Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: **Transoral Robotic Surgery: A Review of Clinical and Cost-Effectiveness**

DATE: 12 January 2015

CONTEXT AND POLICY ISSUES

Minimally invasive surgical techniques, such as laparoscopic robotic assisted surgery, represent advancement within the surgical community.[1,2] Presently the da Vinci Robotic Surgical System is the only robotic surgery system available.[1,2] It is indicated for general, urological, gynecological, transoral otolaryngology (for both benign and malignant diseases), and thoracic laparoscopic surgical procures.[1,2] Four versions of the da Vinci system have been released, with all models including a surgeon console, surgical cart, and vision cart.[1,3] The surgeon sits at the console at a distance from the patient and controls the surgical and vision carts, which include the robotic arms, endoscopic instruments and video camera.[1,3] Training requirements are technical and procedure specific. The manufacturers of the da Vinci system, Intuitive Solutions, provide technical training support in the form of a detailed training program.[1] It is the responsibility of the individual institution to ensure procedure specific competency is achieved.[1] The purported benefits of minimally invasive surgical techniques such as transoral robotic surgery (TORS) include improved visualized surgical field, decreased surgical complications such as dysphagia and bleeding, decreased need for tracheostomy and shortened recovery times.[2-4] Potential disadvantages of TORS include lack of tactile feedback, difficult hemostasis and initial investment costs.[5]

Malignant lesions of the oral or oropharyngeal cavity are relatively uncommon. The estimated annual incidence worldwide is approximately 123,000, with 79,000 deaths annually.[6] Cancers of the oral and oropharyngeal mucosa are most often squamous cell carcinomas and arise from the palate, tonsils, base of tongue, vellecula and aryepiglottic folds.[3,6] Several risk factors are known to be associated with the development of oropharyngeal squamous cell carcinoma (OPSCC) including smoking, alcohol, and oncogenic strains of the human papilloma virus (HPV).[3,6] Cancers associated with HPV may carry a better prognosis.[7] However, presently the treatment approach of OPSCC is the same regardless of the cause.[6] The tumor, node, metastasis (TMN) staging from the American Joint Committee on Cancer is generally used to classify OPSCC.[6] Early stage (stage I and II) is defined as tumors <4cm in diameter (T1 and T2) without invasion into surrounding tissue or lymph nodes.[6] The general treatment approach to early stage OPSCC includes chemoradiation or surgery.[3] While traditionally, an open surgical approach has been taken, minimally invasive surgical techniques such as TORS and transoral

laser microsurgery are gaining popularity within the surgical community.[3,4,6] While TORS is only indicated for the management of early stage oral and oropharyngeal cancer, evidence is growing in support of its use, along with chemotherapy and radiation, in the management of late stage metastatic and recurrent disease.[1,2,8]

Conversely, benign diseases of the oropharynx, such as obstructive sleep apnea (OSA), represent a significant health problem. It is estimated that OSA affects approximately 2 to 4% of men and 1 to 2 % of women in the United States.[4,9] OSA is associated with numerous medical complications including cardiovascular disease, hypertension, depression, and cerebrovascular disease such as stroke.[4,5,9] Presently, the standard of treatment for OSA is the use of nocturnal positive pressure ventilation.[4,9] However, this management strategy is associated with poor compliance and patient tolerability.[4,9] Since the late twentieth century there has been a growing interest in surgical management of OSA as a means to bypass or remove the posterior pharyngeal obstruction.[4] Early in 2010, case reports began to be published on the use of TORS as a surgical modality for the management of OSA.[9]

Many claims of the advantages and disadvantages of TORS for the management of benign and malignant lesions of the oropharynx are available in the literature.[1-5,9] However, uncertainty remains as to whether this surgical modality is associated with improved clinical outcomes for patients. Uncertainty also surrounds the cost-effectiveness of implementation and maintenance of a TORS system.

The purpose of this report is to summarize the clinical and cost-effectiveness for the use of TORS in the management of early stage oral and oropharyngeal cancer and OSA compared to open surgical techniques, increased doses of chemoradiation, or no treatment.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of TORS for patients with early stage oral or oropharyngeal cancer?

2. What is the clinical effectiveness of TORS for patients with OSA?

3. What is the cost-effectiveness of TORS for patients with early stage oral or oropharyngeal cancer?

4. What is the cost-effectiveness of TORS for patients with OSA?

KEY FINDINGS

The evidence addressing the clinical effectiveness of TORS in the management of early stage oral and oropharyngeal cancer is of limited quality. Health technology assessments (HTA) and systematic reviews included in the report were limited to studies with case-series design. Registry studies show that compared to open or non-robotic approaches, TORS confers no mortality benefit but reduces the duration of hospitalization. The benefits of TORS on the reduction in the need for gastrostomy and tracheostomy tubes and post-operative dysphagia are conflicting. There does not appear to be a reduction in bleeding complications associated with TORS.

No evidence regarding the clinical or cost effectiveness of TORS in the management of OSA was identified.

No studies addressing the cost-effectiveness of TORS in the management of early stage oral and oropharyngeal cancer were identified. Compared to conventional surgical approaches, evidence from non-randomized studies is conflicting as to whether TORS offers cost savings. An activity-based cost calculation found that the total cost of TORS was more than conventional surgery, however the cost differences were attributed to initial purchase costs as well as ongoing training and equipment maintenance.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and December 3, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria in table 1.

Table 1: Selection Criteria

Population	Patients with early stage oral or oropharyngeal cancer; Patients with obstructive sleep apnea (OSA)
Intervention	Transoral robotic surgery (TORS)
Comparator	Open surgery or higher chemoradiation doses; or no comparator
Outcomes	Benefits (e.g., improved return to function [swallowing], avoiding tracheostomy, shorter length of hospital stay, reduced morbidity from lower chemoradiation, shortened wait times; elimination of sleep apnea) Harms (e.g., surgical risks) Cost effectiveness
Study Designs	HTA/ Systematic review/Meta-analysis Randomized controlled trials Non-randomized studies Economic evaluations

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, case reports or case series, or were published prior to 2009. Articles were also excluded if they were reported as part of an included HTA or systematic review.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[10] was used to critically appraise the HTA and systematic reviews. The Newcastle-Ottawa Quality Assessment Scale[11] was used for cohort studies and the Drummond Checklist was used for economic studies.[12]

For the critical appraisal, a numeric score was not calculated. Instead, the strengths and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 352 articles were identified from the literature search and 14 articles from the grey literature search for a total of 366 articles; 45 were selected for full-text screening. Eight of the full-text references screened met the inclusion criteria.

There was one HTA,[3], two systematic reviews,[13,14] and four cohort studies[7,15-17] identified evaluating the clinical effectiveness of TORS in patients with early stage oral or oropharyngeal cancer. No randomized controlled trials were identified. One economic evaluation was identified which addressed the cost of TORS for patients with early stage oral or oropharyngeal cancer.[18] There were no studies which met the inclusion criteria that addressed the clinical or cost effectiveness of TORS for OSA.

Appendix 1 describes the PRISMA flowchart of the results of the literature review for this report.

Summary of Study Characteristics

Characteristics of the included HTA, systematic reviews, non-randomized studies and economic study are summarized below and details are provided in Table 2 and Appendix 2.

<u>Health Technology Assessment</u>

The Australia and New Zealand Horizon Scanning Network (ANZHSN) published a Horizon Scanning Technology Prioritising Summary in 2009 evaluating the use of TORS for head and neck cancers.[3] This HTA focused on the use of the da Vinci Surgical System and included two case series, one which included 27 patients with mainly late stage (stage III/IVa) tonsillar cancer and a second which included 20 patients with head and neck cancer (mainly early stage squamous cell carcinoma). Surgical complications including mortality, blood loss, tracheostomy, and gastrostomy were reported at 6 months follow-up. Cost impact was also reported, although no formal cost-effectiveness analysis was undertaken. The cost of the da Vinci Surgical System as well as the cost of the annual service contract and surgical instruments was reported.

Systematic Reviews

Two systematic reviews[13,14] that addressed the clinical effectiveness of TORS for patients with early stage oral or oropharyngeal cancer were identified. Both were conducted in Canada and published in 2014.[13,14] Both systematic reviews included studies that used TORS as the primary treatment of early stage (T1 and T2) OPSCC. Kelly and colleagues[13] included 11 studies, all of which were case series published between 2009 and 2013. The total number of patients was 190, all of whom underwent TORS as primary treatment for early stage (T1-2) OPSCC. Other patient characteristics at baseline were not reported. The mean follow-up time was 19.9 months (range 1 to 51 months). de Almeida et al.[14] also published a systematic review in 2014. This systematic review included 20 case-series published between 2007 and 2012. Twelve of the case series included 772 patients with predominantly early stage (T1 or T2) OPSCC who underwent TORS. The comparator group was 1,287 patients reported in 8 case-series who underwent intensity-modulated radiotherapy (IMRT). Other patient characteristics at baseline were not reported. Follow-up of patients ranged from 2.5 months to 12.7 years. Three case-series were included in both of the systematic reviews. Outcomes reported in both systematic reviews included oncological success rates (recurrence and survival) as well as surgical complications and adverse events.

Non-Randomized Studies

Four non-randomized studies were included, all of which were cohort studies.[7,15-17] Three studies were retrospective database studies[7,16,17] conducted in the United States between 2008 to 2011. Chen[16] included 5,146 patients with stage T1-T2 OPSCC. Chung[17] and Richmon[7] included 6,944 and 9,601 patients, respectively. Chung[17] included patients with “mild to moderate” and “major to extreme” disease and reported outcomes for these subgroups separately. Up to 18% of patients in the study by Chung[17] had undergone chemotherapy or radiation prior to enrolment and the majority of patients (>90%) in the study by Richmon[7] had not undergone previous radiotherapy. The registry studies compared TORS to open surgery,[17] non-robotic surgery,[16] and non-TORS procedures.[7] Hammoudi[15] conducted a retrospective historical cohort study in France that compared TORS with conventional surgery in 52 patients with squamous cell carcinoma of the head and neck, the majority of which were stage T1 or T2 oropharyngeal lesions. The outcomes reported across these trials were hospital length of stay,[7,17] surgical complications such as bleeding,[7,17,19] tracheostomy or gastrostomy tube requirement,[15,17,19] oncological outcomes,[15,16] and cost[7,15,17]. Chung[17] considered hospital inpatient charge and cost data, inflated to 2013 prices. Richmon[7] used cost to charge ratios to convert hospital charges to institutional costs for each admission and adjusted for inflation. Hammoudi[15] considered the costs of surgery, hospitalization and treatment. The registry study periods ranged from one[7,16] to 4 years[17]. The follow-up duration was a mean of 19 months for TORS and 51 months for conventional surgery in the historical cohort study by Hammoudi.[15]

Economic Studies

One economic analysis[18] was identified in addition to one HTA[3] and three of the non-randomized studies that reported on costs associated with TORS intervention.[7,15,17] Dombree and colleagues conducted a cost comparison of an open surgical approach, transoral laser microsurgery, and TORS in Belgium in 2014.[18] An activity cased cost-calculation model was undertaken using supraglottic laryngectomy with sentinel node biopsy and unilateral neck dissection as the reference case based on 2013 costs. Estimations made in the model included

250 procedures being completed annually and clinical lifespan of computer hardware lifetime five years, robot lifespan of seven years and 20 years for general surgery equipment. The cost calculations were based on the time the patient was in the operating room and include identification of activities, linking activities through cost drivers, and consumption of resources.[18] Activities considered as part of the model included patient preparation, anaesthesia, surgery, cleaning, administration and sterilization.

Table 2: Table of Characteristics of Included Economic Studies

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient Population	Intervention (n)	Comparator(s) (n)	Assumptions
Dombree, 2014, Belgium	Activity based cost calculation Single hospital perspective	Reference Case: Supraglottic laryngectomy with sentinel node biopsy and unilateral dissection	TORS (n=NR)	Open surgery (n=NR)	NR

NR=not reported

Summary of Critical Appraisal

Strengths and limitations of the HTA, systematic reviews, individual non-randomized studies and economic study are provided in Appendix 3.

Health Technology Assessment

The included HTA[3] was of poor quality. No clear objective was stated and the search strategy was unclear. There was no list of included or excluded studies available. It was unclear which databases had been searched and if grey literature was included. Two case-series were included, both of which had small sample sizes and no quality appraisal was undertaken. A formal economic analysis was not conducted. The HTA provided commentary on the practicalities of institutional implementation of TORS. The authors also clearly address the limited quality of included evidence when making their conclusions.

Systematic Reviews

Overall, the quality of the two systematic reviews[13,14] was fair. In both, the objectives and inclusion criteria were established *a priori*. Study selection and data abstraction were conducted in duplicate. In the systematic review by Kelly et al.[13] the data abstraction was conducted in triplicate. Both completed a comprehensive literature search using at least three electronic medical databases. Kelly et al.[13] reported a list of included studies as well as quality assessment. The systematic review by de Almeida et al.[14] did not report a list of included studies, although a quality assessment was published in an online appendix. In both systematic reviews, the quality of studies was limited by the case-series design. It was unclear whether

Kelly et al.[13] searched the grey literature or included studies regardless of their publication status, whereas de Almeida et al.[14] searched the unpublished and grey literature for included studies. Kelly et al.[13] used appropriate statistical measures before combining data, and de Almeida et al.[14] did not pool data but rather provided a narrative summary of study outcomes. In neither systematic review was a list of excluded studies provided, baseline characteristics of included studies were not provided, and the likelihood of publication bias was not addressed. In their conclusions, the authors address the need for comparative studies. Authors of both systematic reviews declared no conflict of interest.

Non-Randomized Studies

Overall, the quality was limited by the non-randomized cohort study design leading to potential selection bias and inherent differences between study groups. Three[7,17,20] of the four included cohort studies were of fair quality. All three obtained their sample and comparator groups from large nationwide databases. Exposure and outcomes were ascertained by ICD-9-CM codes and record linkage with no indication that the outcomes of interest were present at the outset of the study. Comparability of groups was variable across studies. No matching was undertaken in any study. Chung et al.[17] controlled for severity of underlying disease, while the others[7,16] conducted a multivariate analysis for their primary outcomes. It is possible that other variables, which were not identified, could influence the study outcomes. The length and adequacy of follow-up was unclear in all three studies. Hammoudi et al.[15] was of poor quality. The sample size was small and drawn from a single centre and an individual surgeon performed surgery in the majority of patients, limiting generalizability. The comparability of intervention and comparator groups was unclear as no confounding variables were controlled for, which is especially important as the intervention group was compared to a historical cohort and confounders may have changed over time. Method of outcome ascertainment was not described. Intervention and comparator groups had different follow up durations, which is important when considering outcomes such as disease recurrence and survival.

Economic Study

The main limitation of the included economic study by Drombree et al.[18] was the design. The authors undertook an activity-based costing analysis at a single centre in Belgium. The study objectives were clear and activities and costs were comprehensive and clearly described. The authors undertook a sensitivity analysis to identify activities and costs that had significant impact on the cost analysis. No formal cost-effectiveness analysis was undertaken and clinical outcomes were not considered, which further limits the applicability of the study findings to policy decision making within the Canadian health care system.

Summary of Findings

The overall findings from the systematic review and non-randomized studies are summarized below and details are available in Table 3 and Appendix 4.

Clinical effectiveness of transoral robotic surgery (TORS) for patients with early stage oral or oropharyngeal cancer

Health Technology Assessment

The ANZHSN Horizon Scanning Technology Summary[7] reported no deaths associated with TORS. In one of the included case-series, operative complications occurred in 5 of 27 patients, one of which was minor nasal bleeding. There were no post-operative haemorrhages in the second case report. Mean blood loss in both case-series ranged from 80 to 189mL and no blood transfusions were required. One patient required a tracheostomy. In one case series all 27 patients underwent gastrostomy, and 96% of patients in that study were able to swallow at 6 months. In the second case-series no patient required a tracheostomy, 100% of patients were swallowing at 30 days follow-up and the mean hospital stay was 1.7 days. The authors conclude, based on two small case-series, that TORS is feasible, but that additional studies are needed to better understand the clinical effectiveness and risks of the procedure.

Systematic Reviews

Kelly et al.[13] demonstrated good oncologic outcomes in patients with early stage oropharyngeal cancer who underwent TORS. In 140 patients, local disease control was achieved in 96.2%, regional disease control in 91%, distant disease control in 100%, disease free survival in 90% and overall survival of 95% over a mean follow up period of 19.9 months. At 12 months, 5% of patients had a gastrostomy tube and no patient required a tracheostomy. Ten patients experienced post-operative haemorrhage, two requiring surgical intervention to achieve hemostasis. The authors conclude that TORS was associated with good disease control and functional outcomes with low surgical morbidity and mortality, but that further study is required to recommend TORS over conventional approaches. de Almeida et al.[14] compared TORS to IMRT and found that two-year disease free survival was 79% compared to 82-90%, and that two-year overall survival was 82-94% compared to 84-96%. P-values were not reported for any of the comparisons made between treatment modalities. Post-operative bleeding occurred in 2.4%, neck hematomas in 0.4%, and pharyngocutaneous fistulas in 2.5% of patients who underwent TORS. Information on these complications was not reported for patients who underwent IMRT. Tracheostomy was required in 12% of TORS patients and not reported for IMRT. The authors conclude that multimodal treatment is required for early T-stage oropharyngeal cancer, that survival is comparable between TORS and IMRT, and that differences between these treatment modalities likely arise in their harms profile.

Non-Randomized Studies

Three studies reported no difference in mortality between TORS and conventional (open or non-robotic) treatment of oropharyngeal cancer.[7,15,17] All four non-randomized studies reported a significant reduction in the length of hospitalization with TORS compared to conventional treatment. One study[17] reported a reduction in the need for gastrostomy tubes, while two studies[15,17] reported a significant reduction in tracheostomy with TORS compared to open or conventional intervention. The results for dysphagia were conflicting with one study[17] demonstrating a significant reduction while another[7] did not. Bleeding rates were reported in one study[17] and were not significantly different between TORS and open surgery.

Table 3. Outcomes with TORS versus conventional (Open or non-robotic) approach				
Outcome	**Chung[17] N=6944**	**Chen[16] N=5146**	**Richmon[7] N=9601**	**Hammoudi[15] N=52**
Death	0 vs. 0* 0 vs. 0** 0 vs. 0°	NR	0 vs. 0.9% p=NR	1 vs. 1
Length of hospitalization (days)	3.7 vs. 5.2* *P*<0.001 3.54 vs. 5.06** *P*<0.001 4.8 vs. 4° *P*=0.044	4.7 vs. 3.5 *P*<0.001	-1.5 with TORS	11 vs. 19 *P*=0.001
Gastrostomy tube (%)	1.7 vs. 11.6* *P*<0.001 17.7 vs. 11.5** *P*=0.055 14.5 vs. 5.1° *P*=0.003	NR	0 vs. 19.4 *P*=0.4110	NR
Tracheostomy	1% vs. 26.9%* *P*<0.001 4.1% vs. 26.7%** *P*<0.001 7.4% vs. 19.1%° *P*=0.012	NR	0 vs. 36.1% *P*=0.3057	4 vs. 20 *P*<0.001
Dysphagia	19.5% vs. 8.0%* *P*<0.001 10.2% vs. 6%** *P*=0.071 14.7 vs. 4.9%° *P*=0.002	NR	9.4% vs. 8.7% p=0.9792	NR
Bleeding	3.1% vs. 2.8%* *P*=0.746 0 vs. 0** 0 vs. 0.9%° *P*=1.0	NR	NR	NR
NR=not reported; **TORS**=transoral robotic surgery				

*partial pharyngectomy for mild to moderate disease **partial glossectomy for mild to moderate disease (tongue base) °partial glossectomy for mild to moderate disease (anterior tongue)

Clinical effectiveness of TORS for patients with OSA

There were no studies identified that met the inclusion criteria to address this question.

Cost-effectiveness of TORS for patients with early stage oral or oropharyngeal cancer

Health Technology Assessment

No cost-effectiveness studies were included in the HTA.[7] Authors report that the da Vinci system with software upgrades cost approximately $1.5 million USD with an additional service contract of $100,000USD annually. It should be noted that these prices were based on estimates from 2009.

Non-Randomized Studies

Three studies[7,15,17] reported on the cost of TORS. Compared to open surgery, Chung and colleagues[17] demonstrated a significant reduction in both mean total charges and mean total cost for TORS partial pharyngectomy and partial glossectomy (tongue base) in mild to moderate disease compared to open surgery. There was no significant difference between treatment group for partial glossectomy of the anterior tongue. Richmon[7] demonstrated that compared to non-TORS surgery, TORS was associated with a cost savings of $4,285 in patients with malignant oropharyngeal neoplasm. In 2014, Hammoudi[15] showed that TORS was associated with a significantly higher cost of surgery ($7781 vs. $4375; *P*<0.001) and cost of treatment

compared to conventional intervention ($27,926 vs. $20,885; *P*=0.03), although the mean cost of hospitalization was significantly lower ($13,103 vs. $23,551; *P*=0.01), likely owing to the shorter hospital stay with TORS. It is unclear whether Chung[17] and Richmon[7] considered hospital-related charges from admission to discharge, and it is unclear whether the cost of the robot is considered in their cost calculations. The mean hourly cost of TORS and related supplies was considered in the cost analysis by Hammoudi.[15]

Economic Analysis

In an activity-based cost calculation in Belgium in 2014, Dombree and colleagues[18] found that the total cost of TORS was €5,650 compared to €3,349 for open surgery. Cost calculations were based on the time spent in the operating room. The activity-based costing analysis first identified key activities, linked activities through cost drivers and finally linked activities to the consumption of resources. Activities included in the cost calculation were preparation of patient for surgery, anaesthesia, surgery, cleaning, administration and sterilization. Direct and indirect costs, such as materials, wages, equipment, overhead and space were considered. The robot purchase cost is considered as part of equipment costs with seven years of service estimated. The model assumes 250 procedures performed annually. The authors postulate that the higher cost of TORS is mainly influenced by initial purchase costs associated with training and equipment.[18] Duration of hospital admission was not considered as part of the model.

Cost-effectiveness of TORS for patients with OSA

There were no studies identified that met the inclusion criteria to address this question.

Limitations

No evidence addressing the clinical or cost-effectiveness of TORS in the management of OSA met the inclusion criteria for this review. Existing evidence for TORS for OSA treatment is low quality and limited primarily to case series. Conclusions that can be drawn from case-series are limited by the risk of selection bias and lack of comparator group.

Studies included in this report were limited to the use of TORS in the management of oral or oropharyngeal cancer. The main limitation of this report is the low quality of existing evidence, which included one HTA[3] and two systematic reviews[13,14], all of which consisted of case series, and four cohort studies[7,15-17]. No randomized controlled trials were identified and non-randomized studies were of fair to poor quality. The HTA[3] was undertaken in 2009, prior to the majority of published data on the use of TORS in the management of oral and oropharyngeal cancer. This limits the generalizability and applicability of the findings of this HTA in the context of a larger body of evidence that exists today. Three of the cohort studies had large sample sizes, although differences exist in the baseline characteristics, limiting comparability of the treatment groups. The objective of this report was to summarize the evidence for TORS in the management of early stage oral and oropharyngeal cancer, yet none of the included studies examined pure early stage populations. This may limit the generalizability of study results as late stage malignancy may be associated with different risks of surgical complication and carry poorer prognosis. HPV status of the patient may affect their long-term prognosis in OPSCC and this was often not reported in studies with two exceptions.[16,17]. The duration and adequacy of follow up in most studies was unclear or inadequate.

The included economic data available was limited to total cost and activity-based costing, which was conducted in Belgium limiting the generalizability of study results to the Canadian health care system. No formal cost-effectiveness analysis was undertaken which limits applicability of this evidence to policy decision-making.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence addressing the clinical effectiveness of TORS in the management of early stage oral and oropharyngeal cancer is of limited quality. The included studies often did not include a patient population limited to early disease and did not control for confounders, such as HPV status, which may impact patient outcomes. The effect on overall survival and disease recurrence is unclear. There is some evidence from registry studies that TORS may reduce the duration of hospitalization by approximately one day. Some studies show that TORS may reduce the need for gastrostomy and tracheostomy tubes post-operatively, however these results are conflicting, as is the evidence for a reduction in dysphagia or post-operative bleeding.

No evidence regarding the clinical or cost-effectiveness of TORS in the management of OSA was identified. Presently, the evidence supporting the use of TORS in OSA is limited to case-series.[4,5,9]

No cost-effectiveness analysis was available addressing the use of TORS in the management of early stage oral or oropharyngeal cancer. Presently, the da Vinci is the only TORS device available on the market. Based on available cost data, purchasing this machine represents a significant up front as well as ongoing cost in the form of maintenance, training and software upgrades. Currently, there is conflicting evidence as to whether investment in TORS represents a pure cost savings. Based on the results from one registry study,[17] TORS may offer cost savings in the form of a reduction in duration of hospital stay. This information must be interpreted in the context of the low quality of available evidence and uncertain long-term improvement in disease control and survival. The lack of proven clinical benefit must be balanced against initial up front costs of investing in new technology and training personnel to use the technology.

Future research in the form of randomized controlled trials with longer term follow up data and appropriate subgroup analysis incorporating prognostic factors as well as formal cost-effectiveness analysis will better define the role of TORS for head and neck surgery in Canada.

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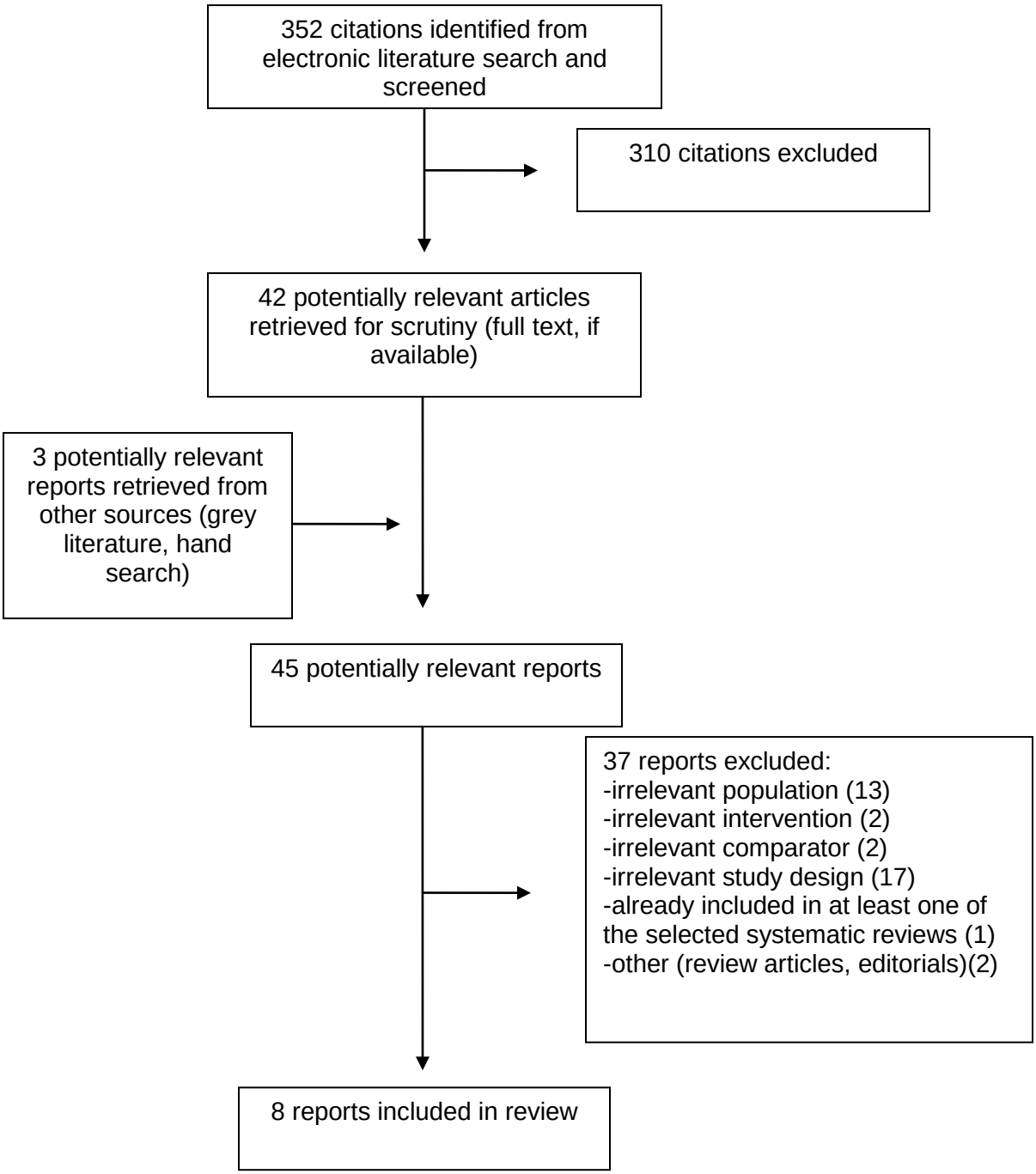
ABBREVIATIONS

ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IMRT	intensity modulated radiotherapy
HPV	human papilloma virus
HTA	health technology assessment
OPSCC	oropharyngeal squamous cell carcinoma
OSA	obstructive sleep apnea
TORS	transoral robotic surgery

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Studies (Oropharyngeal Cancer)

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Australia and New Zealand Horizon Scanning Network, 2009, Australia	HTA Follow-up: 6 months	2 case series n=27 patients with tonsillar cancer n=20 patients with head and neck cancer	TORS	--	Operative time, blood loss, tracheostomy gastrostomy, cost impact
Kelly, 2014, Canada	Systematic Review English language publications, 1947 to September 2013 Follow-up (mean): 19.9 months (range 1 to 51 months)	11 studies n=190 patients with early stage oropharyngeal squamous cell carcinoma undergoing TORS for primary treatment	TORS	--	Local, regional or distant recurrence Overall survival Long-term gastrostomy and tracheostomy, surgical margin assessment, complication rates and types
de Almeida, 2014, Canada	Systematic Review Publications up until September 2012 Follow-up: 2.5 months to 12.7 years	20 case-series (12 TORS , 8 IMRT) n=772 patients with predominantly early stage (T1 or T2) oropharyngeal squamous cell carcinoma underwent TORS n=1,287 patients underwent IMRT	TORS 654/687 underwent a neck dissection Adjuvant radiotherapy 26% (154/590) Adjuvant chemoradiotherapy 41% (244/590)	IMRT Concurrent chemotherapy 43% Neck dissections 30%	Recurrence, survival Local, regional, distant control Adverse events/ complications

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Non-randomized Studies					
Chung, 2014, USA	Retrospective database study US Agency for Healthcare Research and Quality 2010 to 2011	Patients undergoing elective partial pharyngectomy (n=2067) or partial glossectomy (n=4877) for oropharynx or tongue malignancy	TORS	Open Surgery	Complications (Tracheostomy Gastrostomy Death Blood transfusion Peri-operative hemorrhage Dysphagia) Length of stay Total charges Total cost
Chen, 2014, USA	Retrospective Database Review National Cancer Database 2010 to 2011	n=5146 patients with oropharyngeal squamous cell carcinoma (majority stage T1-T2)	TORS (n=877) 80% underwent neck dissection	Non-robotic surgery (n=4269) 60% underwent neck dissection	Length of stay Likelihood of adjuvant therapy Margin status Unplanned readmission
Richmon, 2014, USA	Retrospective Database review 2008 to 2009	n=9601 patients with malignant oropharyngeal neoplasm	TORS (n=116)	Non-TORS procedures (n=9485)	Post-operative complications Length of hospitalization Cost
Hammoudi, 2014, France	Retrospective cohort study Follow-up: TORS: 19 months Conventional Surgery: 51 months	n= 52 patients with squamous cell carcinoma of the head and neck (mainly T1 and T2 stage oropharyngeal lesions)	TORS (n=26)	Conventional Surgery (n=26)	Disease free survival Tracheostomy Duration of nasogastric feeding Duration of hospitalization Treatment cost

HTA=health technology assessment; **IMRT**=intensity modulated radiotherapy; **TORS**=transoral robotic surgery; **USA**=United States of America

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year	Strengths	Limitations
Health Technology Assessment		
Australia 2009[3]	• Evaluated practicalities of implementing TORS • Limited quality of evidence was address in the conclusion	• Objective and search methods were not reported • Study selection and data abstraction was not conducted in duplicate • Unclear if grey literature was searched • Only included 2 case series • List of included and excluded studies was not provided • Quality appraisal of included studies was not complete • Publication bias was not addressed • No formal cost effectiveness analysis was undertaken • Limited to studies prior to 2009
Systematic Reviews		
Kelly 2014[13]	• Research question and inclusion criteria were established apriori • Duplicate study selection and triplicate data abstraction • A comprehensive literature search of three electronic medical databases was conducted • List of included studies, with quality assessment using the Newcastle Ottawa Quality Assessment Scale, was included • Some limitations of available studies was addressed in the conclusion and recommendation • Statistical measures (I^2 statistic) were used to assess for heterogeneity of study results • Authors declared no conflict of interest	• Unclear if studies were included regardless of their publication status, unclear if grey literature was searched and included • List of excluded studies was not provided • Baseline characteristics of the included studies was not provided • Likelihood of publication bias was not assessed
de Almeida 2014[14]	• Research question and inclusion criteria were established apriori • Study selection and data	• List of included and excluded studies was not provided • Baseline characteristics of the included studies was not provided

First Author, Publication Year	Strengths	Limitations
	abstraction were completed in duplicate • A comprehensive literature search of five electronic medical databases was conducted • Unpublished data sources were searched and included in the systematic review • Quality assessment of included studies was undertaken and reported in an online appendix • Need for comparative studies is addressed in conclusion • Authors declared no conflict of interest	• Pooling of data was not undertaken • Likelihood of publication bias was not assessed
Non-Randomized Controlled Trials		
Chung 2014[17]	• Included cohort was collected from a nation-wide database (Nationwide Inpatient Sample funded by the US Agency for Healthcare Research and Quality) and therefore likely representative of population undergoing TORS • The comparator cohort was taken from the same sample as the TORS cohort • Exposure was ascertained based on ICD-9-CM procedure codes • Outcomes of interest were not present at outset of study • Outcomes were gathered base don record linkage	• Severity of underlying disease was the only variable controlled for in outcome reporting • Length and adequacy of follow-up unclear
Chen 2014[16]	• Included cohort was collected from a nation-wide database (National Cancer Data Base) and therefore likely representative of population undergoing TORS • The comparator cohort was taken from the same sample as the TORS cohort • Exposure was ascertained based on ICD-9-CM procedure	• Length and adequacy of follow-up unclear

First Author, Publication Year	Strengths	Limitations
	codes • Outcomes of interest were not present at outset of study • Authors conducted a multivariate regression analysis controlling for various demographic, clinical and pathological characteristics for their primary outcome • Outcomes were gathered based on record linkage	
Richmon 2014[7]	• Included cohort was collected from discharge data from three databases; Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, and Agency for Healthcare Research and Quality and therefore likely representative of population undergoing TORS • The comparator cohort was taken from the same sample as the TORS cohort • Exposure was ascertained based on ICD-9-CM procedure codes • Outcomes of interest were not present at outset of study • Authors conducted a multivariate regression analysis and reported variable that affected the primary outcome (post-operative complications) • Authors conducted a generalized linear regression analysis and reported on variables that affected the primary outcomes (length of stay and hospital costs) • Outcomes were gathered based on record linkage	• American Joint Commission on Cancer tumor stage, tumor grade, histological subtype and outcome post-discharge were not available from the database • Length and adequacy of follow-up unclear
Hammoudi 2014[15]	• Exposed and unexposed cohorts were from the same patient population • Outcomes of interest were not present at outset of study	• The exposed and unexposed cohort was selected from a single center and therefore only somewhat representative • The TORS cohort (2008-2013) was

First Author, Publication Year	Strengths	Limitations
		compared to a historical cohort of patients (2005-2008) undergoing conventional surgery • No description for how exposure to TORS or conventional surgery was ascertained • Surgical intervention was carried out by the same surgeon in the majority of cases • The comparability of cohorts is unclear, the authors did not control for any potentially confounding variables • No description was provided for method of outcome ascertainment • Study groups had different lengths of follow-up: TORS group was followed up for an average of 19 months compared to 56 months in the conventional surgery group • The completeness of follow-up was not described by the authors
Economic Studies		
Dombree 2014[18]	• Study objective was clearly defined • Clear description of activities contributing to the cost were included • Costs appear to be measured accurately • A sensitivity analysis was conducted to identify critical costs and activities • Conclusions appeared to be justified by the evidence presented	• Evidence of established efficacy of TORS was not reported. Activity-based costing was not linked to clinical efficacy data • A formal cost-effectiveness analysis was not undertaken and therefore clinical outcomes were not considered • Perspective was limited to an individual hospital in Belgium therefore extrapolation to Canadian health care system is difficult

APPENDIX 4: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Health Technology Assessment		
Australia, 2009	Operating Time (mean): 1hour, 43 minutes (range: 26 minutes to 3 hours) 84 minutes (range: 45 to 150 minutes) Blood Loss (mean): 189mL (range: 0 to 500mL) 80mL (range: 20 to 200mL) Tracheostomy: 1 patient 0 patients Swallowing: 96% at 6 months follow-up 100% at 30 days follow-up Hospital stay (mean): 1.7 days (range: 1 to 3 days)	Lack of high quality evidence on the use of TORS Complication rate similar to open or transoral surgical approaches No cost effectiveness studies evaluating the use of TORS in Head and Neck Cancer TORS is feasible but the long term efficacy and harms are yet to be established
Systematic Reviews		
Kelly, 2014	Oncologic Outcomes (n=140): Local disease control: 96.2% Regional disease control: 91% Distant disease control: 100% Disease-free survival: 90% Overall survival: 95% Functional Outcomes: Gastrostomy tube (n=170) at 12 months: 5% Tracheostomy tube (n=159) at 12 months: 0 Surgical Outcomes: Post-operative hemorrhage: 10 patients (2 requiring surgical intervention to achieve hemostasis)	Results suggest good disease control rates, good functional outcomes with low surgical morbidity and mortality when using TORS for early stage oropharyngeal cancer. Recommendation regarding the use of TORS over other therapy requires further study including a direct comparison.
de Almeida, 2014	Two-year disease specific survival: 90 to 98% vs. 97.7% P=NR Two-year disease-free survival: 79% vs. 82 to 90% P=NR	In most cases of early T-stage oropharynx cancer multimodal treatments are used. Survival between TORS and

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	Two-year overall survival: 82 to 94% vs. 84 to 96% P=NR Post-operative Bleeding (7 studies): 2.4% (6/247) vs. NR Neck Hematoma (7 studies): 0.4% (1/247) vs. NR Pharyngocutaneous Fistula (8 studies): 2.5% (10/395) vs. NR Tracheostomy: 12% (31/258) vs. NR	IMRT is comparable and the differences likely arise in their toxicity and complication profile
Non-randomized studies		
Chung, 2014	<u>Partial Pharyngectomy for Mild-Moderate Disease</u> Mean Length of Stay (days): 3.7 vs. 5.2 p<0.001 Mean total charges ($): 67,317 vs. 98,228 p<0.001 Mean total cost ($): 20,706 vs. 29,635 p<0.001 Tracheostomy 1% vs. 26.9% p<0.001 Gastrostomy 1.7% vs. 11.6% p<0.001 Death: 0 vs. 0 Peri-operative Hemorrhage: 3.1% vs. 2.8% p=0.746 Blood Transfusion: 0 vs. 3.1% p<0.001 Dysphagia 19.5% vs. 8.0% p<0.001 <u>Partial Glossectomy for Mild to Moderate Disease (Tongue Base):</u> Mean Length of Stay (days): 3.54 vs. 5.06 p<0.001 Mean total charges ($): 52,054 vs. 68,605 p=0.001 Mean total cost ($): 19,091 vs. 23,414 p=0.003 Tracheostomy 4.1% vs. 26.7% p<0.001 Gastrostomy 17.7% vs. 11.5% p=0.055 Death: 0 vs. 0 Peri-operative Hemorrhage:	Findings demonstrate a clinical and cost benefit for TORS partial pharyngectomy and partial glossectomy for base of tongue but no benefit in partial glossectomy of the anterior tongue

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	0 vs. 0 Blood Transfusion: 0 vs. 2.3% p=0.092 Dysphagia 10.2 vs. 6% p=0.071 <u>Partial Glossectomy for Mild to Moderate Disease (Anterior Tongue):</u> Mean Length of Stay (days): 4.8 vs. 4 p=0.044 Mean total charges ($): 71,478 vs. 59,906 p=0.066 Mean total cost ($): 22,111 vs. 21,376 p=0.744 Tracheostomy 7.4% vs. 19.1% p=0.012 Gastrostomy 14.5% vs. 5.1% p=0.003 Death: 0 vs. 0 Peri-operative Hemorrhage: 0 vs. 0.9% p=1.00 Blood Transfusion: 0 vs. 2.6% p=0.419 Dysphagia 14.7% vs. 4.9% p=0.002	
Chen, 2014	Hospital length of stay (days): 4.7 vs. 3.5 p<0.001 Unplanned hospital readmission: 4.4% vs. 3.2% p=0.07 Positive Margins 20.2% vs. 31.0% p<0.001 Adjuvant Chemoradiation vs. adjuvant radiotherapy: OR: 0.50; 95%CI, 0.39-0.63	TORS is associated with a lower rate of positive margins compared to non-robotic surgery.
Richmon, 2014	Post-operative Complications: NS Dysphagia: 9.4% vs. 8.7% p=0.9792 Gastrostomy Tube: 0% vs. 19.4% p=0.4110 Tracheostomy: 0% vs. 36.1% p=0.3057 Death: 0 vs. 0.9% p=NR Length of Hospitalization: -1.5 days with TORS Cost: -$4,285 with TORS	TORS is associated with lower perioperative gastrostomy and tracheostomy tube placement and significantly decreases length of hospitalization and hospital related costs

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Hammoudi, 2014	Tracheostomy: 4 vs. 20 p<0.001 Duration of Hospitalization (days): 11 vs. 19 p=0.001 Duration of feeding by NG tube (days): 9 vs. 16 p=0.01 Number of Complications: 1 vs. 2 p=0.45 Overall Survival at 3 years: 81% vs. 95% p=0.33 Disease Free Survival at 3 years: 89% vs. 85% p=0.76 Mean cost of surgery ($): 7781 vs. 4375 p<0.001 Mean cost of hospitalization ($): 13,103 vs. 23,551 p=0.01 Mean cost of treatment ($): 27,926 vs. 20,885 p=0.03	TORS might result in lower morbidity and treatment costs for selected head and neck cancers, with no increase in complication rate or disease control
Economic Evaluations		
Dombree, 2014	Total Cost (€): 5,650 vs. 3,349	TORS is more expensive compared to standard approaches, mainly influenced by initial purchase costs

NR=not reported; **OR**=odds ratio; **TORS**=transoral robotic surgery