head of the patient has a role in safety. Exposure time in preparing the surgical field: 24+/1 14 min (10-60 min) Mean overall surgical time was 67 ± 46 min with a range of 12–180 min Operative segment of the procedure reduced in length from 88 ± 53 to 47 ± 29 min (p = 0.020). For the overall procedure, time was reduced from 117 ± 64 to 66 ± 33 min (p = 0.014). The trend was for operative and total times to reduce, however time taken for exposure was not reduced. Mean hospital LoS was 9 days (2-50 days) oral feeding resumed at 3 days (1-20 days).	NA	NA	NA	NA	Lawson, Georges; Matar, Nayla; Remacle, Marc; Jamart, Jacques; Bachy, Vincent. Transoral robotic surgery for the management of head and neck tumors: learning curve. Eur Arch Otorhinolaryngol 2011;0(0):0.	NA	TORS is feasible, safe, oncologically and functionally efficacious. It has a short learning curve for surgeons already trained in transoral surgery.	Non randomised prospective case series reviewed in retrospective. Follow-up short and no reporting of oncological outcomes.
2++	Other	NA	Transoral Robotic Surgery (TORS)	Cost effectiveness	Comparative cost effectiveness and Quality Adjusted Life years (QALY) TORS / (chemo) radiotherapy	Over a 10-year time horizon, the cost of TORS compared to the cost of (chemo)radiotherapy is expected to result in a cost savings to the society of $1366 USD per patient treated and incremental effectiveness of 0.25 QALY/ patient (QALY for TORS was 7.11 and 6.86 for (chemo) radiotherapy) treated in a base case analysis based on systematic literature review (de Almeida JR et al , 2014) . This indicates a 99.7% likelihood of cost effectiveness at 50,000USD/QALY. However, in two-way sensitivity analysis, with increasing adjuvant therapy, TORS become less cost-effective than (chemo)radiotherapy but overall cost-effectiveness remained at societal value of 50,000 USD per QALY.	NA	NA	NA	NA	de Almeida, John R.; Moskowitz, Alan J.; Miles, Brett A.; Goldstein, David P.; Teng, Marita S.; Sikora, Andrew G.; Gupta, Vishal; Posner, Marshall; Genden, Eric M.. Cost-effectiveness of transoral robotic surgery versus (chemo)radiotherapy for early T classification oropharyngeal carcinoma: A cost-utility analysis. Head Neck 2014;0(0):42248.	NA	-	In the absence of randomised control trials (de Almeida JR et al, 2014), the probability of treatment pathways in this study is based on a systematic review and pooled analysis which demonstrates clinical effectiveness of TORS. The wider application of this model is limited by the clinical costs in one centre in the US (de Almeida JR et al, 2014). Capital costs for robotic unit of LINAC have not been included in the analysis.
2-	Cohort	410	TORS (alone or with chemo/radio therapy)	Clinical effectiveness of the intervention	Survival	The 2- year loco regional control rate was 91.8%(95%CI, 87.6%-94.7%), disease-specific survival 94.5%(95%CI, 90.6%-96.8%), and overall survival 91%(95%CI, 86.5-94.0%)..	NA	NA	NA	NA	de Almeida, John R.; Li, Ryan; Magnuson, J. Scott; Smith, Richard V.; Moore, Eric; Lawson, Georges; Remacle, Marc; Ganly, Ian; Kraus, Dennis H.; Teng, Marita S.; Miles, Brett A.; White, Hilliary; Duvvuri, Umamaheswar; Ferris, Robert L.; Mehta, Vikas; Kiyosaki, Krista; Damrose, Edward J.; Wang, Steven J.; Kupferman, Michael E.; Koh, Yoon Woo; Genden, Eric M.; Holsinger, F. Christopher. Oncologic Outcomes After Transoral Robotic Surgery : A Multi-institutional Study. JAMA Otolaryngol Head Neck Surg 2015;.	One death due to operative complications	NA	364 (88.8%) of patients had only one type of cancer- oropharyngeal cancer. The treatment included other modalities i.e. while all patients had TORS, some received radiotherapy ((31%) or chemoradiotherapy (21%). The study was not adjusted for improvement/changes in surgical techniques and surgeon skill over the five years period of intervention. This could have been accounted for through sub-group analysis by centres/ teams / surgeons or by annual cohorts. If this was not feasible in the study design, it should have been identified as a potential confounder (procedural/person).

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	Transoral robotic surgery Robotic assisted surgery Robotic surgery da Vinci Robotic surgical procedures Robotics Remote Operations Telerobotics Transoral laser surgery Radiation therapy Chemoradiation therapy Concomitant chemotherapy with radiation therapy Open surgery Transcervical surgery Transoral laser surgery Intensity Modulated radiation therapy Image guided radiation therapy Tomotherapy Rapid Arc vMAT
Updated search terms - Population	Oropharyn* Hypopharyn* Laryn* Nasopharyn* Neoplasm* Cancer*
Updated search terms - Intervention	Robotic* Transoral Trans-oral "da Vinci"
Updated search terms - Comparator	Laser Transoral Trans-oral “Image-guided” “Intensity modulated” Radiotherap* Tomotherap* Chemoradiotherap* Radiochemotherap* Arc therap*
Updated search terms - Outcome	“disease free survival” “disease specific survival” “Oncological outcomes” Survival Mortality Adverse Events “Perioperative complications” “peri-operative complications” perioperative “Functional outcomes” Quality of Life QOL Treatment Outcome cost-effectiveness cost effectiveness
	General inclusion criteria
	In order of decreasing priority, the following are included: 1. All relevant systemic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not

Inclusion criteria	superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	Adult English language <5 years Title/Abstract 2 additional articles per the suggestion of the PWG clinical lead: a. de Almeida, John R.; Li, Ryan; Magnuson, J. Scott; Smith, Richard V.; Moore, Eric; Lawson, Georges; Remacle, Marc; Ganly, Ian; Kraus, Dennis H.; Teng, Marita S.; Miles, Brett A.; White, Hilliary; Duvvuri, Umamaheswar; Ferris, Robert L.; Mehta, Vikas; Kiyosaki, Krista; Damrose, Edward J.; Wang, Steven J.; Kupferman, Michael E.; Koh, Yoon Woo; Genden, Eric M.; Holsinger, F. Christopher. Oncologic Outcomes After Transoral Robotic Surgery : A Multi-institutional Study. JAMA Otolaryngol Head Neck Surg 2015;. b. de Almeida, John R.; Moskowitz, Alan J.; Miles, Brett A.; Goldstein, David P.; Teng, Marita S.; Sikora, Andrew G.; Gupta, Vishal; Posner, Marshall; Genden, Eric M.. Cost-effectiveness of transoral robotic surgery versus (chemo)radiotherapy for early T classification oropharyngeal carcinoma: A cost-utility analysis. Head Neck 2014;0(0):42248.
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with >
	Specific exclusion criteria
	None